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Nordic Nutrition Recommendations 2012

Integrating nutrition and physical activity




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5th edition

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Nordic co-operation

Nordic co-operation is one of the world's most extensive forms of regional collaboration, involving Denmark, Finland, Iceland, Norway, Sweden, and the Faroe Islands, Greenland, and Åland.

Nordic co-operation has firm traditions in politics, the economy, and culture. It plays an important role in European and international collaboration, and aims at creating a strong Nordic community in a strong Europe.

Nordic co-operation seeks to safeguard Nordic and regional interests and principles in the global community. Common Nordic values help the region solidify its position as one of the world's most innovative and competitive.

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Secretary General's Preface

There has been an increasing interest in food and nutritional science in recent years. Food programmes are a staple of most television channels and cookbooks top the bestseller lists. At the same time, it can be a bit of a challenge to find your way through the jungle of advice on what we should eat facing the average consumer.

That is why we need a work like the Nordic Nutrition Recommendations, one of the most well-researched and thoroughly documented works within nutritional science worldwide. They give a scientific basis for formulating dietary guidelines and are an excellent example of what the Nordic countries can achieve when they work together.

The Nordic Council of Ministers funds the extensive scientific effort behind the Nordic Nutrition Recommendations. We do this as a means to inform the public debate on food-related matters. But maybe more importantly, the NNR also serve as the main reference point for the various national nutrition recommendations in the Nordic countries.

The Nordic Nutrition Recommendations are also the foundation for the criteria developed for the Nordic nutritional label the Keyhole, informing the shopping decisions of millions of consumers in the Nordic region on a daily basis.

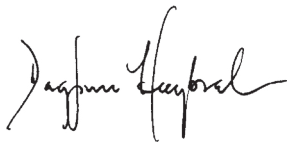
Finally, the NNR form part of the overall Nordic action plan *A better Life through Diet and Physical Activity.* In its aim to ensure the best-possible health for the population at large, this can be seen as an expression of the Nordic model, with its focus on an inclusive and holistic approach to society and the welfare of its citizens.

This is the fifth edition of the Nordic Nutrition Recommendations. As such, this publication is one of many examples of a long and fruitful Nordic co-operation over the last decades.

As a new step, we have decided to publish a free PDF version of the NNR along with a series of e-publications of individual chapters. The NNR will also for the first time ever be published as an e-book and they have thus entered the digital era.

I would like to thank the hundreds of scientists, experts and officials involved in compiling the Nordic Nutrition Recommendations and hope

that the quality of the work itself, as well as the many new forms of publication, will help ensure the widespread use that the NNR deserve.



Dagfinn Høybråten
Secretary General, Nordic Council of Ministers

Preface

The 5th edition of the Nordic Nutrition Recommendations, NNR 2012, has been produced by a working group nominated by the Working Group on Food, Diet and Toxicology (NKMT) under the auspices of the Nordic Committee of Senior Officials for Food Issues (ÄK-FJLS Livsmedel). The NNR 2012 working group was established in 2009 and consisted of Inge Tetens and Agnes N. Pedersen of Denmark; Ursula Schwab and Mikael Fogelholm of Finland; Inga Thorsdottir and Ingibjorg Gunnarsdottir of Iceland; Sigmund A. Anderssen and Helle Margrete Möltzer of Norway; and Wulf Becker (Chair), Ulla-Kaisa Koivisto Hursti (Scientific secretary), and Elisabet Wirfält of Sweden.

More than 100 scientific experts have been involved in this revision. Existing scientific evidence has been reviewed for setting dietary reference values (DRVs) that will ensure optimal nutrition and help prevent lifestyle-related diseases such as cardiovascular diseases, osteoporosis, certain types of cancer, type-2 diabetes, and obesity as well as the related risk factors for these diseases. The experts have assessed the associations between dietary patterns, foods, and nutrients and specific health outcomes. The work has mainly focused on revising areas in which new scientific knowledge has emerged.

Systematic reviews (SR) were conducted by the experts, with assistance from librarians, for the nutrients and topics for which new data of specific importance for setting the recommendations has been made available since the 4th edition. Less stringent updates of the reference values were conducted for the other nutrients and topics.

Peer reviewers for each nutrient and topic have also been engaged in the process of reading and commenting on the SRs and the updates conducted by the expert groups. A reference group consisting of senior experts representing various fields of nutrition science both within and outside the Nordic countries has also been engaged in the project. A steering group with representatives from national authorities in each country has been responsible for the overall management of the project.

All chapters were subject to public consultations from October 2012 to September 2013. The responses and actions to the comments by the NNR working group are published separately.

The SRs and the updates form the basis for deriving the DRVs. In the process of deriving the NNR 2012, emphasis has been put on the whole diet and the current dietary practices in the Nordic countries. This evaluation was performed by the NNR 2012 working group and was not part of the SRs conducted by the expert groups. The SRs were used as major and independent components – but not the only components – for the decision-making processes of the working group that was responsible for deriving the NNR 2012.

The SRs are published in the Food & Nutrition Research journal and the other background papers can be found on the Nordic Council of Ministers (NCM) website.

The 5th edition, the Nordic Nutrition Recommendations 2012, is published by the NCM and is also available in electronic form.

The following experts and peer reviewers have been engaged in performing SRs and chapter updates.

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Calcium experts: Christel Lamberg-Allardt, Kirsti Uusi-Rasi and Merja Kärkkäinen, Finland.
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Peer reviewers: Helle Margrete Meltzer, Norway, Peter Lauerberg, Denmark.

Iron experts: Magnus Domellöf, Sweden, Ketil Thorstensen, Norway, Inga Thorsdottir, Iceland.
Peer reviewers: Olle Hernell, Sweden, Lena Hulthén, Sweden, Nils Milman Denmark.

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Introduction

For several decades, the Nordic countries have collaborated in setting guidelines for dietary composition and recommended intakes of nutrients. Similarities in dietary habits and in the prevalence of diet-related diseases, such as cardiovascular diseases, osteoporosis, obesity and diabetes, has warranted a focus on the overall composition of the diet, i.e. the intake of fat, carbohydrate, and protein as contributors to the total energy intake. In 1968, medical societies in Denmark, Finland, Norway, and Sweden published a joint official statement on "Medical aspects of the diet in the Nordic countries" (Medicinska synpunkter på folkkosten i de nordiska länderna). The statement dealt with the development of dietary habits and the consequences of an unbalanced diet for the development of chronic diseases. Recommendations were given both for the proportion of fat in the diet and the fat quality, i.e. a reduced intake of total fat and saturated fatty acids and an increase in unsaturated fatty acids.

The Nordic Nutrition Recommendations (NNR) are an important basis for the development of food, nutrition, and health policies; for formulation of food-based dietary guidelines; and for diet and health-related activities and programmes. Previous editions mainly focused on setting dietary reference values (DRVs) for the intake of, and balance between, individual nutrients for use in planning diets for various population groups. The current 5th edition puts the whole diet in focus and more emphasis is placed on the role that dietary patterns and food groups play in the prevention of diet-related chronic diseases.

The NNR are intended for the general population and not for groups or individuals with diseases or other conditions that affect their nutrient requirements. The recommendations generally cover temporarily increased requirements, for example, during short-term mild infections or certain medical treatments. The recommended amounts are usually not suited for long-term infections, malabsorption, or various metabolic disturbances or for the treatment of persons with a non-optimal nutritional status. They are meant to be used for prevention purposes and are not specifically meant for treatment of diseases or significant weight reduction. The NNR do, however, cover dietary approaches for sustainable weight maintenance

after significant and intentional weight reduction. For specific groups of individuals with diseases and for other groups with special needs or diets, dietary composition might have to be adjusted accordingly.

After a thorough revision in which experts have reviewed a vast amount of scientific publications, most of the recommendations from the 4th edition (2004) remain unchanged. However, the RIs for vitamin D in children older than 2, adults, and the elderly ≥75 years of age and for selenium in adults have been increased. An emphasis has been put on the quality of fat and carbohydrates and their dietary sources. The recommendation for protein has been increased for the elderly ≥65 years of age. No recommended intakes have been set for biotin, pantothenic acid, chromium, fluoride, manganese, or molybdenum due to insufficient data, and this represents no change from the 4th edition.

The primary aim of the NNR 2012 is to present the scientific background of the recommendations and their application. A secondary aim is for the NNR 2012 to function as a basis for the national recommendations that are adopted by the individual Nordic countries.

The NNR 2012 are to be used as guidelines for the nutritional composition of a diet that provides a basis for good health. The basis for setting recommendations is defined for each individual nutrient using the available scientific evidence. In many cases, the values for infants and children are derived from adult data using either body weight or energy requirement as a basis for the estimations. As new scientific knowledge emerges with time, the NNR have to be reassessed when appropriate and should, therefore, not be regarded as definitive.

The NNR are based on the current nutritional conditions in the Nordic countries and are to be used as a basis for planning a diet that:

- satisfies the nutritional needs, i.e. covers the physiological requirements for normal metabolic functions and growth, and
- supports overall good health and contributes to a reduced risk of diet-associated diseases.

The NNR are valid for the average intake over a longer period of time of at least a week because the dietary composition varies from meal to meal and from day to day. The recommended intakes refer to the amounts of nutrients ingested, and losses during food preparation, cooking, etc. have to be taken into account when the values are used for planning diets.

The NNR can be used for a variety of purposes:

- as guidelines for dietary planning
- as a tool for assessment of dietary intake
- as a basis for food and nutrition policies
- as a basis for nutrition information and education
- as guiding values when developing food products

1 Nordic Nutrition Recommendations 2012 – A summary

Background

The current 5th edition of the Nordic Nutrition Recommendations (NNR 2012) puts the whole diet in focus. The recommendations emphasize food patterns and nutrient intakes that, in combination with sufficient and varied physical activity, are optimal for development and function of the body and that contribute to a reduced risk of certain diet-associated diseases. The development of the NNR is based on current scientific knowledge and an overall assessment of the available evidence.

Previous editions of the NNR mainly focused on setting DRVs for the intake of, and balance between, individual nutrients for use in planning diets for various population groups. In the current 5th edition, however, more emphasis is put on the role of dietary patterns and food groups in contributing to the prevention of the major diet-related chronic diseases. Nutrition research has traditionally strived to identify the specific mechanisms and health impacts of single nutrients, but most foods contain many nutrients as well as a multitude of other potential bioactive constituents that can affect bioavailability, uptake, and metabolic responses. Nutrients and other constituents interact with each other and the surrounding food matrix in complex ways. Thus, associations between single factors and chronic disease can be difficult to identify and difficult to interpret. In contrast, studies of dietary patterns or whole diets examine the association of combinations of many foods and nutrients with health.

The NNR 2012 has established the scientific evidence for an optimal intake and combination of nutrients for various groups in the general population. The evidence underlying the DRVs for nutrients includes the scientific evidence regarding food and nutrient intakes and dietary patterns and thus also accounts for factors other than nutrients.

Long-term energy balance and adequate physical activity are other important characteristics of healthy nutrition and lifestyle. NNR 2012 puts emphasis on the importance of adequate physical activity that, in combination with an appropriate food pattern, supports the long-term maintenance of a healthy body weight.

The scientific documentation is found in the individual chapters.

What characterises a healthy diet?

In recent years, much new data from both observational and experimental studies have been published on the health impact of foods, food patterns, and whole diets. These studies do not search for the specific mechanism or influence of a single nutrient but strive to capture the combined effects of all nutrients and food components consumed. As a result, there is currently a large body of evidence directly supporting the importance of specific food patterns or dietary patterns in maintaining good health. This evidence might facilitate the formulation of food-based dietary guidelines and recommendations for nutrient intakes. In addition, the evidence for the importance of early nutrition in terms of both short- and long-term health is growing. Promoting and supporting exclusive breastfeeding for the first 6 months of an infant's life followed by partial breastfeeding until the age of one year is one strategy to promote adequate growth and prevent obesity later in life.

By also considering factors like food production characteristics, seasonal food supply, and food origin when selecting food items, a diet that supports health can also be sustainable from an environmental and ecological perspective.

Dietary patterns and health – scientific evidence

SRs of prospective population studies as well as RCTs regarding associations between dietary patterns and the risk for chronic diseases such as coronary heart disease, myocardial infarction, postmenopausal breast cancer, and obesity reach similar conclusions. Dietary patterns rich in vegetables, including dark green leaves, fresh peas and beans, cabbage, onion, root vegetables, fruiting vegetables (e.g., tomatoes, peppers, avocados, and olives), pulses, fruits and berries, nuts and seeds, whole grains, fish and seafood, vegetable oils and vegetable oil-based fat spreads (derived from, for example, rapeseed, flaxseed, or olives), and low-fat dairy products are,

compared to Western-type dietary patterns (see below), associated with lower risk of most chronic diseases. These observations are similar to SRs of the health impact of diets such as the Mediterranean-like diets. Such plant food-dominated dietary patterns provide high amounts of micronutrients (essential minerals and vitamins), and the types of fats (including essential fatty acids) and carbohydrates in these diets are generally favourable to good health. This type of plant food-based diet also provides a number of potential bioactive components such as antioxidants, phenolic compounds, and phytoestrogens that have been associated with protection against many chronic diseases. In addition, randomised controlled intervention trials of whole diets have repeatedly and convincingly demonstrated that diets in line with current dietary recommendations are associated with important health benefits. Several such trials have been conducted in the US, Europe, and the Nordic countries.

In contrast, Western-type dietary patterns that are characterized by high consumption of processed meats and red meats (i.e., beef, pork, and lamb) and of food products low in essential nutrients but high in added sugar and fat (i.e., foods with high energy density) and high in salt are associated with adverse health effects and chronic diseases. Evidence also exists that suggests that food preparation and manufacturing methods that involve prolonged treatment at very high temperatures might contribute to adverse health effects.

The findings mentioned above underscore the fact that single food items or nutrients cannot alone ensure overall health and that diet as a whole needs to be considered.

Foods and health – scientific evidence

Plant foods such as vegetables, fruits and berries, nuts and seeds, and whole-grain cereals are rich in dietary fibre, micronutrients, and potential bioactive constituents. There is strong scientific evidence that natural fibre-rich plant foods contribute to decreased risk of diseases such as hypertension, cardiovascular diseases, type-2 diabetes, and some forms of cancer. The low energy density and the physico-chemical properties of most plant foods can contribute to weight maintenance. Because obesity and excessive body fat are established risk factors for most chronic diseases, including many types of cancer, low energy-density diets might also contribute to protection against a majority of chronic diseases. Fatty fish, nuts, seeds, and vegetable oils provide different kinds of unsaturated fatty acids. Seed

oils such as rapeseed and flaxseed oils are rich in both n-3 and n-6 fatty acids. The very long-chain n-3 fatty acids found in fish are of special health importance. There is strong scientific evidence supporting unsaturated fats as the major part of the total fat intake.

Animal foods such as meat, dairy, and eggs are important protein and mineral sources in the diet. Because meat and dairy are also major contributors of saturated fatty acids, high-fat products should be exchanged for low-fat dairy and low-fat meat alternatives. There is strong epidemiological evidence that high consumption of processed meat increases the risk of colorectal cancer, type-2 diabetes, obesity, and coronary heart disease. Similar, but weaker, associations have been observed for red meat. Replacing processed and red meat with vegetarian alternatives (such as pulses), fish, or poultry reduces the risk. High consumption of low-fat milk products has been associated with reduced risk of hypertension, stroke, and type-2 diabetes.

High consumption of beverages with added sugars is linked to increased risk of type-2 diabetes in both epidemiological and randomized controlled trials. Diets with plenty of meat, refined grains (i.e., white bread and products made with sifted flour), sweets, sugar-rich drinks, and desserts predict more weight gain and larger waist circumference. There is also strong scientific evidence that high salt (NaCl) intakes lead to increased risk of hypertension.

Implications of documented diet-related disease risks

Based on the scientific evidence documented in the 5th edition of the NNR, an overall micronutrient-dense dietary pattern and a set of food selection changes have been identified to promote health and wellbeing in the Nordic populations. These are summarized in Table 1.1.

– *Decrease energy density, increase micronutrient density, and improve carbohydrate quality*

Diets dominated by naturally fibre-rich plant foods will generally be lower in energy density compared to diets dominated by animal foods. Energy density is generally high in food products high in fat and added sugar (e.g., desserts, sweets, candy bars, cakes and biscuits, savoury snacks, some breakfast cereals, ice-cream, and some milk products). Whole grains and whole-grain flour are rich in dietary fibre and have lower energy density compared to refined grains and sifted flour. Limited consumption of sugar-

sweetened beverages will contribute to increased micronutrient density and reduced intake of added sugars.

– *Improve dietary fat quality by balancing the fatty acid proportions*
Fatty fish, nuts and seeds, vegetable oils, and vegetable oil-based fat spreads that provide essential and unsaturated fatty acids should be prioritized. Animal products high in fat contribute saturated fatty acids. A switch from high-fat to low-fat dairy will contribute to an improved fat quality while sustaining micronutrient density.

– *Limit processed and red meat*
Limited processed and red meat consumption, and a switch from high-fat to low-fat meat, will contribute to both an improvement of dietary fat quality and to lower energy density in the diet.

– *Limit the use of salt in food products and food preparation*
Manufactured foods provide a large proportion of the total salt intake. A reduction of the salt intake can be achieved by choosing low-salt varieties and limiting the amount of salt added during food preparation.

Table 1.1. Dietary changes that potentially promote energy balance and health in Nordic populations

Increase	Exchange	Limit
Vegetables Pulses	Refined cereals → Wholegrain cereals	Processed meat Red meat
Fruits and berries	Butter Butter based spreads → Vegetable oils Vegetable oil based fat spreads	Beverages and foods with added sugar
Fish and seafood	High-fat dairy → Low-fat dairy	Salt
Nuts and seeds		Alcohol

Nutrients and health – scientific evidence

Macronutrients

NNR 2012 establishes Recommended Intake Ranges for macronutrients. The current scientific evidence used to set recommended intake ranges is strong for certain sub-categories of macronutrients but less so for the intake of total carbohydrates and fat. The scientific evidence for the fatty

acid composition in the diet is stronger than for the total fat intake with respect to development of chronic diseases such as coronary heart disease, type-2 diabetes, and certain cancers. Also, the dietary sources of major fatty acid categories play an important role in the associations with health. The same applies to carbohydrates where the content and profile of the various dietary constituents determine the physiological and health effects. Frequent consumption of plant foods that are rich in dietary fibre, such as whole-grain cereals, is generally associated with health benefits, and frequent consumption of foods rich in refined grains and sifted flour and added sugars is associated with increased risk of chronic diseases. Scientific evidence also indicates that the health effects of fat intake can be modified by the amount and food sources of carbohydrates and fibre.

Vitamins and minerals

NNR 2012 sets Recommended Intakes (RI) for most essential micronutrients. These RIs are based on different types of scientific evidence, and should, when consumed as part of a varied, well-balanced diet, assure optimal function and development and contribute to a reduced risk of major chronic diseases. RIs have traditionally been based on criteria for optimal development and maintenance of body functions. In recent decades, however, more emphasis has been put on criteria such as the influences on the risk factors for chronic disease and on the risk of chronic diseases. Thus recent national nutrition surveys and dietary patterns in the Nordic countries indicate that emphasis needs to be put partly on certain micronutrients (e.g., vitamin D, selenium, iodine, sodium, iron, and folate) and partly on the quality of carbohydrates and fats.

Dietary Reference Values for nutrient intakes intended for dietary planning

NNR 2012 includes recommended intake ranges for macronutrients, upper or lower threshold levels for certain subcategories, and RIs of essential micronutrients. The macronutrient sub-categories are polyunsaturated, monounsaturated, saturated, and trans-fatty acids; protein; dietary fibre; and added, refined sugars. Recommendations are also given for alcohol consumption for adults.

Recommended intakes of macronutrients (excluding energy from alcohol)

Adults and children from 2 years of age

Fatty acids (expressed as triglycerides)

Intake of cis-monounsaturated fatty acids should be 10–20% of the energy intake (E%).

Intake of cis-polyunsaturated fatty acids should be 5–10 E%, of which n-3 fatty acids should provide at least 1 E%.

Cis-monounsaturated and cis-polyunsaturated fatty acids should constitute at least two thirds of the total fatty acids in the diet.

Intake of saturated fatty acids should be limited to less than 10 E%.

Intake of trans-fatty acids should be kept as low as possible.

The total fat recommendation is 25–40 E% and is based on the recommended ranges for different fatty acid categories.

Linoleic (n-6) and alpha linolenic (n-3) acids are essential fatty acids and should contribute at least 3 E%, including at least 0.5 E% as alpha linolenic acid. For pregnant and lactating women, the essential fatty acids should contribute at least 5 E%, including 1 E% from n-3 fatty acids of which 200 mg/d should be docosahexaenoic acid, DHA (22:6 n-3).

Partly replacing saturated fatty acids with cis-polyunsaturated fatty acids and cis-monounsaturated fatty acids (oleic acid) from vegetable dietary sources (e.g., olive or rapeseed oils) is an effective way of lowering the serum LDL-cholesterol concentration. Replacement of saturated or trans-fatty acids with cis-polyunsaturated or cis-monounsaturated fatty acids decreases the LDL/HDL-cholesterol ratio. Replacing saturated and trans-fatty acids with cis-polyunsaturated fatty acids reduces the risk, for example, of coronary heart disease, and replacement of saturated and trans-fatty acids with cis-monounsaturated fatty acids from vegetable dietary sources (e.g., olive or rapeseed oils) has similar effects.

Even though total fat intake varies widely, population and intervention studies indicate that the risk of atherosclerosis can remain quite low as long as the balance between unsaturated and saturated fatty acids is favourable. In addition to the quality of fat, it is important to pay attention to the quality of carbohydrates and the amount of dietary fibre, that is, the recommendations for dietary fibre and carbohydrates (with low intakes of

added sugar) should be achieved through an ample supply of plant-based foods. The recommended range for the total amount of fat is 25–40 E% based on the sum of the ranges of the recommendations for individual fatty acid categories.

For the intake of total fat, a suitable target for dietary planning is 32–33 E%.

At total fat intakes below 20 E%, it is difficult to ensure sufficient intake of fat-soluble vitamins and essential fatty acids. A reduction of total fat intake below 25 E% is not generally recommended because very low-fat diets tend to reduce HDL-cholesterol and increase triglyceride concentrations in serum and to impair glucose tolerance, particularly in susceptible individuals.

Carbohydrates and dietary fibre

Health effects of dietary carbohydrates are related to the type of carbohydrate and the food source. Carbohydrates found in whole-grain cereals, whole fruit, vegetables, pulses, and nuts and seeds are recommended as the major sources of carbohydrates. Total carbohydrate intakes in studies on dietary patterns associated with reduced risk of chronic diseases are in the range of 45–60 E%. A reasonable range of total carbohydrate intake is, however, dependent on several factors such as the quality of the dietary sources of carbohydrates and the amount and quality of fatty acids in the diet.

Dietary fibre

Adults: Intake of dietary fibre should be at least 25–35 g/d, or approximately 3 g/MJ.

Children: An intake corresponding to 2–3 g/MJ is appropriate for children from 2 years of age. From school age, the intake should gradually increase to reach the recommended adult level during adolescence.

An adequate intake of dietary fibre reduces the risk of constipation and contributes to a reduced risk of colorectal cancer and several other chronic diseases such as cardiovascular disease and type-2 diabetes. Moreover, fibre-rich foods help in maintaining a healthy body weight. Intake of appropriate amounts of dietary fibre from a variety of foods is also important for children.

For dietary planning purposes, a suitable target is >3 g/MJ from natural fibre-rich foods such as vegetables, whole grains, fruits and berries, pulses, and nuts and seeds.

Added sugars

Intake of added sugars should be kept below 10 E%.

A restriction in the intake of added refined sugars[1] is important to ensure adequate intakes of micronutrients and dietary fibre (nutrient density) as well as to support a healthy dietary pattern. This is especially important for children and persons with a low energy intake. Consumption of sugar-sweetened beverages has been associated with an increased risk of type-2 diabetes and excess weight gain and should, therefore, be limited. Frequent consumption of sugar-containing foods should be avoided to reduce the risk of dental caries. The recommended upper threshold for added sugar is also compatible with the food-based recommendation to limit the intake of sugar-rich beverages and foods.

The recommended range for the total amount of carbohydrate is 45–60 E%. For dietary planning purposes, a suitable target for the amount of dietary carbohydrate is 52–53 E%.

Protein

Adults and children from 2 years of age: Protein should provide 10–20% of the total energy intake (E%).

Elderly (≥65 years): Protein should provide 15–20 E%, and with decreasing energy intake (below 8 MJ/d) the protein E% should be increased accordingly.

In order to achieve an optimal intake in a varied diet according to Nordic dietary habits, a reasonable range for protein intake is 10–20 E%. This intake of protein should adequately meet the requirements for essential amino acids.

1 Added sugars include sucrose, fructose, glucose, starch hydrolysates (glucose syrup and high-fructose syrup), and other isolated sugar preparations used as such or added during food preparation and manufacturing.

For food planning purposes, a suitable target for the amount of protein intake should be 15 E%. This corresponds to about 1.1 g protein per kg body weight and day.

For food planning purposes in the elderly, a suitable target for the amount of protein intake should be 18 E%. This corresponds to about 1.2 g protein per kg body weight and day.

Alcohol

The consumption of alcohol should be limited and should not exceed approximately 10 g alcohol per day for women or 20 g per day for men. The energy contribution from alcohol should not exceed 5 E% in adults. Pregnant women, children, and adolescents are recommended to abstain from alcohol.

Recommended intakes of macronutrients for children up to 2 years of age

Exclusive breastfeeding is recommended for infants during the first 6 months. Recommendations for the intake of energy-yielding nutrients for children 6–23 months are given in Table 1.2. There is convincing evidence that the risk of obesity in childhood and adolescence increases with increased protein intake during infancy and early childhood. Protein intake should increase from about 5 E% (the level in breast milk) to the intake range of 10–20 E% for older children and adults.

n-6 fatty acids should contribute at least 4% of the total energy intake (E%) for children 6–11 months and 3 E% for children 12–23 months of age.

n-3 fatty acids should contribute at least 1 E% for children 6–11 months and 0.5 E% for children 12–23 months.

During the first year, the intake of trans fatty acids should be kept as low as possible.

From 12 months, the recommendation on saturated and trans-fatty acids for older children and adults should be used.

Table 1.2. Recommended intake of fat, carbohydrates, and protein
Expressed as per cent of total energy intake (E%) for children 6–23 months[a]

Age	E%
6–11 months	
Protein	7–15
Fat	30–45
Carbohydrates [b]	45–60
12–23 months	
Protein	10–15
Fat	30–40
Carbohydrates [b]	45–60

[a] Because exclusive breastfeeding is the preferable source of nutrition for infants <6 months, no recommendations for fat, protein, or carbohydrate intakes are given for this age group. For non-breastfed infants, it is recommended that the values for infant formula given in the EC legislation (REGULATION (EC) No 1243/2008 and Directive 2006/141/EC) be used. If complementary feeding has started at 4–5 months, the intakes recommended for 6–11 month olds should be used.

[b] Intake of added sugars should be kept below 10 E%.

Recommended intake of vitamins and minerals

The RIs of certain vitamins and minerals, expressed as average daily intakes over time, are given in Table 1.3. The values for RIs are intended mainly for planning diets for groups of individuals of the specified age intervals and sex. The values include a safety margin accounting for variations in the requirement of the group of individuals and are set to cover the requirements of 97% of the group. An alternative way to plan a diet is to use the requirements in combination with the distribution of reported or usual intakes for the specific nutrients (see Chapter 3 Use of Nordic Nutrition Recommendations).

The NNR 2012 do not cover all known essential nutrients because the scientific basis for establishing recommendations was considered incomplete for some nutrients.

Table 1.3. Recommended intake of certain nutrients
Expressed as the average daily intake over time for use in planning diets for groups.[a] The requirements are lower for almost all individuals

Age mo/ years	Vit. A RE [c]	Vit. D [d] µg	Vit. E α-TE [e]	Thiamin mg	Riboflavin mg	Niacin NE [f]	Vit. B_6 mg	Folate µg	Vit. B_{12} µg	Vit. C mg
<6 mo [b]	-	-	-	-	-	-	-	-	-	-
6–11 mo	300	10	3	0.4	0.5	5	0.4	50	0.5	20
12–23 mo	300	10	4	0.5	0.6	7	0.5	60	0.6	25
2–5 y	350	10	5	0.6	0.7	9	0.7	80	0.8	30
6–9 y	400	10	6	0.9	1.1	12	1.0	130	1.3	40
Females										
10–13	600	10	7	1.0	1.2	14	1.1	200	2.0	50
14–17	700	10	8	1.2	1.4	16	1.3	300	2.0	75
18–30	700	10	8	1.1	1.3	15	1.2	400	2.0	75
31–60	700	10	8	1.1	1.2	14	1.2	300[g]	2.0	75
61–74	700	10	8	1.0	1.2	13	1.3	300	2.0	75
≥75	700	20	8	1.0	1.2	13	1.3	300	2.0	75
Pregnant	800	10	10	1.5	1.6	17	1.4	500	2.0	85
Lactating	1100	10	11	1.6	1.7	20	1.5	500	2.6	100
Males										
10–13	600	10	8	1.1	1.3	15	1.2	200	2.0	50
14–17	900	10	10	1.4	1.7	19	1.6	300	2.0	75
18–30	900	10	10	1.4	1.6	19	1.5	300	2.0	75
31–60	900	10	10	1.3	1.5	18	1.5	300	2.0	75
61–74	900	10	10	1.2	1.4	16	1.5	300	2.0	75
≥75	900	20	10	1.2	1.3	15	1.5	300	2.0	75

[a] Refers to the consumed amount, and losses during preparation, cooking, etc. must be accounted for.
[b] Exclusive breastfeeding is the preferable source of nutrition for infants during the first six months of life. Therefore, recommendations for single nutrients are not given for infants <6 months. If breastfeeding is not possible, infant formula formulated to serve as the only food for infants should be given (see Chapter on breastfeeding). If complementary feeding has started at 4–5 months, the recommended intakes for 6–11 month old infants should be used.
[c] Retinol equivalents; 1 retinol equivalent (RE) = 1 µg retinol = 12 µg β-carotene.
[d] From 1–2 weeks of age, infants should receive 10 µg vitamin D_3 per day as a supplement. For people with little or no sun exposure, the recommended intake is 20 µg per day. This can be achieved by taking a daily supplement of 10 µg vitamin D_3 in addition to the dietary intake or by choosing foods rich in vitamin D. For the elderly ≥75 years of age, the recommended intake can be achieved by selecting foods naturally high in vitamin D and vitamin D-enriched foods in combination with a supplement if necessary.
[e] α-tocopherol equivalents; 1 α-tocopherol equivalent (α-TE) = 1 mg RRR α-tocopherol.
[f] Niacin equivalent; 1 niacin equivalent (NE) = 1 mg niacin = 60 mg tryptophan.
[g] Women of reproductive age are recommended to have an intake of 400 µg/d.

Table 1.3., continued. Recommended intake of certain nutrients
Expressed as average daily intake over time for use in planning diets for groups. The requirement is lower for almost all individuals

Age mo/ years	Calcium mg	Phosphorus mg	Potassium g	Magnesium mg	Iron[h] mg	Zinc[i] mg	Copper mg	Iodine µg	Selenium µg
<6 mo[b]	-	-	-	-	-	-	-	-	-
6–11 mo	540	420	1.1	80	8	5	0.3	50	15
12–23 mo	600	470	1.4	85	8	5	0.3	70	20
2–5 y	600	470	1.8	120	8	6	0.4	90	25
6–9 y	700	540	2.0	200	9	7	0.5	120	30
Females									
10–13	900	700	2.9	280	11	8	0.7	150	40
14–17	900	700	3.1	280	15[l]	9	0.9	150	50
18–30	800 j	600 [j]	3.1	280	15[l]	7	0.9	150	50
31–60	800	600	3.1	280	15[k]/9[l]	7	0.9	150	50
61–74	800	600	3.1	280	9	7	0.9	150	50
≥75	800	600	3.1	280	9	7	0.9	150	50
Pregnant	900	700	3.1	280	-- [m]	9	1.0	175	60
Lactating	900	900	3.1	280	15	11	1.3	200	60
Males									
10–13	900	700	3.3	280	11	11	0.7	150	40
14–17	900	700	3.5	350	11	12	0.9	150	60
18–30	800 [j]	600 [j]	3.5	350	9	9	0.9	150	60
31–60	800	600	3.5	350	9	9	0.9	150	60
61–74	800	600	3.5	350	9	9	0.9	150	60
≥75	800	600	3.5	350	9	9	0.9	150	60

h The composition of the meal influences the utilization of dietary iron. The availability increases if the diet contains abundant amounts of vitamin C and meat or fish daily, and it is decreased with simultaneous intake of polyphenols or phytic acid.

i The utilization of zinc is negatively influenced by phytic acid and positively influenced by animal protein. The recommended intakes are valid for a mixed animal/vegetable diet. For vegetarian cereal-based diets, a 25%–30% higher intake is recommended.

j 18–20 year olds are recommended to consume 900 mg calcium and 700 mg phosphorus per day.

k Menstrual flow and its associated iron losses can vary considerably among women. This means that some women require a larger iron supply than others. At an availability of 15%, 15 mg/d will cover the requirement of 90% of women of reproductive age. Some women require more iron than the habitual diet can supply.

l Recommended intake for post-menopausal women is 9 mg per day.

m Iron balance during pregnancy requires iron stores of approximately 500 mg at the start of pregnancy. The physiological need of some women for iron cannot be satisfied during the last two thirds of pregnancy with food only, and supplemental iron is needed.

Sodium as salt

A gradual reduction in the intake of sodium expressed in the form of sodium chloride is desirable. The population target is 6 g/d salt for adults. This corresponds to 2.4 g/d of sodium. The salt intake of children should also be limited, and for children below 2 years of age the sodium density, expressed as salt, should not exceed 0.5 g/MJ. This is to prevent children becoming accustomed to a diet with a high salt content. From 2 years up to 9 years of age, salt intake should be limited to about 3–4 g/d.

Dietary supplements

In general, the nutrient requirements can be met with a varied and balanced diet. However, dietary supplements might be needed by certain population groups or during certain life-stages, for example, infants or the elderly in nursing homes.

Prolonged intakes of nutrients from supplements have generally not been associated with decreased risk of chronic diseases or other health benefits in healthy individuals eating a varied diet that covers their energy requirements. In contrast, there is a large body of evidence suggesting that elevated intakes of certain supplements, mainly vitamins with antioxidative properties, might even increase the risk of certain adverse health effects, including mortality. Thus, there is no scientific justification for using supplements as a tool for adjusting an unbalanced diet.

Recommendations for planning diets for heterogeneous groups

In planning diets for groups with a heterogeneous age and sex distribution, the amounts of nutrients per MJ given in Table 1.4. can be applied. For each nutrient, the values are based on the age and sex category of individuals 6–65 years old for which the highest nutrient density is necessary to meet the RIs. These recommendations are not intended for pregnant and lactating women or for adult diets with an energy intake of less than 8 MJ per day. They are also not suitable for planning diets with an energy intake above 12 MJ per day in which a lower density of many nutrients might be sufficient.

An energy intake of 6.5–8 MJ is considered a low-energy intake with an increased risk of an insufficient intake of micronutrients. A very low energy intake is defined as an energy intake below 6.5 MJ/d and is associated with a considerable risk of an insufficient intake of micronutrients.

A very low energy intake is related to either a very low physical activity level or to a low body weight. Low body weight is related to small muscle mass and, therefore, to low energy expenditure. Very low energy intake is found among persons on slimming diets and among persons with eating disorders, food intolerances, etc. A suitable way to prevent low and very low energy intake is to increase the physical activity level.

With low energy intakes it might be difficult to meet the needs for all the nutrients using the values in Table 1.3. In such cases, the recommended nutrient density per MJ from Table 1.4. should be followed and supplementation with a multivitamin/mineral tablet should be considered. For groups with a very low energy intake (<6.5 MJ), the diet should always be supplemented with a multivitamin/mineral tablet.

Table 1.4. Recommended nutrient density (per MJ) to be used for planning diets for groups of individuals 6–65 years of age with a heterogeneous age and sex distribution. The values are adapted to the reference person requiring the highest dietary nutrient density

		Content per MJ
Vitamin A	RE*	80
Vitamin D	µg	1.4
Vitamin E	α-TE*	0.9
Thiamin	mg	0.12
Riboflavin	mg	0.14
Niacin	NE*	1.6
Vitamin B_6	mg	0.13
Folate	µg	45
Vitamin B_{12}	µg	0.2
Vitamin C	mg	8
Calcium	mg	100
Phosphorus	mg	80
Potassium	g	0.35
Magnesium	mg	32
Iron	mg	1.6
Zinc	mg	1.2
Copper	mg	0.1
Iodine	µg	17
Selenium	µg	5.7

* See Table 1.3. for definitions.

Reference values for energy intake

Both excessive and insufficient energy intake in relation to energy requirements can lead to negative health consequences in the long term. In adults, therefore, an individual's long-term energy intake and energy expenditure should be equal.

In Table 1.5., reference values are given for energy intake for groups of adults with two different physical activity levels. An active lifestyle, corresponding to PAL 1.8, is considered desirable for maintaining good health. An activity level of PAL 1.6 is close to the population median and corresponds to a common lifestyle with sedentary work and some increased physical activity level during leisure time. The reference body weights used for the calculations are based on Nordic populations. The original weights have been adjusted so that all individuals would have a body mass index (BMI) of 23. Therefore, the reference values indicate an energy intake that would maintain normal body weight in adults.

Specific recommendations for energy intake cannot be given due to the large variation between individuals with respect to metabolic rate, body composition, and degree of physical activity.

Tables 1.6. and 1.7. contain reference values for energy intakes in groups of children. It must again be mentioned that individual energy requirements might be very different from these group-based average values.

Table 1.5. Reference values for energy intakes in groups of adults with sedentary and active lifestyles[a]

Age, years	Reference weight[b] kg	REE[c] MJ/d	Average PAL[d] 1.6 MJ/d	Active PAL 1.8 MJ/d
Females[f]				
18–30	64.4	5.8	9.4	10.5
31–60	63.7	5.5	8.8	9.9
61–74[e]	61.8	5.0	8.1	9.1
Males				
18–30	75.4	7.3	11.7	13.2
31–60	74.4	6.9	11.0	12.4
61–74[e]	72.1	6.1	9.7	10.9

a It should be noted that these estimations have a large standard error due to inaccuracy in estimation of both REE and PAL. Therefore, the results should be used only for estimation on the group level. See chapter on Energy for more details.

b Reference weight corresponds to a body mass index (BMI) of 23 kg/m^2; data based on actual heights of populations in all Nordic countries.

c REE = Resting Energy Expenditure.

d PAL = Physical Activity Level.

e The REE for 61–74 year olds was calculated by using the equation for 61–70 year olds.

f During pregnancy the energy requirement increases, mainly during the second and third trimesters. An increase in energy intake of approximately 0.4, 1.4 and 2.2 MJ/d in the first, second and third trimester, respectively, is applicable for both activity levels provided that the level (1.6 or 1.8 MJ/d) is unchanged. During lactation the energy requirement increases by approximately 2–2.8 MJ/d for the reference woman provided that the level of physical activity is unchanged. For many pregnant and lactating women, the increased energy requirement is compensated for by a decreased amount of physical activity.

Table 1.6. Reference values for estimated average daily energy requirements (per kg body weight) for children 6–12 months assuming partial breastfeeding

Age months	Average daily energy requirements kJ/kg body weight	
	Boys	Girls
6	339	342
12	337	333

Table 1.7. Reference values for estimated daily energy requirements (MJ/d) for children and adolescents (from 2 to 17 years)[1]

Age	Reference weight, kg	REE MJ/d	Estimated energy requirement MJ/d
2–5 y	16.1	3.6	5.3
6–9 y	25.2	4.4	6.9
Girls			
10–13 y	38.3	5.0	8.6
14–17 y	53.5	5.7	9.8
Boys			
10–13 y	37.5	5.4	9.3
14–17 y	57.0	6.8	11.8

[1] PALs (average) for age groups: 1–3 years = 1.39; 4–9 years = 1.57; 10–17 years = 1.73.

Recommendations on physical activity

Adequate physical activity contributes to the prevention of lifestyle-related diseases such as cardiovascular disease, osteoporosis, and certain types of cancer. Daily physical activity is, therefore, recommended as part of a healthy lifestyle together with a balanced diet. There is also emerging evidence that extended daily periods of sedentary behaviour (several hours of sitting or lying during the daytime) increase the risk for chronic diseases. Therefore, it is recommended to reduce sedentary behaviour.

Adults

The following are the recommendations on physical activity for adults including elderly:

1. Adults should engage in least 150 minutes of moderate-intensity physical activity throughout the week, or engage in at least 75 minutes

of vigorous-intensity physical activity throughout the week, or engage in an equivalent combination of moderate- and vigorous-intensity activity.
2. Aerobic activity should be performed in bouts of at least 10 minutes duration.
3. For additional health benefits, adults should increase their moderate-intensity physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or engage in an equivalent combination of moderate- and vigorous-intensity activity.
4. Reduce sedentary behaviour.

Even though there is a lack of conclusive data, it seems that the amount of daily activity needed to avoid weight gain is about 60 minutes of moderate-intensity activity or a somewhat shorter duration of vigorous-intensity activity.

Children and adolescents

The following are the recommendations on physical activity for children and adolescents:

1. Children and adolescents should accumulate at least 60 minutes of moderate to vigorous-intensity physical activity daily.
2. Physical activity of amounts greater than 60 minutes daily will provide additional health benefits.
3. Activities should be as diverse as possible in order to provide optimal opportunities for developing all aspects of physical fitness, including cardio-respiratory fitness, muscle strength, flexibility, speed, mobility, reaction time, and coordination. Vigorous-intensity activities should be incorporated, including those that strengthen muscle and bone, at least 3 times per week.
4. Reduce sedentary behaviour.

Overweight and obesity

Obesity is one of the main health problems in the Nordic countries, and reducing the prevalence of obesity requires both effective treatment of obesity and prevention of weight gain. The focus of the NNR is on the prevention of obesity and excessive weight gain.

Long-term weight change is one of the main outcomes when defining

the recommended intake ranges of macronutrients and food groups. In prospective studies on macronutrients and weight change, the evidence linking a higher dietary fibre intake to reduced weight gain is clear. No other evident associations between macronutrients and weight change in adults were observed in the NNR SR on diet and long-term weight change. However, combined results from intervention studies not designed for intentional weight loss show that reduced total fat intake was associated with a modest weight reduction. Also, reduced intake of sugar and sugar-sweetened beverages has been associated with modest weight loss. The evidence linking proportions of macronutrients (fats, carbohydrates, and proteins) to weight change in adults is partly conflicting, and this indicates that gross macronutrient composition per se does not seem to be a major predictor of long-term weight change or maintenance. The observed effects on body weight changes among adults might, therefore, be partly mediated by food-related factors that affect long-term energy intake. In contrast, high protein intake in early childhood might induce obesity later in life.

There is clear evidence to conclude that fibre-rich foods (e.g., whole grains, vegetables, fruits, berries, legumes, nuts, and seeds), and perhaps also dairy products, are associated with reduced weight gain. In contrast, refined cereals, sugar-rich foods and drinks, red meat, and processed meat are associated with increased weight gain in long-term studies. Diets based on natural plant foods generally have lower energy density compared to diets rich in animal foods and to food products high in fat and sugar.

In addition, adequate physical activity will contribute to maintaining a healthy body weight in the long-term.

Reference values for assessing nutrient intakes

Vitamins and minerals

Assessing nutrient adequacy

Table 1.8. gives values for the estimated average requirement (AR) and lower intake level (LI) for certain vitamins and minerals. The values are intended only for use in assessing results from dietary surveys. Before comparing intake data with these reference values, it is crucial to check whether the intake data derived from a particular survey are suitable for assessing adequacy. More guidance on this topic and on how to use NNR in this context is given in Chapter 3 (Use of Nordic Nutrition Recommendations).

The AR is the value to be primarily used to assess the risk for inadequate intake of micronutrients in a certain group of individuals. The percent-

age that has an intake below the AR indicates the proportion having an increased risk of inadequate intake.

Long-term intakes below the LI are associated with an increased risk of developing deficiency symptoms. There is substantial uncertainty in several of these values so they should be applied with caution and, if possible, related to clinical and biochemical data. Furthermore, intake of nutrients above these values is no guarantee that deficiency symptoms could not occur in certain individuals.

It should be noted that a comparison with AR and LI values can never determine whether intake is adequate or not, it can only indicate the probability that it is. This is because nutrient intake data are not absolute values but are calculated using food composition tables and reported food consumption, both of which have a considerable error margin. Therefore, in order to find out whether an intake of a particular nutrient is adequate, biochemical measurements and thorough dietary assessments are necessary.

Assessing high intakes

For some nutrients, high intakes can cause adverse or even toxic symptoms. Upper intake levels (UL) have thus been established for some nutrients (Table 1.9.). For certain nutrients, especially preformed vitamin A (retinol), vitamin D, iron, and iodine, prolonged intakes above these levels can lead to an increased risk of toxic effects. For other nutrients the adverse effects might be different and milder, e.g. gastrointestinal problems or interference with the utilization of other nutrients. The ULs are not recommended levels of intake but are maximum levels of daily chronic intakes judged to be unlikely to pose a risk of adverse health effects in humans. The ULs are derived for the normal healthy population, and values are given for adults. For other life stages, such as infants and children, specific data might exist for deriving specific values or such values could be extrapolated. To establish whether a population is at risk for adverse effects, the fraction of the population exceeding the UL and the magnitude and duration of the excessive intake should be determined. There is a substantial uncertainty in several of the ULs, and they must be used with caution for single individuals. UL values do not necessarily apply in cases of prescribed supplementation under medical supervision.

Energy-providing nutrients

The assessment of macronutrient intake mainly concerns the energy distribution (as energy per cent, E%) from protein, fat, fatty acids, added

sugars, and total carbohydrates. For protein intake, i.e. gram per kg body weight and day, is also used and for dietary fibre the intake amount is given per day or per MJ.

In the assessment of the usual energy contribution from protein, fat, and carbohydrates, the proportion of the group that has energy contributions from these macronutrients within (or outside) the recommended intake range is estimated. In the assessment of the energy contribution from macronutrients with a recommended upper threshold (i.e., saturated fat and added sugars) the proportion of the group that exceeds this threshold is estimated. Likewise, when energy contribution from macronutrients with a recommended lower threshold (e.g., dietary fibre) is assessed, the proportion of the group that goes below this level is estimated.

Table 1.8. Estimated average requirement (AR) and lower intake level (LI) for certain vitamins and minerals for adults. The values are intended for use only in assessing results from dietary surveys. Long-term intakes below the LI are associated with an increased risk of developing deficiency symptoms. An intake of nutrients above these values is no guarantee that deficiency symptoms could not occur in certain individuals

Nutrient		Women		Men	
		LI	AR	LI	AR
Vitamin A	RE	400	500	500	600
Vitamin D	µg	2.5[a]	7.5	2.5[a]	7.5
Vitamin E	a-TE	3	5	4	6
Thiamin	mg	0.5	0.9	0.6	1.2
Riboflavin	mg	0.8	1.1	0.8	1.4
Niacin	NE	9	12	12	15
Vitamin B6	mg	0.8	1.1	1.0	1.3
Folate	µg	100	200	100	200
Vitamin B_{12}	µg	1	1.4	1	1.4
Vitamin C	mg	10	50	10	60
Calcium	mg	400	500	400	500
Phosphorus	mg	300	450	300	450
Potassium	g	1.6	-	1.6	-
Iron	mg	(5)[b, c]	10 (6)[b]	7	7
Zinc	mg	4	5	5	6
Copper	mg	0.4	0.7	0.4	0.7
Iodine	µg	70	100	70	100
Selenium	µg	20	30	20	35

[a] Primarily for individuals >60 years of age.
[b] () Refers to post-menopausal women.
[c] A lower limit cannot be given for women of fertile age without considering the woman's iron status as determined by clinical and biochemical methods.

Table 1.9. Estimated upper intake levels (UL) for average daily intake of certain nutrients for adults. The ULs are maximum levels of daily chronic intakes judged to be unlikely to pose a risk of adverse health effects in humans. The ULs are derived for the normal healthy population. There is a substantial uncertainty in several of the UL values, and they must be used with caution for single individuals. UL values do not necessarily apply in cases of prescribed supplementation under medical supervision

Nutrient		UL per day
Preformed vitamin A[a]	µg	3,000[b]
Vitamin D	µg	100
Vitamin E[c]	α-TE	300
Niacin[c]		
nicotinic acid	mg	10[d]
nicotinamide	mg	900
Vitamin B_6[c]	mg	25
Folic acid[c]	µg	1,000
Vitamin C	mg	1,000
Potassium[c]	g	3.7
Calcium	mg	2,500
Phosphorus	mg	3,000
Iron	mg	25[e]
Zinc	mg	25
Copper	mg	5
Iodine	µg	600
Selenium	µg	300

[a] As retinol and/or retinylpalmitate.
[b] Intake of retinol above 3,000 µg/d in pregnant women has been associated with an increased risk of foetal malformations. The upper tolerable level might not adequately address the possible risk of bone fracture in vulnerable groups. Postmenopausal women who are at greater risk for osteoporosis and bone fractures should, therefore, restrict their intake to 1,500 µg/d.
[c] In the form of supplements and fortification only.
[d] Not applicable for pregnant and lactating women.
[e] 10 mg in addition to habitual dietary iron intake.

2 Principles and background of the Nordic Nutrition Recommendations

Background

The Nordic Nutrition Recommendations (NNR) constitute the scientific basis for the planning of diets for population groups and for the development of food-based dietary guidelines in the Nordic countries. The recommendations serve as a basis for assessing nutrient intakes by groups of healthy individuals and for developing national and regional nutrition policies, nutritional educational programs, food regulations, and action programmes. The NNR are primarily valid for groups of healthy individuals with various levels of physical activity (excluding competitive athletes). For individuals with diseases and other groups with special needs, the dietary composition and energy content might have to be adjusted accordingly. Based on current scientific knowledge, the NNR give values for the intake of, and balance between, individual nutrients that are adequate for development and optimal function and that reduce the risk of developing certain diet-related diseases. If a diet provides enough food to cover the energy requirements, complies with the ranges for distribution of energy from macronutrients, and includes foods from all food groups, the requirements for practically all nutrients will be met. Exceptions might be vitamin D, iron, iodine, and folate in certain subgroups of the population or during certain life-stages.

The NNR are primarily valid for groups of healthy individuals with various levels of physical activity (excluding competitive athletes).

Historically, the main objective of nutrition recommendations was to determine the level of nutrient intake that would prevent deficiency disorders. Certain vitamin and mineral deficiency diseases, such as iodine and vitamin D deficiency, were common before these essential nutrients were recognised as vital components of the diet.

The concept of setting recommended dietary intakes dates back to the 1920s and 1930s. The first international table of energy and protein requirements by age and sex was published in 1936 by the League of Nations (1) and was followed by reference values for fat and some micronutrients. Recommended dietary allowances (RDA) for macronutrients and several micronutrients were published in 1941 by the National Academy of Sciences in the United States to serve as a guide for planning adequate nutrition for the general population (2). Since then, the concept has evolved to take into account not only the avoidance of clinical or subclinical deficiencies but also a reduction in the risk of development of overweight and obesity and major lifestyle diseases such as cardiovascular diseases, type-2 diabetes, cancer, and osteoporosis. More recently, the concern for health promotion through the diet has led to the concept of an optimal level of nutrient intake that is defined as an intake level that maximises physiological and mental functions and minimises the risk of development of chronic diseases (Figure 2.1.). Because new scientific data on the relationships between nutrient intakes, food patterns, physical activity, and health are being published regularly, our knowledge about the relationship between nutrient intake, nutrient status, and health is gradually increasing. Nutrition recommendations, therefore, need to be updated regularly.

For most nutrients, a hierarchy of criteria for nutrient adequacy can be established ranging from prevention of clinical deficiency to optimal levels of body stores and functionality. A higher intake of a nutrient is, however, not necessarily better for health. Beyond a certain intake level a higher intake might even lead to adverse health effects.

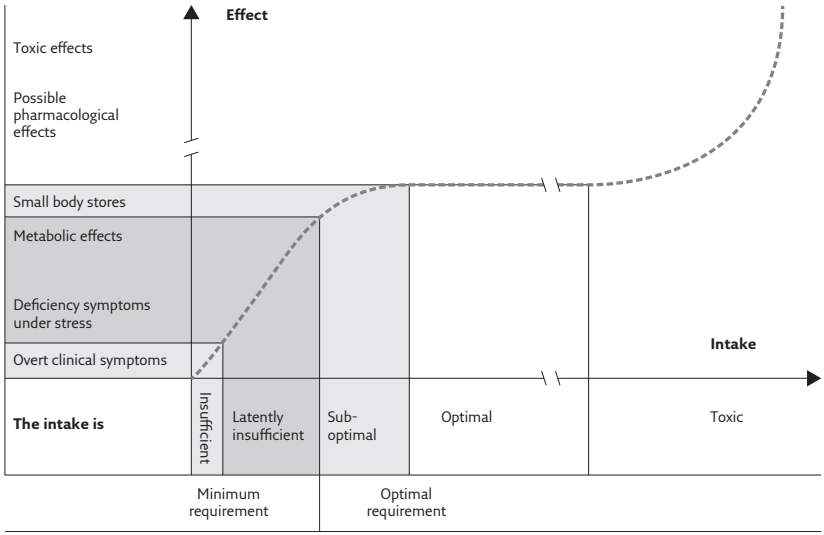


Figure 2.1. The theoretical relationship between intake of a nutrient and the effect on the organism

It should be noted that normally there is a transitional phase from deficiency diseases and/or symptoms to optimal conditions and even to toxicological effects of a certain intake level of a nutrient. There is also a transitional phase between overt toxic effects at very high intakes and milder adverse effects at lower intakes.

General approach

The main objective of the nutrition recommendations is to use the best available scientific evidence to ensure a diet that provides energy and nutrients for optimal growth, development, function, and health throughout life. It should be noted that a certain recommendation for a given nutrient is only applicable if the supply of other nutrients and energy is adequate.

The recommendations are intended for healthy individuals. Generally, the recommendations cover increased requirements such as during short-term mild infections or certain medical treatments. The recommended amounts are usually not suited for long-term infections, mal-absorption, and various metabolic disturbances or for treatment of persons with a non-optimal nutritional status. They are meant to be used for prevention purposes and are not specifically meant for treatment of diseases or for sig-

nificant weight reduction. The NNR, however, do cover dietary approaches for sustainable weight maintenance after significant, intentional weight reduction. For individuals with disease and for other groups with special needs, the dietary composition might have to be adjusted accordingly.

The 5th edition of the NNR is an update of the 4th edition from 2004 and focuses on the existing scientific evidence for updating the Nordic dietary reference values for nutrients in the context of a balanced diet. In the present NNR, an evidence-based approach has been adapted for deriving NNR reference values. For selected nutrients and topics, a systematic review (SR) has been used that includes a quality assessment of all pertinent studies and a final grading of the overall evidence. This approach has also been used as a basis for the food-based dietary guidelines. For the other nutrients and topics, an updated review has been undertaken using the documentation published in NNR 2004 as a starting point. In all reviews, data from observational and intervention studies have been used as the basis to estimate nutrient requirements for micronutrients and for establishing recommendations for optimal ranges of macronutrient intakes. Randomized clinical trials (RCTs) have been used where possible. Animal and in vitro studies have been included when needed to explain mechanisms of action. Thus, the NNR values are based on the totality of the available evidence (3, 4).

Terminology and definitions

The term 'NNR' refers to a set of dietary reference values (DRVs) for essential nutrients that includes the average requirement (AR), recommended intake (RI), upper intake level (UL), lower intake level (LI), and reference values for energy. All of the values are expressed as daily intakes and recommended intake ranges of macronutrient intakes.

Average requirement (AR)

The *average requirement (AR)* is defined as the lowest long-term intake level of a nutrient that will maintain a defined level of nutritional status in an individual. In the NNR, the *AR* value is used to define the level of a nutrient intake that is sufficient to cover the requirement for half of a defined group of individuals provided that there is a normal distribution of the requirement (Figure 2.2.).

In general, the selected criteria for establishing the *AR* apply to micronutrients and are usually based on data on biochemical markers of

adequate nutritional status. However, the *AR* can also be derived for some macronutrients such as protein and essential fatty acids.

Deficiency of a nutrient would imply that the supply is so small that specific symptoms of disturbances in body functions emerge. During serious, manifest deficiency, overt clinical symptoms or signs such as bleeding of the gums during scurvy or neurological symptoms due to vitamin B_{12} deficiency would arise. Data on biochemical markers can include the activity of certain enzymatic systems in which nutrients have a role as co-factors or concentrations of a nutrient in cells or fluids as a measure of tissue stores. Low activities or concentrations might be associated with deficiency symptoms or impaired function. Moreover, it is possible to define an interval between manifest deficiency and optimal intake level in which clinical symptoms are more diffuse or do not exist at all. This level is sometimes called latently insufficient (Figure 2.1.). Such indicators are available only for a limited number of nutrients, e.g. vitamin D, iron, folate, and vitamin B_{12}.

The definition of *AR* corresponds to the term 'Estimated Average Requirement' (EAR) used in the UK and US recommendations (2, 5). The European Food Safety Authority (EFSA) uses the term 'Average Requirement' (6).

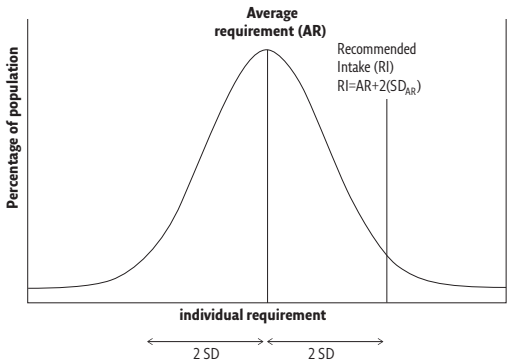


Figure 2.2. Frequency distribution of an individual nutrient requirement. SD = Standard deviation

It is important to distinguish between the average requirement for a nutrient and the recommended intake of a nutrient. The recommended intake represents more than the requirement for the average person and also covers the individual variations in the requirement for the vast majority of the population group (**Figure 2.2**.). Depending on the criteria used for setting the average requirement, the safety margin between the average requirement and recommended intake can vary.

Recommended intake (RI)

The term *recommended intake (RI)* refers to the amount of a nutrient that meets the known requirement and maintains good nutritional status among practically all healthy individuals in a particular life stage or gender group. When the distribution of a requirement among individuals in a group can be assumed to be approximately normally distributed (or symmetrical) and a standard deviation (SD) can be determined, the *RI* can be set as follows (Figure 2.2.):

$$RI = AR + 2(SD_{AR})$$

For other nutrients where data about the variability in requirements are insufficient to calculate an SD_{AR}, an approximate coefficient of variation (CV) of 10%–15% can be used (see Figure 2.2.).

The *RI* corresponds to the amount of a nutrient that is consumed, and this means that losses during handling, preparation, processing, etc. have to be taken into consideration in dietary planning. The *RI* is appropriate for an average intake of a group expressed per day over a longer period of one week or more. The body can adapt and retain some nutrients when the intake is lower than the immediate requirement. The storage capacity for nutrients varies and is highest for the fat-soluble vitamins (several months) while the stores of water-soluble vitamins (with the exception of vitamin B_{12}) are usually lower.

Where sufficient scientific evidence is available on interactions with other dietary factors, these are accounted for. Examples are the enhancing effect of ascorbic acid on non-haem iron absorption and the effect of folate on homocysteine levels in the blood. When establishing the *RI* values, these aspects have been taken into consideration.

High doses of certain vitamins and minerals can have pharmacological effects different from their primary nutritional effects. Generally, this concerns amounts that the target group could not normally obtain from the diet. The effect of high doses of nicotinic acid as a lipid-lowering agent and the effect of fluoride on dental caries can be considered pharmacological rather than nutritional effects. Such effects have not been taken into consideration in the establishment of the *RI*.

The *RI* is intended for healthy individuals and is not necessarily appropriate for those with different needs due to diseases such as infections. In general, the *RI*s are only applicable when the supply of other nutrients and energy is adequate.

The definition of *RI* corresponds to the term 'Recommended Intake' used in the UK and 'Recommended Dietary Allowance' (RDA) used in the US (2). The EFSA uses the term 'Population Reference Intake' (PRI) to denote "the level of nutrient intake that is enough for virtually all healthy people in a group" (6).

Setting RI for micronutrients

In setting recommendations for micronutrients, the NNR use the classical approach with the following steps:

The **first step** includes an evaluation of the average physiological and dietary requirement for the population group in question as judged by criteria that have to be set specifically for every individual nutrient. The establishment of these criteria includes considerations of clinical and biochemical deficiency symptoms, body stores, body pool turnover, and tissue levels. The nutritional requirements are influenced mainly by different biological factors such as age, sex, growth, height, weight, pregnancy, and lactation.

The **second step** includes an estimation of a safety margin to ensure that all individual variations are considered and added to the requirement to obtain a level of recommended intake. The size of this safety margin depends on several factors, among others the variation in the requirements between individuals and potential adverse effects of high intakes. Furthermore, the precision of the estimation of the requirement should be taken into consideration (**Figure 2.2**.).

Upper intake level (UL)

For most nutrients, high intakes might cause adverse effects or even toxic symptoms. The *upper intake level (UL)* is defined as the maximum level of long-term (months or years) daily nutrient intake that is unlikely to pose a risk of adverse health effects in humans. The threshold for any given

adverse effect varies depending on life-stage, sex, and other individual characteristics just as it does for any nutrient requirement. However, there are insufficient human data to establish distributions of thresholds for each adverse effect. The different steps in setting the *UL* include the identification of the critical endpoint, which is the lowest dose at which an adverse effect occurs, and using a surrogate measure for the threshold (Figure 2.3.). The thresholds are the following:

No observed adverse effect level (NOAEL), which is the highest intake of a nutrient with no observed adverse effects;

Lowest adverse effect level (LOAEL), the lowest intake level with an observed adverse effect.

Based on these evaluations, a *UL* is derived by taking into account the scientific uncertainties in the data by dividing the *NOAEL* by an uncertainty factor (UF) (Figure 2.3.). This factor should account for uncertainties in human inter-variability or, in the case of insufficient human data, an extrapolation from animals to humans as well as other uncertainties or deficiencies in the data. The definition of *UL* corresponds to the term 'Tolerable upper intake level' used in the US (2) and by the EFSA (6).

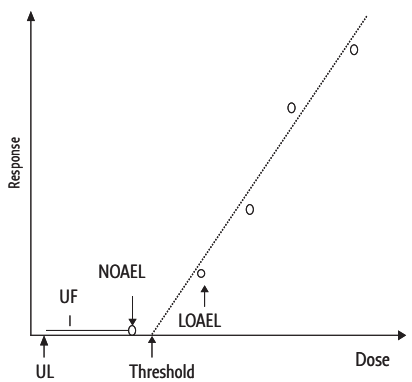


Figure 2.3. Derivation of Upper Intake Level (UL). For explanation see text

Lower intake level (LI)

The *lower intake level (LI)* is defined as a cut-off intake value below which an intake could lead to clinical deficiency symptoms in most individuals. Establishment of an *LI* is thus based on observations of individuals and is in many cases based on criteria other than the average requirement.

The definition of *LI* differs from the term 'Lower reference nutrient intake' (LRNI) used in the UK (5), which is defined as EAR minus 2 SD (5).

The EFSA uses the term 'Lower threshold intake' (LTI) to define the level of intake below which almost all individuals will be unlikely to maintain 'metabolic integrity' according to the criterion chosen for each nutrient (6).

Reference values for energy intake

The term *reference value for energy intake* is used in the NNR and refers to the calculated estimated energy requirement for groups of healthy individuals with normal body size and various levels of physical activity. Setting the *reference value for energy intake* requires a different approach compared to the reference values for vitamins and minerals. For some vitamins and minerals, *RI*s can be given with large margins because the absorption can be limited or the excess broken down or secreted. The *RI*s might, therefore, exceed the defined requirements of the individual on a long-term basis. For energy intake, the situation is different because an energy intake consistently above or below the energy requirement will result in weight gain or weight loss that can adversely affect health. As a consequence and to prevent under- or overconsumption, energy intake should equal energy expenditure. The *reference value for energy intake* is expressed as the average energy requirement for a defined population group with various levels of physical activity (excluding competitive athletes). Thus, the *reference value for energy intake* should be considered as a theoretical value intended to be used as a reference for the entire population group.

Recommended intake range of macronutrients

The term *recommended intake range of macronutrients* is used to emphasise the importance of the distribution of energy between energy-providing nutrients (macronutrients). The current major lifestyle diseases mainly result from over-nutrition and nutritional imbalances rather than from under-nutrition and deficiency symptoms. The intention of setting the recommended intake range of macronutrients is, therefore, to derive a dietary macronutrient composition that will provide an adequate intake of essential nutrients for optimal health and a reduced risk of major lifestyle diseases (Figure 2.1.).

The *recommended intake range of macronutrients* is based on an overall assessment of current knowledge about the impact of macronutrient intake on health and/or risk of disease. This requires various types of scientific data primarily from RCTs, prospective cohort studies, and other epidemiological studies. Where possible, studies providing evidence of a causal relationship and dose-response effects are used. A direct causal

relationship between intake of a single nutritional factor and a specific function or selected criterion, such as reduction of risk of diseases, is not always evident from the scientific data due, for example, to interactions between several energy-providing nutrients. In such cases, effects due to substituting different energy-providing nutrients are taken into consideration under energy-balance conditions (e.g. replacing saturated fat with unsaturated fat or complex carbohydrates). In these cases, the *recommended intake range of macronutrients* is based on an overall assessment of the scientific evidence and includes specific considerations about known patterns of intake of nutrients and foods and the actual composition of available foods in the Nordic countries. On this basis, the *recommended intake range of macronutrients* should be considered as 'optimal' in Nordic conditions.

The recommended intake range of macronutrients refers to appropriate ranges of usual intake in the majority of individuals in the population (7). For planning purposes, a value approximately in the middle of this range can be used as the target.

An upper threshold is used to specify a maximum level of intake for certain macronutrients (i.e. saturated fat and added, refined sugar) below which the intake of all individuals in a group is recommended. Likewise, a lower threshold denotes a certain minimum level of intake (i.e. dietary fibre) above which the intake of all individuals in a group is recommended.

Food-based dietary guidelines

Food-based dietary guidelines are based on an overall assessment of the present knowledge about the impact of food and food groups on health and/or risk of disease. Setting food-based dietary guidelines requires various types of scientific data, especially RCTs, prospective cohort studies, and other epidemiological studies. These guidelines are considered as a translation of nutrient recommendations into foods. They also take into consideration the habitual dietary patterns and scientific evidence of the effects of foods on different health outcomes. A causal relationship between food intake and risk of diseases is not always available from the scientific data. The food-based dietary guidelines are, therefore, based on an overall assessment of the scientific evidence and include specific considerations about known patterns of intake of foods and food groups and the actual composition of available foods in the Nordic countries. On this basis, the food-based dietary guidelines should be considered as 'optimal' in Nordic countries.

Physical activity

Guidelines for physical activity are an integral part of the NNR. Physical activity (and inactivity) influence growth, development, and long-term health and interact with food intake and dietary patterns. The physical activity guidelines generally apply to a physical activity level corresponding to an 'active lifestyle' as further defined in the physical activity chapter.

Methodological considerations

Types of data used and extrapolation

A variety of different types of studies have been used for setting the dietary reference values. For some nutrients (especially micronutrients) the basic *AR*s and *RI*s are derived from data on maintenance of body stores and/or function along with a safety factor. For other nutrients, evidence from experimental and/or observational human studies on the relationship between dietary intake and risk of chronic diseases (8) forms the basis for setting *RI*s (see above and Figure 2.4.). A similar approach is also used for deriving guidelines on breastfeeding and physical activity.

Original data for various life-stage groups have been preferred in deriving values for the NNR (9). Where original data are lacking or due to a lack of sufficient data for some nutrients and some subgroups, extrapolation from one group to another is often necessary. The most common method is to extrapolate values from adults to children using a weight or metabolic factor and adjusting for growth. This approach has also been applied in the current NNR.

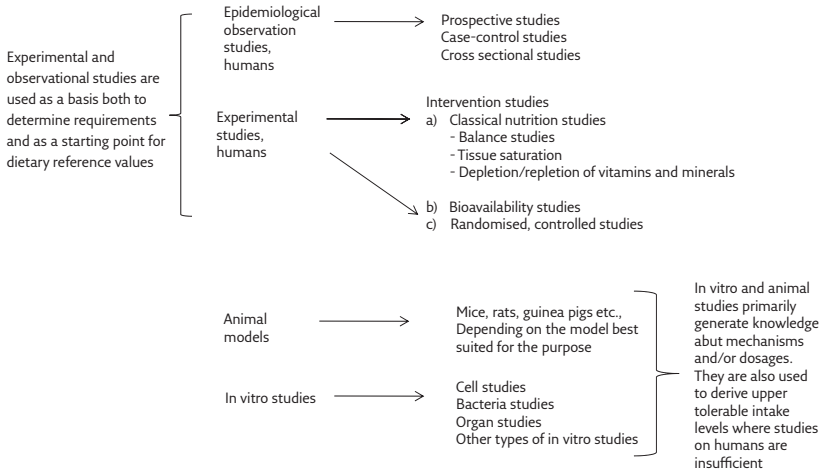


Figure 2.4. Types of studies used as a basis for dietary reference values

Interpretation of nutrition epidemiology studies

In the NNR, evidence from observational studies, mainly prospective cohort studies, is used extensively to assess the relationship between diet and nutrient intake and health. A number of issues influence the quality and interpretation of the results and are related to the complexity of foods and diets, subject characteristics, dietary assessment methods, and the statistical approaches used in analysing the data.

In addition to energy and essential nutrients, foods also contain a large number of other bioactive components that have potentially important effects on metabolic processes and health. The diet, therefore, is an extremely complex matrix of exposures. Some important issues to consider include:

- The co-variation between nutrients could be considerable because single foods might contain many nutrients and other bioactive substances. It can be difficult to isolate the biological effect of a specific nutrient or to examine the independent effect during statistical analysis.
- Socio-economic factors and lifestyle often show co-variation with food habits and it can be difficult to isolate dietary influences from these other factors.
- Characteristics of the individual can influence the examined associations. For instance, genetic factors can modify the effects of nutrients.

In dietary assessments, food records and dietary recalls collect detailed and quantitative, but episodic, information from specific days ("current diet") while diet history interviews and questionnaires collect semi-quantitative information about the overall diet ("usual diet"). Some other important issues to consider include:

- Food choices might vary greatly from one day to the next. Many repeated records (or recalls) or records covering a longer time period might, therefore, be needed when using "current diet" assessment methods to capture the "usual" (habitual, average) nutrient intake of an individual. This varies between nutrients and depends on how often foods rich in the nutrient are eaten and if the nutrient is present in many food items.
- Self-reported dietary data often have skewed distributions in contrast to physiological data, and zero-consumption might be common. As a consequence, it might be impossible in epidemiological studies to examine the health benefit of certain foods or nutrients at certain intake levels because very few individuals are regular consumers.

Obtaining a full picture of dietary habits is a methodological challenge. Different biases or mis-classifications of exposures arising from the methodology itself or from the individual's self-reporting are common in dietary data collection. Some important issues to consider include:

- Personal characteristics such as a desire to please others (social desirability) or dietary concerns might lead the individual to describe their food habits in a way that does not mirror their actual diet.
- Nutrition epidemiological studies usually examine the relative ranking of individuals. So although dietary intake variables are often continuous (e.g. gram, mg), nutrition epidemiological studies do not examine the influence of nutrients at specific intake levels. Instead, studies often use categorical variables (e.g. quintiles) of exposure and simultaneously reduce the influence of extreme or uncertain values.

In summary, the interpretation of results in nutrition epidemiology is often a challenge. The researcher must take several confounders into account including a lack of data about the composition of foods and food practices in the examined populations as well as issues concerning measurement errors in dietary assessment and the statistical handling of dietary data.

Approaches used in evaluating the scientific evidence

This 5th edition of the NNR consists of two approaches:

1. An SR is used for nutrients for which new data of specific importance for setting the NNR are available since the previous 4th edition of the NNR. The SR approach is also applied to nutrition for specific groups (e.g. children, the elderly, pregnant and lactating women), weight maintenance and for food-based dietary guidelines.
2. A less stringent updating of current reference values is applied for the other nutrients and topics not subject to SR.

Systematic review

An SR approach is used to study the available scientific evidence to allow firm conclusions to be drawn and to minimise potential reporting bias through comprehensive and reproducible literature searches. In SRs, clearly defined search strategies are used together with clearly defined and described selections and reporting protocols to provide a comprehensive and distilled evidence document for the decision makers/working group and to enhance the transparency of the decision-making process (10).

The key characteristics of the SR include:

- a clearly stated set of objectives and research questions with predefined eligibility criteria for the studies (including the outcomes of interest)
- an explicit, reproducible methodology
- a systematic search that attempts to identify all studies that would meet the eligibility criteria
- an assessment of the validity of the findings of the included studies through an assessment of the quality of the studies (to minimize risk of bias)
- a systematic presentation and synthesis of the characteristics and findings of the included studies
- a grading of the overall evidence

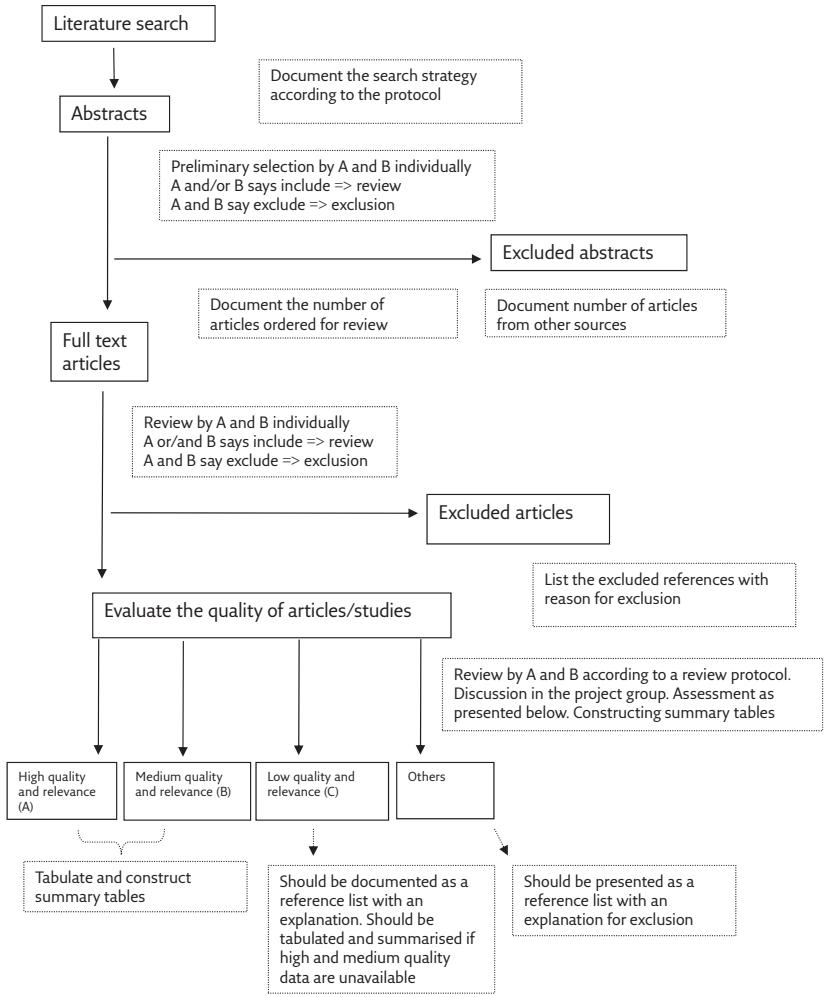


Figure 2.5. Flow chart of the reviewing process in the Systematic Review (SR)

The first step in the SR is identifying and defining the research questions. This is done using a PICO/PECO approach (Population/Participants, Intervention/Exposure, Control, and Outcome). Examples of research questions are shown in Box 2.1. In the next step, the protocol and search strategy is performed, and appointed experts for each nutrient or topic collaborate closely with a methodologist (librarian) who specialises in performing database searches (Figure 2.5.). After the literature search, the first selection is carried out. Abstracts of articles identified in the database searches are screened for potentially relevant articles in a consistent, comprehensive

manner by a minimum of two independent experts according to the eligibility criteria. The abstracts not fulfilling the predefined inclusion criteria are excluded. For the remaining articles, full-text papers are collected and reviewed and the articles excluded from the SR are listed with reasons for exclusion according to predefined eligibility criteria. The methodological quality of the remaining articles is assessed using a three-category grading system (Box 2.2.). Tools for the assessment of the different study categories – clinical trials, prospective cohort studies, retrospective case-control studies, nested case-control studies, cross-sectional studies, and an AMSTAR quality assessment for systematic reviews used by the experts – are included in the SR guide (NNR guide).

After the quality assessment of the individual studies, the studies not fulfilling the quality criteria, such as those that have such a serious bias that the results are not useful for the purpose of deriving NNR, are excluded. A list of the excluded articles, together with reasons for exclusion, is included in the SR. The results from the remaining articles/studies are then tabulated and summarised. In summarising their findings, the experts describe the methods used for their review, including details of data sources, databases searched, and search strategies. Preference is given to data published in peer-reviewed journals, but other sources such as official or expert reports and government-funded research can also be used to obtain valuable information so long as there is a clear indication of the source. Basic statistical information is included in order to indicate the strength of the findings. This information consists of at least the number of cases included in the analysis and the 95% confidence interval. After summarizing the results, the grading of the evidence is conducted according to criteria defined by the World Cancer Research Fund (11) with minor modifications (Box 2.3.). The grading of evidence is based on the analysis of the scientific basis (the study quality, consistency, generalizability, effect size, risk for publication bias, imprecise data, or other aspects such as correlation of dose-response) by the expert group. The strengths and the weaknesses that the summarised evidence for each outcome measure is based on are specified. The grading of the evidence results in one of the following grading categories: 'convincing', 'probable', 'limited –suggestive', and 'limited – no conclusion' (Box 2.3.; Figure 2.5.).

The conclusions of the SR provide an overall summary of the reviewed evidence. Where appropriate, the conclusions also point out principal areas of uncertainty and areas where further research is required.

Box 2.1. Example of two research questions

1. What is the influence of sugar intake on type 2 diabetes, cardiovascular disease and related metabolic risk factors, and all-cause mortality?

2. What is the effect of different *dietary macronutrient compositions* on long-term (≥ 1 y) changes in weight, waist circumference, and body fat in the general adult population?

Box 2.2. Assessing methodological quality of the studies: The three-category quality grading system*

A. The results from studies that have an acceptably low level of bias are considered valid. These studies adhere mostly to the commonly held concepts of high quality including the following: a comprehensive study design; clear description of the participants, setting, interventions, and control group(s); appropriate measurement of outcomes; appropriate statistical and analytical methods and reporting; less than 30% percent dropout (depending on the length of the study, see the QAT for clinical studies) or over 50% participation rate for prospective cohort studies; clear reporting of dropouts; and no obvious bias. Where appropriate, studies must provide a valid estimation of nutrient exposure from dietary assessments and/or biomarkers within a reasonable range of measurement error and justification for approaches to control for confounding in the design and analyses.
B. Studies may have some bias, but not sufficient to invalidate the results. They do not meet all the criteria in category "A" and they have some deficiencies, but these are not likely to cause major bias. The study might be missing information making it difficult to assess limitations and potential problems.
C. Studies have significant bias that might invalidate the results. These studies have serious errors in design, analysis, or reporting and there are large amounts of missing information or discrepancies in reporting.

* Tufts Evidence-based Practice Center. Vitamin D and Calcium: A Systematic Review of Health Outcomes. Boston: Agency for Healthcare Research and Quality US Department of Health and Human Services, 2009.

Box 2.3. Criteria for assigning grade of evidence (modified from WCRF) connected to the three category quality grading system (AHQR)

This box lists the criteria modified from the WCRF cancer report that have been connected to the three-category quality grading system developed by the AHQR. The grades used in the NNR are 'convincing', 'probable', 'limited – suggestive', and 'limited – no conclusion'.

Convincing (High)

These criteria are for evidence strong enough to support a judgement that there is a convincing causal relationship or absence of relationship. A convincing relationship, or absence of relationship, should be robust enough to be highly unlikely to be modified in the foreseeable future even as new evidence accumulates. All of the following criteria are generally required:

- Evidence from more than one study type (RCT, prospective cohort, or nested case-control studies). For some outcomes (e.g. some risk factors) evidence from several RCTs might be sufficient.
- Evidence from at least two independent cohort studies (see above).
- No substantial unexplained heterogeneity within or between study types or in different populations in relation to the presence or absence of an association or the direction of effect.
- Several good quality studies (quality grading category A) with consistent findings to confidently exclude the possibility that the observed association, or absence of association, results from random or systematic error, including confounding, measurement error, or selection bias.
- Presence of a biological gradient ('dose response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical exposures in humans can lead to relevant outcomes.

Probable (Moderate)

These criteria are for evidence strong enough to support a judgement of a probable causal relationship. All of the following criteria are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies. For some outcomes (e.g. some risk factors) evidence from a few RCTs might be sufficient.
- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association or the direction of effect.
- Several good quality studies (quality grading category A and B) with consistent findings to confidently exclude the possibility that the observed association, or absence of association, results from random or systematic error, including confounding, measurement error, or selection bias.
- Evidence for biological plausibility in the case of an observed association.

Limited – suggestive (Low)
These criteria are for evidence that is too limited to permit a probable or convincing causal, or absence of causal, relationship but where there is evidence suggestive of a direction of effect. The evidence might have methodological flaws or be limited in quantity but show a generally consistent direction of effect. All of the following criteria are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity might be present.
- Several studies of at least moderate quality (quality grading category B).
- Evidence for biological plausibility.

Limited – no conclusion (Insufficient)
Evidence is so limited that no firm conclusion can be made. A body of evidence for a particular exposure might be graded 'limited – no conclusion' for a number of reasons. The evidence might be limited by the amount of evidence in terms of the number of studies available, by inconsistency in direction of effect, by poor quality of the studies (for example, lack of adjustment for known confounders), or by any combination of these factors. Most of the studies are in the quality grading category C, or there are two or more high (A) or moderate (B) quality studies with contradicting results.

Other nutrients/topics

Some nutrients or topics have not been subject to an SR. The reason for this is that comprehensive scientific reports were already available; that few major new scientific data were available; or that the nutrient is of little public health concern. The reference values and topics have been updated with a similar approach as was used in the previous NNR and build on the evidence included in the 4th edition from 2004. The review of the literature was concentrated on papers and other reports published after 2000 primarily using PubMed and SweMed+ as a database sources. Studies on Nordic population groups have been included where available. Other important data sources included scientific reports and recommendations published by national and international institutions and expert groups. Additional papers and reports were identified during the work through reference lists. The reference lists in the individual chapters not subject to an SR include major key references used for the establishment of the reference values but do not intend to cover all of the literature that might be relevant to the basic issues of each nutrient or topic.

Derivation of the Nordic Nutrition Recommendations

The framework that has evolved during recent years for the development of dietary reference values is increasingly recognized as being similar to that developed in other fields and is referred to as risk analysis (12). However, when setting DRVs the focus lies more on the assessment of health benefits associated with intakes of nutrients and foods than on the assessment of avoiding risks, although the term 'health benefit' also covers reduced risk of developing chronic disease (13). Thus it is appropriate to use the term 'risk-benefit analysis'. In the development of the NNR, the risk assessment in a risk analysis can be compared to the process of conducting an SR. The next step of the risk analysis, risk management, also plays a role in the development of the NNR. The process of deriving the NNR includes consideration of the evidence for each nutrient or topic as well as possible inter-relations and consequences for the diet as a whole. In addition, classical risk analysis includes consideration of risk communication.

In general, an assessment of the evidence as 'convincing' or 'probable' (Box 2.3.) justifies the use of that evidence as a basis for a recommendation, but evidence judged as 'limited – suggestive' or 'limited – no conclusion' cannot be used. However, rating the quality of the evidence and the strength of the conclusions is, as mentioned above, not the last stage in the evaluation process. The SR and rating of the evidence are used as the basis for deriving the dietary reference values in the NNR. The process of deriving the NNR includes considerations of whole-diet approaches and current dietary practices. This evaluation was performed by the NNR5 working group and was not a part of the SR conducted by the expert groups. The SRs were used as primary and independent components – but not the only components – for the decision-making processes performed by the NNR5 working group that is responsible for developing the recommendations.

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3 Use of Nordic Nutrition Recommendations

The Nordic Nutrition Recommendations (NNR) were established in the 1980s for planning purposes only. Today the NNR comprise a set of Nordic dietary reference values based on the scientifically grounded relationships between nutrient intakes and indications of adequacy, the promotion and maintenance of good health, and the prevention of diet-related lifestyle diseases in the general population. These values have been adapted to the Nordic region.

The NNR were developed in recognition of the growing need for quantitative values for a range of purposes:

- as a tool for assessment of dietary intake
- as guidelines for dietary planning
- as a basis for food and nutrition policies
- as a basis for nutrition information and education
- as guiding values when developing food products

The NNR define the following dietary reference values (DRVs): Average requirement (AR), Recommended Intake (RI), Lower Intake Level (LI), and Upper Intake Level (UL) for micronutrients and Recommended Intake Ranges for macronutrients. An overview of the conceptual framework originally proposed by Beaton (1) is shown in **Figure 3.1.**, and the different approaches available for dietary assessment and planning purposes are described below.

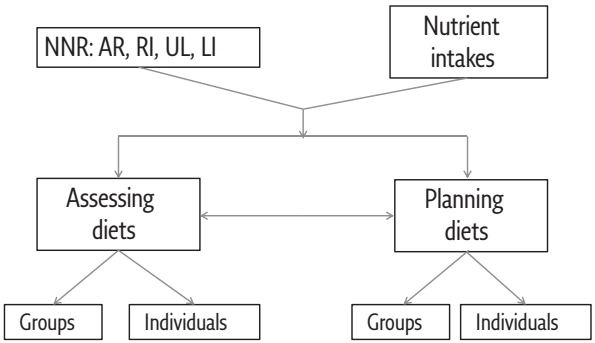


Figure 3.1. Conceptual framework of the use of the Nordic Nutrition Recommendations (NNR) *Adapted from Beaton (1)*

Application of the NNR for assessment and planning purposes

The applications of the NNR for assessment and planning purposes are based on the statistical concept of a distribution curve with an adjacent probability of adequacy or inadequacy as well as excessive intakes. For micronutrients, the application of the NNR makes use of the distribution of nutrient requirement and the distribution of nutrient intake (Figure 3.2.) (2).

The distribution of nutrient requirement reflects the variability in requirements between individuals in a group where a group can be defined in terms of sex, age, and body size. For micronutrients for which requirements are normally distributed, the mean nutrient requirement of the group corresponds to the AR, which means that 50% of the individuals are estimated to have a higher requirement and 50% to have a lower requirement. In such cases, the RI is generally set to the AR + 2 SD and is thus estimated to cover the requirements of 97–98% of the individuals in the group (see Chapter 2 Principles and background).

The AR is a key reference value. When assessing nutrient intakes, nutrient intakes below the AR value are associated with a considerable probability of not meeting the requirement according to the selected criterion. Intakes between AR and RI do not exclude the probability of inadequate intakes.

Figure 3.2. illustrates how the probability approach can be applied to estimate the prevalence of inadequacy when usual intake is compared with the AR. Based on a continuous probability-of-inadequacy scale, the

distribution of the usual intake is used to estimate the probability of inadequacy. Based on such data the following questions can be answered:

1) What proportion of the group has a minimal probability of inadequacy? If minimal probability of inadequacy is defined as a risk of less than 2%, this means that the proportion of the group with a usual intake above the RI has a minimal probability of inadequacy (in Figure 3.2., example A illustrates a situation in which the distribution of intake of 100% of the population is above the RI).

2) What proportion of the group has a relatively high probability of inadequate intake? If a relatively high probability of inadequate intake is defined as a probability above 50%, this means that the proportion of the group with a usual intake below the AR has a relatively high probability of inadequacy (in Figure 3.2., examples B and C illustrate the situation in which 0% or 10%, respectively, of the population is below the AR).

3) What proportion of a group has a very high probability of inadequate intake? If very high probability of inadequate intake is defined as an intake below the LI, this means that the proportion of a group with a very high probability of inadequate intake is the proportion of the group with a usual intake below the LI.

This approach gives a rough estimate of the overall situation. This estimate can be elaborated upon by also looking at the remaining part of the group with intakes between the reference points applied above, for example those between AR and RI. For a detailed description of this approach and its assumptions, see (2).

When the AR is not established and the RI is based on the average observed daily intake level in a defined population group, the RI value is used for both planning and assessment purposes.

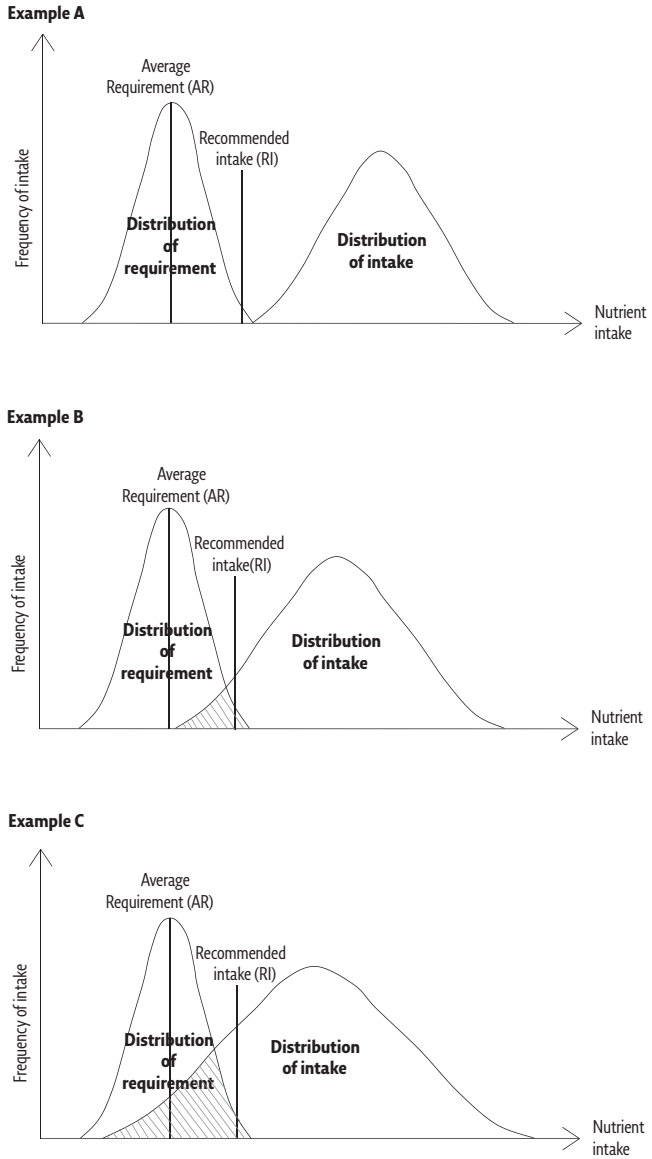


Figure 3.2. Examples of distributions of average requirements (AR) and average usual intakes of micronutrients illustrating different scenarios in assessment and planning of nutrient intakes

The distribution of nutrient intakes reflects the day-to-day variability in the intake of an individual and the variability between individuals within a group. For application purposes, the usual intake of nutrients is an im-

portant concept, and usual intake is defined as the average intake over a longer period of time.

The distribution curve for nutrient intakes depend on the actual intake, dietary assessment methodology, and sample size (3). The dietary assessment methodology chosen depends on the purpose of the survey. Dietary intake data obtained from only a single day (a one-day food record or a single 24-hour recall) will have a relatively wide distribution curve compared with intake obtained over a longer period (Figure 3.3.). Intake data obtained from a single one-day assessment can, therefore, lead to a gross overestimation of the probability of inadequate or excessive intakes. These measurements are not considered suitable for assessment of dietary (in)adequacy unless the intake distribution is adjusted based on the intake of a subgroup of the sample over several days. Several statistical methods are available to obtain "usual intake" distributions from dietary assessment methods looking at one or several days (4, 5). Sample size is another important factor that will influence the reliability of the probability of inadequate or excessive intakes (3). Several other issues should also be addressed before making an assessment of nutrient intakes (Table 3.1.).

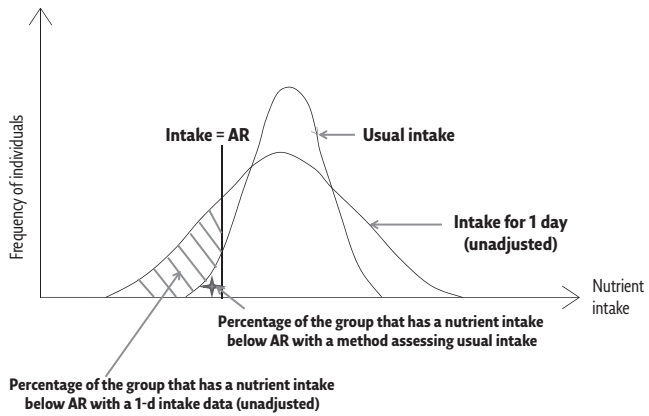


Figure 3.3. The frequency distribution of a nutrient intake by a group assessed with a one-day dietary method and by a method assessing usual intake (including a longer period of time). AR (average requirement)

Table 3.1. Checklist for issues to be addressed before assessment of nutrient intake data

a)	How many days per individual are the nutrient intake data based on? Is the number of days sufficient to reflect "usual intake"? Is the number of days sufficient to estimate the proportion of individuals considered at risk? Is the number of days sufficient for assessment of a specific individual's intake?
b)	Do the intake data include total intake from the diet? Is the dietary record/interview covering all 24 hours of the day? Water, tea, coffee, and other non-energy beverages are often excluded from the calculated intake, but they might be important sources of certain minerals and trace elements.
c)	Is the reported energy intake acceptable? Underreporting of energy intake is common in dietary assessments and implies underreporting of most nutrients (including vitamins and minerals). Check for underreporting in the group as a whole, and in subgroups, before assessment of nutrient intake. This can be done by using published cut-off values for physiologically plausible EI/BMR ratio). If a subgroup shows low intake of a micronutrient, check for underreporting of energy intake in that group. Over reporting of energy intake is less common than underreporting.
d)	Do the data include nutrient supplements? Can information on nutrient supplements be analysed separately? Is the information on nutrient content and dose in supplements specific enough for calculating intake from these sources?
e)	Do the data include fortified foods? Can information on fortified foods be analysed separately? Is the information on nutrient content in foods specific enough for calculating intake from these sources?
f)	Have losses of nutrients during cooking been taken into account in calculation of nutrient intakes? This is particularly important for nutrients such as ascorbic acid and folate, for which substantial losses can occur during cooking/processing.
g)	Is the quality of the food composition database acceptable for all the nutrients calculated? Certain trace elements in particular databases can have missing values even for commonly consumed foods, and this can result in substantial underestimation of calculated intake. Database values for a specific nutrient can also be based on out-dated analytical methods that might provide systematically higher or lower values than the method currently in use.

Dietary assessment

How to assess the nutrient intake of a group

Micronutrients

The goal of assessing nutrient intake of groups is to determine the prevalence of inadequate or excessive nutrient intakes within a pre-defined group of individuals. Assessing nutrient intake of groups is an integral part of dietary monitoring, for example, in national dietary surveys or dietary intervention studies. Before comparing intake data with the DRVs, it is crucial to check whether the intake data reflect the usual nutrient intake and are suitable for an assessment (Table 3.1.).

It is a common misunderstanding that the intake of a group *by definition* is adequate if the average intake of the group is equal to or above the RI. The key to an appropriate assessment of inadequacy at the group level is to think in terms of a continuous probability-of-inadequacy scale where the prevalence of inadequacy increases as intake decreases (illustrated in Figure 3.2.).

The AR is the primary reference value for evaluation of nutrient intakes, and the RI, LI, and UL can be used as complementary values. Assessment of inadequate or excessive nutrient intakes is based on the distribution intakes of individuals in the group with the underlying assumption that nutrient intakes and requirements are not directly correlated (this is true for most nutrients – with the exceptions of a few, such as iron) (Figure 3.2.).

For nutrients with an AR, assessment of nutrient intakes within a group starts with the division of the distribution of the usual intakes into percentiles. Based on these data, the following questions can be answered:

1. What proportion of the group has a minimal probability of inadequacy? – *defined as the proportion of the group that has an intake above the RI.*
2. What proportion of the group has a relatively high probability of inadequate intake? – *defined as the proportion below the AR.*
3. What proportion of the group has a very high probability of inadequate intake? – *defined as the proportion of the group that has an intake below the LI.*
4. What proportion of the group has a high probability of excessive intake? *defined as the proportion of the group that has an intake above the UL.*

For a detailed description of this approach and its assumptions, see IoM (6) and example 1.

Table 3.3. The intake distribution of vitamin C (mg/d) for a group of Danish women 18–75 years old (n = 1785)*

Percentile	1st	5th	10th	25th	50th	75th	90th	95th	99th
Vitamin C intake (mg/d)	24	39	50	69	100	144	190	227	321

* [7].

Example 1: Example of assessing the usual intake of vitamin C.

Table 3.3. shows that about 10% of the group has an intake below 50 mg/d (AR) and about 70% has an intake above 75 mg/d (RI). This means that almost 10% of the group has a relatively high probability of acquiring inadequate amounts of vitamin C from the usual diet (intake below AR, probability of inadequacy >50%). About 70% of the group has a minimal probability of inadequacy (intake above RI). None of the women in the group have an intake above UL (1,000 mg/d). In conclusion, the intake distribution data indicate that approximately 10% of the group has a relatively high probability of inadequacy and that none of the women have an intake below the lower intake level (LI).

If the assessment results in a high prevalence and thus a high probability of inadequate nutrient intake that can only be explained by an implausibly low reported energy intake, the results might indicate that the risk is real. Biochemical measurements of nutritional status, however, are necessary to substantiate whether there is an actual lack of intake of the nutrient in question. The probability approach has recently been successfully applied to a nutrient status biomarker (7), and this can be used as a complementary tool for assessing adequacy or excess.

For nutrients with no AR, the assessment of the group intakes of nutrients is relatively simple and is based on just the mean intake of the group (8). If the mean intake of the group is at or above the RI, there is probably a low prevalence of inadequacy. If the mean intake is below the RI, no firm conclusions can be drawn regarding the prevalence of inadequacy at the group level.

The UL values can be used to estimate the proportion of a group with intakes above the UL and, therefore, at potential risk of adverse health effects from excess nutrient intake.

Energy

In the assessment of energy intake at the group level, the estimated average energy intake is compared with the reference value for energy intake for the specific group in which body size, age, sex, and appropriate levels of physical activity are taken into account. The proportion of the group with intakes above or below the reference value can be assessed. A prerequisite for an appropriate assessment of energy intake at the group level is to ensure that energy intake is accurately assessed, and the approach suggested by Black (9) is useful in this regard.

Assessment of energy intakes over a longer period of time should be supported by measurements of body weight at several points in time because changes in body weight reflect an imbalance in energy intake.

Macronutrients

The main focus in the assessment of macronutrient intake is to determine the energy distribution from protein, fat, fatty acids, sugars and total carbohydrates, and, in the case of dietary fibre, the amount of dietary fibre per day or per MJ. In the assessment of the usual energy contribution from protein, fat, and carbohydrates, the proportion of the group that has a usual energy contribution from these macronutrients within or outside the recommended intake range is estimated. In the assessment of the usual energy contribution from macronutrients with a recommended upper threshold (e.g. saturated fat and added, refined sugar) the proportion of the group that exceeds this threshold is estimated. Likewise, when the energy contribution from macronutrients with a recommended lower threshold (e.g. dietary fibre) is assessed, the proportion of the group that exceeds this level is estimated.

How to assess nutrient intake by individuals

Micronutrients

The goal of dietary assessment of an individual's usual nutrient intake is to assess the probability of inadequacy for an individual. Using the probability approach is conceptually simple; one compares the individual's usual intake of a nutrient to his or her requirement (10).

The probability approach for individuals can be used for nutrients with an AR as illustrated in Figure 3.4., which shows a theoretical example of the usual nutrient intake (I) of 3 individuals and their individual requirement (R). In this example, the nutrient intake of two of the individuals (I1 and I2) is above their individual requirements (R1 and R2) and, therefore, both individuals have a minimal probability of inadequate intake of the particular nutrient. The situation for individual 3, who has a usual nutrient intake (I3) below his/her requirement (R3), is different and no conclusion can be drawn on the probability of inadequate nutrient intake. Taking into consideration that it is extremely difficult to obtain the usual nutrient intake and virtually impossible to know the requirement of an individual, biochemical and other clinical measurements of nutritional status will, therefore, be necessary in the situation of individual 3 to clarify whether there is an actual situation with inadequate intake of the nutrient in question.

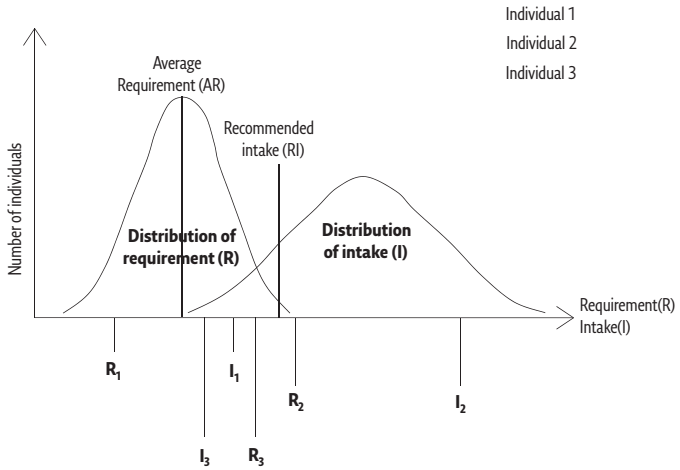


Figure 3.4. The distribution of the nutrient requirement and nutrient intake in a group and highlighting the individual requirement (R) and usual intake (I) of three theoretical individuals 1, 2, and 3. The larger the overlap between the two distributions curves, the higher the risk of inadequacy

Energy

In the assessment of energy intake of an individual, the estimated average usual energy intake is compared with the reference value for energy intake for the individual in which body size, age, sex, and appropriate levels of physical activity are taken into account. A prerequisite for an appropriate assessment of energy intake at the individual level is that energy intake is accurately assessed. Here the approach suggested by Black (9) can be useful. Assessment of energy intakes over a longer period of time should be supported by measurements of body weight at several points of time because changes in body weight will reflect an energy imbalance over a period of time.

Macronutrients

As in the assessment of macronutrient intake at the group level, the main focus in the assessment of macronutrient intake of an individual is the energy distribution from protein, fat, fatty acids, sugars and total carbohydrates, and, in the case of dietary fibre, the amount of dietary fibre per day or per MJ. In the assessment, it is estimated whether the usual intake is within the recommended range for protein, fat and carbohydrates. In the case of macronutrients with a recommended upper threshold (i.e. saturated fat and added, refined sugar) or lower threshold (i.e. dietary

fibre) it can be estimated if the usual intake of the nutrient is above or below the threshold.

Dietary planning

How to plan a diet for a group

Micronutrients

The goal of dietary planning for groups is to compose a varied diet that meets the requirements of most individuals in the group and to obtain an acceptably low prevalence of intakes below the AR (Figure 3.2.) while not exceeding the UL for the particular nutrient. Planning diets for groups includes food planning in the public meal sector, food fortification, and assuring food safety. Dietary planning is not intended for use on a daily basis but as an average over a longer period of preferably at least a week. The nutrient intakes are considered as "net-intake" of nutrients and losses of vitamins and minerals during peeling, cooking, and other handling procedures are subtracted. This is usually the case if the nutrient calculation is based on prepared foods.

For **heterogeneous groups**, the *nutrient density approach* is another approach to planning a diet. Here the goal is to plan a diet with a nutrient intake – expressed per unit of energy (MJ) – that is above the RI for the whole group as illustrated in example A of Figure 3.2. This approach is especially useful for planning a diet for a week or longer for heterogeneous groups with subgroups such as children, women, men, and the elderly because it ensures that the requirement of the "most demanding subject" is met. The recommended nutrient density to be used for planning diets for heterogeneous groups is shown in Chapter 1 (Table 1.4.).

For **homogeneous groups**, it is appropriate in the planning of a whole diet over a longer period of time to use the recommended intake for the relevant age and gender group (Chapter 1, Table 1.3.). The *nutrient density approach* can also be useful for the homogenous groups in question, e.g. men or women in a specific age group. In practice, the planning is done by calculating the planned recommended nutrient intake and expressing it per MJ of energy. For example, for sedentary men between 31 and 60 years old, the RI of vitamin C is 75 mg/d and the reference energy intake 11.0 MJ/d. The recommended density of vitamin C in the diet, therefore, is 6.8 mg/MJ for this group.

The probability approach is another approach to plan a diet. Here the goal is to plan a diet taking into consideration the entire distribution of

usual nutrient intakes within a group (Figure 3.2.). Such planning seeks to achieve a usual intake that meets the requirements of most individuals but at the same time is not excessive. This approach was introduced by the Institute of Medicine as summarized (11). The prerequisite of this method is that the distribution of reported or observed usual intakes of the target group is known. The planning includes a decision on an acceptable prevalence of inadequacy (i.e. prevalence below the AR)(Figure 3.2.) and a decision on a target usual intake distribution positioned within the distribution of usual intakes relative to the AR (12). In other words, how far the distribution of the intake curve is shifted to the right of the distribution of the requirement (Figure 3.2.C). One example is provided in Table 3.4.

Table 3.4. An example of using the probability approach for diet planning for vitamin B_6. Current and target vitamin B_6 intake distribution (mg/d) for Danish women 18–24 years old (n = 150) and the required change (mg/d) to achieve a target intake with a prevalence of inadequacy in the group of 5%

	Current intake* mg/d	Target intake mg/d	Change mg/d
Average	1.3	1.6	+0.3
Percentiles			
1st	0.5	0.8	+0.3
5th	0.7	1.0	+0.3
10th	0.8	1.1	+0.3
25th	1.0	1.3	+0.3
50th	1.2	1.5	-
75th	1.5	1.8	-
90th	1.7	2.0	-
95th	1.9	2.2	-
99th	2.4	2.7	-
Per cent below the AR	25%	5%	-20%
Per cent below the LI	10%	1%	-9%

* (13).

Example 2: Table 3.4. shows the distribution of the current usual intake of vitamin B_6 in a representative sample of Danish women aged 18–24 years (n = 150) as assessed by a seven-day food record (13). The AR of vitamin B_6 in this age group is 1.0 mg/d and the RI is 1.3 mg/d. A Comparison of the average intake with the RI would leave the impression that the current intake level would be adequate at the group level. However, using the probability approach, the distribution of the current intake shows that up to 25% of the women in this group might have a relatively high probability of inadequate intake of vitamin B_6, i.e. their intake is below the AR. If the target (or desirable) intake is set to a level where only up to 5% of the group has a relatively high probability of inadequate intake (below the AR), it is necessary to plan for an increase of the usual intake by 0.3 mg/d. Thus, an increase at this level is added to percentiles with lower usual intake and the shape of the lower part of the distribution curve is moved to the right (Figure 3.2.). The next step in the planning is to identify food sources rich in vitamin B_6 and currently consumed by the target group. Finally, the nutritional effects of this change in vitamin B_6 intake should be assessed by appropriate methods.

NB! This example illustrates that RI values should be used with caution in the planning of diets for groups. The challenge is that reliable usual intake data are needed but are not always available.

Energy

For planning of energy intake at group level, the average energy requirement at group level can be used as the reference value after taking into account normal body size, age, sex, and appropriate level of physical activity.

Macronutrients

The recommended intake range of macronutrients refers to appropriate ranges of usual intake in the majority of individuals in the population. For macronutrients with a recommended intake range, a value approximately in the middle of this range can be used as the population target (see Chapter 2). For macronutrients with an upper threshold (e.g. saturated fat and added, refined sugar) the diet should be planned not to exceed this threshold. For the macronutrients with a lower threshold (e.g. dietary fibre), the diet should be planned to exceed this threshold.

How to plan diets for individuals

The goal of dietary planning for individuals is to compose a varied diet that meets the requirements of the individual and to obtain an acceptably low risk of inadequate intake while not exceeding the UL for the nutrient.

National food-based dietary guidelines (FBDGs) can be used as practical

guidelines for achieving a diet that meets the requirements of the individuals. Because the NNR apply to the apparently healthy population, special guidance should be provided by qualified personnel for those with other nutritional needs.

For energy, the reference values (the average energy requirements) relevant to the individual (see Chapter 1, Tables 1.5. and 1.7.) can be used. If the characteristics of the individual in question differ from those in the tables, more specific energy values can be calculated based on sex, age, body weight, height, and usual physical activity level.

Food and nutrition policy

The NNR constitute an important basis for food and nutrition policy formulation and actions. In particular, the recommended composition of diets with regard to the proportions of fat and fatty acids, carbohydrates, dietary fibre and intake of sodium (NaCl), sugars, protein have been a key element in the setting of added national goals for dietary intake in Western countries, including the Nordic countries, for several decades. Development of the Nordic Action Plan in 2006 and subsequent monitoring and assessment of the action plan has made substantial use of the NNR (14, 15).

Health promotion through improved dietary habits and increased physical activity is now an integral part of nutrition and public health policies, and the NNR serve as an important yardstick in the substantiation of need for changes and actions. The NNR also provide reference values for monitoring dietary intakes, the evaluation of programs, and other food and nutrition policy initiatives.

Food and nutrition policies also include the FBDGs. For example, many countries have guidelines on fruit and vegetable intake (as portions/amounts per day) that are estimated to have potential health benefits in relation to diet-related diseases (16). Developing FBDGs based on scientific data on the relationships between the consumption of food groups and health ensures a varied diet that meets most nutrient requirements of the general population and a balanced intake of the whole spectrum of nutrients, including trace elements and other bioactive compounds. Both nutrient recommendations and FBDGs are relevant in the context discussed above. The FBDGs are particularly useful for planning of the food supply at a national level and for evaluating long-term trends in dietary intake based on national food supply statistics. Data on food supply have been

used extensively for several decades, including in the Nordic countries, in spite of the shortcomings of this type of data.

Two aspects of food and nutrition policy deal specifically with vitamins and minerals, namely the addition of nutrients to foods and use of dietary supplements.

Addition of nutrients to foods

Addition of a nutrient to selected foods can be used in nutrition policy as a means to increase the average intake of a specific nutrient in the general population and, in particular, to increase the intake in the portion of the population with usual intake below the AR without increasing the usual intake above the UL. Iodine is added to salt as a means to increase iodine intake in many parts of the world and is one of the classic examples of nutrient fortification. In the Nordic countries, fortification of selected foods began as early as the 1930s with the most common being fortification of household salt, flour, and margarine.

Before the food and/or health authorities decide to introduce fortification with a given nutrient, the following questions need to be answered:

1. Is there a documented need for increasing the intake of this nutrient in this population group?
2. Is fortification an effective way to increase the intake of the target group?
3. Are there other possibilities for increasing the intake of the target group?
4. Are there any risks of potential adverse effects of the fortification in the target group?
5. How can the effect of the fortification be evaluated?

The NNR DRVs serve several purposes in this context, both in the identification of a situation with inadequate intake and in the planning, implementation, and evaluation of a program. First, when assessing the usual nutrient intake of a group or groups in the general population, DRVs are used for evaluating the adequacy of current usual intake. If the dietary intake data suggest that the intake is inadequate, nutritional status information must also be considered. Second, when planning the amount of nutrients to be added to obtain a relevant increase in the usual nutrient intake in the target group, the DRVs should be used. Data on the distribution of the usual current intake are particularly useful.

Examples of on-going fortification programs introduced during the

2000s in the Nordic countries include the iodine fortification program (17, 18) and the vitamin D fortification program in Finland (19, 20).

Dietary supplements

Dietary supplements are defined as concentrated sources of vitamins and minerals that can supplement a normal diet and can have a nutritional or physiological effect either alone or in combination. In nutrition and public health policy, dietary supplements might be recommended for a specific target group that has a requirement that is too high to be met through a varied diet alone.

There are certain life stages and circumstances in which individuals might be especially vulnerable due to relatively high demands for micronutrients for growth. Thus dietary supplements might be relevant for groups such as infants and young children, pregnant and lactating women, the elderly, or others with *very low* energy intakes.

In the Nordic countries, a varied diet that meets the recommendations on macronutrient content and composition and meets the energy needs will usually contain adequate amounts of most vitamins and minerals. For specific groups, and under certain circumstances, attention should be paid to the possible need for dietary supplementation in connection e.g. food allergies and vegan diets. In general, individuals with a very low energy intake (<6.5 MJ/d) often have problems achieving adequate intakes of all micronutrients from the diet alone and a multivitamin/mineral supplement might be relevant in these cases. Due to food and cultural habits, some immigrant groups are particularly vulnerable to specific deficiencies, such as vitamin D deficiency, and supplements might also be considered in these cases. A number of dietary supplements are used in the treatment of certain diseases, but these aspects are mostly outside the scope of the NNR. In addition, attention should be paid to the fact that numerous common drugs can interfere with the absorption and metabolism of vitamins and minerals.

Nutrition information and education

Dietary information and advice

The NNR are a basis for FBDGs and for information regarding practical advice on diet, meal composition, and food selection. The FBDGs are useful tools for use by professionals (nutritionists, dieticians, nutrition educators, and health care providers) to inform and educate groups and

individuals. They are also useful for individual consumers in their planning of an overall healthy diet.

The formulation and focus of FBDGs vary somewhat between the Nordic countries due to cultural and culinary habits. Common features, however, are an emphasis on ample intake of fruits and vegetables, whole grain cereals, frequent consumption of fish, and choice of soft fats.

The introduction of the Keyhole labelling in Sweden in the late 1980s and in Norway and Denmark during the 2000s and the Finnish Heart Symbol are examples of tools for guiding consumers in making healthy food choices. These were introduced by national food agencies and widely adapted by food producers. The Keyhole concept covers a large number of food product categories using category-specific criteria for certain nutrients and is based primarily on the NNR. A similar labelling tool, the Heart Symbol, is used in Finland.

Education

The NNR is an important basis for the teaching of nutrition and food science. The NNR publication can be used directly as teaching material because it contributes to a basic understanding of how the DRVs for different nutrients and energy are derived and how they should be used in an appropriate way for various purposes. Food composition tables and databases, nutrient calculations programs, and data on dietary habits are relevant as supplementary material in this context.

There are some aspects of the NNR that could be stressed more in all levels of teaching and education. First, a primary emphasis could be placed on dietary composition and dietary sources with a focus on the quality of macronutrients and their possible interactions. Second, it should be stressed that the recommended levels do not have to be met every single day even though they are expressed as amounts per day (e.g. g/d or mg/d). Instead, they refer to an average intake over several days or approximately one week. Some days an individual might obtain more of a certain nutrient, and other days less, depending upon the foods consumed. In teaching, as in nutrition information, the nutrient recommendations should be linked to foods and FBDGs as well as to "real life" eating.

Development of new food products

The recommended intake values and other reference values can be used as guidelines when defining the desirable nutrient content of a food product. Obviously, no single food or meal is expected to contain the recommended intake of all nutrients unless it is a special product such as infant formula or a dietetic product used in clinical nutrition. The nutritional content of a food product can be compared with a dietary reference value and it can also be compared with the recommended energy distribution of macronutrients. Complete meals can be evaluated by comparison with the recommended macronutrient composition of the diet. In the European Union, the regulation specifying nutritional labelling includes a set of specific labelling values for certain vitamins, minerals, and macronutrients that must be used in labelling. These values refer to an adult reference person and are compiled from several sources. They might, therefore, differ somewhat from national recommended intakes such as those given in the NNR.

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4 Breastfeeding

The benefits of breastfeeding are well documented. The WHO recommends that infants are breastfed exclusively for about 6 months and given breast milk as part of the diet throughout the first 2 years and that this is continued as long as it suits the mother and child (1). Exclusively breastfed means that the infant is given no food or liquid other than breast milk but can receive additional vitamins, minerals, and/or medications. Vitamin D supplements are recommended for all infants in the Nordic countries from the first weeks of age. Vegan and vegetarian mothers who are breastfeeding should ensure an adequate intake of vitamin B_{12} in order to avoid risk of deficiency in the infant.

Breast milk gives the new-born essential nutrients in an efficiently absorbed combination (2, 3) and has positive health effects on the infant as well as later in life. In addition to the macronutrients, vitamins, and minerals in breast milk, breast milk also contains immune-related factors and hormonal factors that are important for infant health and growth (4, 5). The contents of human breast milk differ significantly from those of other animal milks such as cow's milk (6, 7). If breastfeeding is not possible or is not chosen, commercial infant formula prepared according to Codex standards is recommended.

The impact of breastfeeding and the level of evidence often vary for different health-related outcomes. Research in this area has been active not least because of the high interest in the programming effect that diet can have on future health. It was, therefore, highly relevant to systematically evaluate the scientific evidence for the NNR 2004 (8) to be able to update the guidelines for the NNR 2012. A systematic literature review (SR) was performed on the scientific data valid in a Nordic setting on the short- and long-term health effects of both exclusive breastfeeding, any breastfeeding and breastfeeding in combination with the introduction of other foods (9). The SR only covered immediate and later health effects in the child. Health effects in the mother and other potential effects, such as on the bonding between mother and child, were not reviewed. Studies where the mother

or child was sick at start or at increased risk for disease were excluded from the SR. Studies involving preterm infants were also excluded, but it is likely that the health effects of breastfeeding are more pronounced in vulnerable infants such as these. In addition, too few studies existed to enable a review of the importance of the product vs. the mode of delivery, e.g. differentiating between breastfeeding and breast milk given in a bottle. The number of studies investigating the health effects of partial breastfeeding for 12 months or longer was also too small for any definitive conclusions to be drawn from the literature. The SR graded the evidence for relevant outcomes as convincing, probable, suggestive, or limited/inconclusive.

There is convincing evidence that breastfeeding protects against the development of overweight and obesity and prevents infections in infancy and early childhood (9). The strength of the evidence was lower for other health outcomes. There is probable evidence that breastfeeding has a role in diminishing cholesterol and blood pressure in adulthood; has beneficial effects on children's IQ and developmental scores; has a protective effect against inflammatory bowel disease (IBD) and celiac disease; and, when comparing any breastfeeding to none, has a protective effect against type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) (9). Evidence that breastfeeding protects against cancer is scarce. There is, however, limited but suggestive evidence for a reduced risk of childhood leukaemia, with the protective effect coming after breastfeeding for longer than 6 months, and possibly of other childhood cancers (9). The evidence is insufficient and no conclusions can be drawn regarding breastfeeding and the risk of atopic diseases, asthma, wheezing, and eczema (9). More information is needed especially with regard to exclusive breastfeeding and allergies because this is the effect for which the results vary the most between studies. There is, however, currently no evidence for an association between decreased risk of allergies and later or earlier introduction of supplementary foods. Longitudinal studies in cohorts of new-born infants could help clarify the relationships described above. A summary of the grading of the evidence for relevant outcomes in the SR is shown in Table 4.1. and discussed further in the following text.

Table 4.1. Grading of evidence for health effects associated with breastfeeding in industrialized countries (9)

Outcome	Evidence grading
Acute otitis media	Convincing evidence (grade 1) that breastfeeding protects against acute otitis media.
Gastrointestinal infection	Convincing evidence (grade 1) that breastfeeding protects against gastrointestinal infections.
Lower respiratory infection	Convincing evidence (grade 1) that breastfeeding protects against respiratory tract infections.
Overweight/obesity	Convincing evidence (grade 1) that longer duration of exclusive breastfeeding or any breastfeeding is associated with a protective effect against overweight and obesity in childhood and adolescence.
	Suggestive evidence (grade 3) that breastfeeding protects against overweight and obesity in adulthood.
General growth	Probable evidence (grade 2) that exclusive breastfeeding for longer than 4 months is associated with slower weight gain during the second half of the first year.
Blood pressure	Probable evidence (grade 2) that breastfeeding has a small but significant reductive effect on blood pressure.
Serum cholesterol	Probable evidence (grade 2) that breastfeeding provides a small reduction in blood cholesterol levels later in life or adulthood.
Type 1 diabetes mellitus (T1DM)	Probable evidence (grade 2) that any breastfeeding has a protective effect against T1DM. The evidence for a stronger protective effect for longer duration of breastfeeding is limited but suggestive (grade 3).
Type 2 diabetes mellitus (T2DM)	Probable evidence (grade 2) that any breastfeeding has a protective effect against T2DM. The evidence for a stronger protective effect for longer duration of breastfeeding is limited but suggestive (grade 3).
IQ, neurological development, visual acuity	Probable evidence (grade 2) that prolonged breastfeeding is beneficial for IQ and developmental scores in children.
Celiac disease	Probable evidence (grade 2) that breastfeeding has a protective effect against celiac disease if gluten is introduced in small amounts while still breastfeeding. It is unclear whether the protection only delays the onset of celiac disease or if it provides permanent protection. The evidence is insufficient (grade 4) to conclude which age is best for the introduction of gluten.
Inflammatory bowel disease (IBD)	Probable evidence (grade 2) that breastfeeding provides protection against IBD.
Cancer	Limited but suggestive evidence (grade 3) for a protective effect of breastfeeding for 6 months against leukaemia and possibly other childhood cancers.
Atopic disease	Limited and inconclusive evidence (grade 4) and no conclusions can be drawn for any preventive effects of breastfeeding on the risk for atopic diseases in children.
Asthma	Limited and inconclusive evidence (grade 4) and no conclusions can be drawn for any preventive effects of breastfeeding on the risk for asthma in children.

Health benefits of breastfeeding

Energy yielding nutrients in human milk have multiple functions, such as providing amino acids in adequate amounts and proportions to support growth and maintenance of muscle tissue in breastfed infants and to facilitate optimal development of important physiological functions in new-borns. Increasing numbers of studies have also indicated long-term beneficial effects of breastfeeding on health.

The positive effects seen for breastfeeding depend to a considerable degree on the breast milk itself and its unique composition. They may also depend on the avoidance of certain other foods given to the infant, on the physical closeness during the act of breastfeeding, or on other associated factors. Interpreting the results of different studies is made difficult because the definition of breastfeeding varies and the methodology used to assess breastfeeding is often unclear. However, numerous nutrients and biologically active substances are found in breast milk, including vitamins, minerals, fatty acids, and immune factors, and many of these have proven positive effects on health. Data from prospective longitudinal infant cohorts in Nordic populations are urgently required because such data are likely to provide the best evidence for any benefits associated with the duration of both exclusive and any breastfeeding. In general, more high quality research, such as randomized controlled trials, is needed in this area.

Breastfeeding and infections

There is convincing evidence that breastfeeding has a protective effect against overall infections, acute otitis media, gastrointestinal infections, and respiratory tract infections (9). Breast milk contains many protective factors that might exert long-term health benefits, and the immunological protection against infections appears to last for some years after cessation of breastfeeding. The magnitude of the effect varies depending on the specific outcome and the exclusiveness of breastfeeding. A protective dose/duration-response effect on gastrointestinal or respiratory tract infections was found in the SRs of Duijits et al and Kramer et al (10, 11) as well as in the prospective studies by Fisk et al and Ladomenou et al (12, 13). In other reports, reduced risks of about 20% for otitis media, 50% for gastroenteritis, and about 30% for lower respiratory tract infections have also been cited (1, 3).

Breastfeeding and growth, overweight, and obesity

There is convincing evidence for a protective effect of breastfeeding, exclusive or any, against overweight and obesity in childhood and adolescence. The evidence is probable that exclusive breastfeeding for longer than 4 months is associated with slower weight gain during the second half of the first year compared with shorter duration. No negative health effects are reported for this slower weight gain, and instead the slower growth in infancy appears to help reduce the risk of overweight or obesity later in life (9). Only a few studies have been performed on the association between breastfeeding and overweight or obesity in adulthood, thus the evidence was evaluated to be only suggestive for a protective effect of breastfeeding (9).

The slower weight gain during the second half of the first year seen in children who are exclusively breastfed for longer than 4 months might partly explain the beneficial long-term effects on body weight development. The discrepancy in growth rates between those breastfed and those not breastfed becomes prominent during the latter half of the first year of life (14, 15). Several physiological mechanisms have been suggested to link early nutrition with later obesity. One hypothesis is the programming of high serum leptin concentrations relative to fat mass through formula feeding and faster growth in infancy (16). Another hypothesis is that obesity is an inflammatory condition and that the interactions between brain growth and development and long chain polyunsaturated fatty acids, pro-inflammatory cytokines, neurotransmitters, and bone morphogenic proteins might explain the relationship between breastfeeding and obesity (17). Better self-regulation of energy intake among breastfed infants (18) might also play a part, and this has been linked to a lower metabolic rate and lower weight gain in breastfed infants compared with formula-fed infants (19, 20).

An often overlooked explanation for the protective effect of breast milk against the development of overweight is the issue of the amount and type of other foods used to replace breast milk. Replacement with other foods might result in high protein intake, and this is convincingly associated with growth rate and higher risk of overweight and obesity as shown by Escribano et al (21) and other investigators and is thoroughly discussed in a SR on protein intake in childhood (22) and in the protein chapter in NNR 2012. Infant formula has previously been much higher in protein than breast milk, but the levels have been decreasing and are now closer to that of breast milk. This change will probably decrease the difference

in protein intake between infants fed breast milk and those fed infant formula (REGULATION EC No 1243/2008 and Directive 2006/141/EC).

Selective reporting or publication bias in this area cannot be totally excluded, and well-performed prospective studies with longer duration of breastfeeding and follow-up data are still needed. Kramer et al (23) found that smaller body size was strongly associated with increased risks of premature weaning and of discontinuing exclusive breastfeeding, especially when the infant was between 2 and 6 months old. In other words, if a child is small the parents are more likely to start giving other foods in addition to or instead of breast milk. This is problematic because it makes it more difficult to study and interpret studies on the associations between infant feeding and growth. In an Icelandic randomized controlled trial, all infants were exclusively breastfed for 4 months and then randomized to either continued exclusive breastfeeding until they reached 6 months of age or continued breastfeeding combined with introduction to complementary foods at 4 months (24). Similar growth rates and body compositions were seen at 6 months in the two groups of infants.

International reports have concluded that breastfeeding might reduce the occurrence of overweight and obesity by about 20% in the general population (1, 3, 25), and the WHO has developed new growth charts that are more relevant than the charts formerly used (26). The new charts are based on breastfed infants and give a better picture of normal growth. This might take the pressure off breastfeeding women to give their babies formula or other foods too early and might also decrease the risk of overfeeding (27).

In a recent update of a Cochrane review, Kramer and Kakuma (11) did not find exclusive breastfeeding for 6 months to have long-term effects on reducing the risk of obesity when compared to exclusive breastfeeding for 3–4 months. However, that review compared infants whose breastfeeding probably differed too little to see a difference, i.e., exclusively breastfed for at least 6 months followed by mixed breastfeeding compared to infants exclusively breastfed for 3–4 months of age followed by mixed breastfeeding until or beyond 6 months. The infant groups compared in the Nordic SR, which serves as the main reference for NNR 2012, usually differed more in the duration of exclusive breastfeeding (9).

Breastfeeding and risk factors for cardiovascular disease

The influence of breastfeeding on the risk of cardiovascular disease is unclear, but there is probable evidence of small but significant effects on

the reduction of blood pressure levels and serum cholesterol levels later in adulthood (9). Breastfeeding has also been associated with lower blood pressure levels in childhood and adolescence (28), but more evidence is needed to support such an association. Even though the physiology behind these effects is still unclear, possible explanations might include a higher intake of n-3 fatty acids by breastfed infants that results in increased elasticity of the blood vessels. Another reason could be lower salt intake by breastfed infants. The lower cholesterol in adulthood found among those who were breastfed in infancy might be the result of the metabolic effects of constituents in breast milk such as cholesterol and n-3 fatty acids.

The macronutrient content of breast milk is relatively stable, but the fat composition varies depending on the mother's diet. For example, the levels of long-chain polyunsaturated fatty acids are highly dependent on the mother's intake of seafood, linoleic and linolenic acids, and dietary supplements (29–31). It is also possible that a high intake of omega-6-fatty acids decreases the synthesis of omega-3-fatty acids (29, 31), and the content in breast milk.

Breastfeeding and diabetes mellitus

There is probable evidence that any breastfeeding is protective against type 1 and type 2 diabetes mellitus. The evidence of a larger protective effect based on the duration of breastfeeding is limited, though suggestive, for type 1 diabetes mellitus (9). This protective effect of breast milk might depend on the different proteins in breast milk compared with infant formula, but other routes of association between diabetes and short duration of breastfeeding or the introduction of food and drinks have been suggested. In a study on a high risk population, Virtanen et al found that the overall or exclusive duration of breastfeeding was not associated with the risk of beta cell autoimmunity (which could be a sign for later development of type 1 diabetes mellitus), but it must be noted that all participants in that study were breastfed to some extent (32). A report from the EFSA in 2009 suggested that introduction of gluten-containing foods between 4 and 6 months while still breastfeeding might decrease the risk for type 1 diabetes mellitus (33). A joint statement by COT/SACN in 2011 found the evidence insufficient for a specific age to introduce complementary food except that such introduction should not occur before the age of at least 3 completed months (34). Both SACN (25) and the WHO (1) state that infants who are not breastfed are at greater risk of type 2 diabetes mellitus.

Breastfeeding and IQ, neurological development and visual acuity

There is probable evidence that breastfeeding has beneficial effects on IQ and developmental scores of children and that the benefits increase with increasing duration of breastfeeding (9). The favourable effect of breastfeeding on the healthy neurological development of the infant might be caused by the high content of docosahexaenic acid (also known as DHA) in breast milk because this fatty acid is present in high amounts in nerve cell membranes. The interpretation of studies on the association between breastfeeding and neurological development is complicated because the outcome is not only influenced by whether the child is breastfed or not or by what children are fed instead of breast milk and the exposure that this gives, but also by the facilitating effects breastfeeding can have on mother-infant bonding. Not all studies have found a beneficial effect of breastfeeding on neurological development, but no study has found detrimental effects or that formula feeding is advantageous in comparison. Several strong cohort studies have shown positive effects of breastfeeding, and the few studies showing no or non-significant effects can be explained by their study design. Thus the evidence is probable that breastfeeding is beneficial for IQ and developmental scores in children and that increased benefits are associated with increased duration.

Oken and co-workers (35) studied developmental milestones at 18 months of age, and children who were breastfed for 2–3, 4–6, or >6 months all showed higher scores for motor developmental milestones and total developmental milestones compared to those breastfed <1 month. Children breastfed >6 months also showed higher scores for social and cognitive developmental milestones in comparison to children breastfed <1 month. A stepwise increase in IQ was found with longer duration of breastfeeding, and the highest IQ points and developmental scores were found with breastfeeding that lasted longer than 6 months (36, 37).

Positive results from the PROBIT study in Belarus that compared control areas to intervention areas in which breastfeeding was promoted also provide quite strong support for positive associations between breastfeeding and neurological development (38). The non-results in another paper from the same group (39) can probably be explained by the fact that this latter paper compared children who were exclusively breastfed for 3 or 6 months from both the intervention and control areas. This likely resulted in smaller differences than when the authors compared the two areas with their large differences in overall breastfeeding patterns. In other studies, Zhou and co-workers found a positive association that was attenuated and no lon-

ger significant after adjustment for socioeconomic characteristics (40), but Oddy and co-workers concluded that although the effect sizes were small breastfeeding for 4 months or longer was associated with improved neurological outcomes in children aged 1 to 3 years after adjustment for multiple confounders (41).

Breastfeeding and celiac disease

There is probable evidence for protection against celiac disease if gluten is introduced in small amounts while still breastfeeding (9). The evidence is insufficient, however, to conclude which age is best for the introduction of gluten (9).

In a systematic review, Akobeng and co-workers found a negative association between breastfeeding and celiac disease. The authors found a 50% lower risk if the child was still breastfed when gluten was introduced, but they stated that it was not clear whether breastfeeding only delays the onset of celiac disease or if it provides permanent protection (42).

Both EFSA (33) and ESPGHAN (43) support introducing gluten-containing foods while still breastfeeding, but not later than 6 months of age or too early (<4 months). In a joint statement, COT/SACN (34) agrees with the introduction of gluten while breastfeeding, but it does not consider the evidence sufficient to support a precise statement about age of introduction of gluten except that introduction should not occur before 3 completed months.

Breastfeeding and inflammatory bowel disease (IBD)

The evidence is probable that breastfeeding provides protection against IBD, but it is insufficient to give exact estimates of the risk reduction (9). Well-performed prospective studies with reliable, well-defined breastfeeding data are needed to enable such estimates. Klement and co-workers (44) included 17 studies in an SR and found breastfeeding to have protective effects against ulcerative colitis, giving about a 45% reduction in risk, and an even greater effect against Crohn's disease with close to a 55% reduction in risk.

Breastfeeding and cancer

There is limited but suggestive evidence that breastfeeding decreases the risk for leukaemia and possibly other childhood cancers (9). The effect on childhood leukaemia seems to be greater with longer breastfeeding duration (>6 months), but the amount of data is too small to rigorously

assess this effect (9). In a systematic review, Ip et al concluded that there is an association between a history of breastfeeding of at least 6 months duration and a reduction in the risk of leukaemia (3). Existing research is insufficient to assess any associations between breastfeeding and cancers in adulthood.

Breastfeeding and atopy and asthma

The evidence regarding infant feeding and development of atopic diseases and asthma is conflicting. Previous advice on allergy prevention has included delayed introduction of food items to the infant's diet. Immunomodulatory qualities of breast milk and avoidance of allergens, or a combination of these and other factors, were thought to prevent conditions such as asthma especially if a family history of atopy was present (45). This recommendation has changed due to lack of evidence.

At present the Swedish Paediatric Society (46) concludes that breastfeeding gives some protection against infection-induced, asthma-type airway symptoms but states that breastfeeding has not been proven to decrease the risk of atopy and allergies, and also that there are no advantage in avoiding allergens, neither during pregnancy or in infancy. The American Association of Pediatrics (47) states, however, that there is evidence that breastfeeding for at least 4 months, compared with feeding formula made with intact cow's milk protein (which can be found in some countries) prevents or delays the occurrence of atopic dermatitis and cow's milk allergy in early childhood.

Certain foods are more allergenic than others (i.e. milk, eggs, fish, nuts, and shellfish), and over the past decade it has been discussed if total elimination or if early introduction of these foods in the diet protects against atopic disease and asthma. Findings of prospective studies on high-risk populations suggest that early age at introduction of new foods is associated with decreased risk of atopic asthma and other allergic diseases (48–50). It is not clear whether this is related to the infant's age per se or to increased chances of introduction occurring while breastfeeding is on-going which have been shown to be protective when it comes to gluten introduction and celiac disease. There are studies in progress trying to elucidate if introduction of small amounts of complementary foods while still breastfeeding is beneficial.

The SR performed for the 5th NNR (9) found the existing scientific evidence limited and contradictive. The studies on the association between breastfeeding and asthma found contradictory results, and the evidence

linking breastfeeding or introduction of solid foods to asthma and wheezing was inconclusive. This makes the evidence limited and no firm conclusions can be drawn (9). Two SRs and meta-analysis studying the effect of exclusive breastfeeding for longer than 3 months on the risk for atopic disease got contradictory results. One study found a protective effect (3). The other study found no significant effect for longer duration of exclusive breastfeeding regardless of heredity but did find that any breastfeeding was protective when compared to no breastfeeding (51). Another SR looked at early introduction of solid food (<4 months of age) and concluded that early solid feeding might increase the risk for eczema but that little data supported an association between early solid feeding and other allergic conditions (52). The prospective studies included in the 5th NNR SR did not change the grading of the evidence.

Longitudinal studies in cohorts of new-born infants could help clarify the relationship between exclusiveness and/or duration of breastfeeding, as well as the introduction of solid foods, and atopic diseases. It is important to include data about whether the infants are introduced to new food when still breastfed. It has also been shown that genes might have modifying effects on the associations between breastfeeding and outcomes such as asthma, and this suggests that genetic aspects should be included in future studies (53). Very little is known about active prevention of allergies and asthma by adding specific food components to the diets of pregnant or lactating women or to the diets of infants. Any positive effect of giving different dietary supplements (n-3 fatty acids, pre- and probiotics, or vitamins) remains to be shown.

Breastfeeding and vitamin D and iron status

It has been questioned if breastfeeding provides sufficient amounts of vitamin D and iron to the breastfed infant. Sun exposure is insufficient to prevent rickets in the Nordic countries, and breast milk does not contain sufficient vitamin D for prevention even if the mother takes vitamin D supplements (54). If not given a vitamin D supplement, there is a rapid decrease in the level of 25-OH vitamin D stored in the infant's body during the first weeks of life to the level usually seen in rickets (55). It has long been known that all infants and young children living at northern latitudes need vitamin D supplements. These should be in the form of drops or as cod liver oil, and 10 µg/d is recommended for new-borns from the first weeks of age as discussed in the chapter on vitamin D in NNR 2012.

A recent randomized trial on exclusive breastfeeding for 4 vs. 6 months has reported on the iron status of the infants at 6 months of age. Ferritin levels were lower in the group exclusively breastfed for 6 months compared with the group exclusively breastfed for 4 months and given other food together with breastfeeding until 6 months, but there were no indications or evidence that the difference was of biological or clinical importance (56). An earlier study found iron status to be negatively affected by exclusive breastfeeding for 9 months (57). Another study, however, found that there is no need to give iron supplementation to infants who are breastfed longer than 6 months (58). It seems apparent that the total diet after the age of 6 months, and the choice and amount of breast milk, cow's milk, or formula, is important (59, 60). A recent study, however, suggests that delayed umbilical cord clamping might be an important and easy way to improve iron status in later infancy (61) without risking the overconsumption of iron that can occur with iron supplementation.

Prevalence of breastfeeding in the Nordic countries

Compared to the rest of the world, all of the Nordic countries have relatively high breastfeeding rates. After birth virtually all mothers breastfeed their infants, and between 58% and 80% of the infants are still breastfed at 6 months (Table 4.2.). In spite of the high breastfeeding rates, a relatively low proportion of infants in the Nordic countries are breastfed as recommended, i.e. exclusively breastfed for around the first 6 months of life and partly breastfed until 12 months of age (9). The rate of exclusive breastfeeding is high the first months, but this decreases quickly to only 23% to 63% of infants being exclusively breastfed at 4 months. The majority of infants in the Nordic countries are introduced to other foods before 6 months of age.

Table 4.2. Reported breastfeeding rates (% exclusive and any breastfeeding) among children born in the Nordic countries

	1 week		1 month		2 months		3 months		4 months		5 months		6 months		9 months	12 months
	Excl	Any	Excl	Any	Excl	Any	Excl	Any	Excl	Any	Excl	Any	Excl	Any	Any	Any
Denmark[1]		95	80						60				12			
Finland[2]			46	87	39	80	34	77	23	68	9	66	0	58	39	34
Iceland[3]	86	98	87	94	80	91	67	86	63	84	35	79	8	74	45	27
Norway[4]			82	95	73	91	63	88	46	85	25	82	9	80	63	46
Sweden[5]	83	97			67	87			51	76			11	63	34	16

1 Children born in 2008 and 2009 in 14 municipalities in Denmark. (62).
2 Children born in 2010 Finland. Health and Welfare report 2012 (63).
3 Children born in 2005–2006 in Iceland, Nationwide randomized cohort (60) and children born in 2004–2008, Directorate General of Health, Iceland (64).
4 Children born in 2006 in Norway. National dietary survey. (65, 66).
5 Children born in 2010 in Sweden. National statistics 2012 (67).

The definition of exclusive breastfeeding that is used in the studies is important to take into consideration when looking at breastfeeding statistics and comparing countries and comparing rates within a country over time.

Breastfeeding rates have been increasing in all of the Nordic countries since the mid-1970s. The prevalence of exclusive breastfeeding at 4 months of age presented in the fourth edition of the NNR (8) was 50% in Denmark compared to the current rate of 60% (62, 68); 15% in Finland compared to the current rate of 23% (63, 69); 46% in Iceland compared to the current rate of 63% (15, 60, 64); and 44% in Norway compared to the rate of 46% in 2006 (65, 66, 70). However, in Finland exclusive breastfeeding at 4 months increased from 10% in 1995 to 15% in 2000 and further to 34% in 2005, but decreased in 2010 to 23%. The rate of any breastfeeding in Finland has, though, consistently increased from 1995 to 2010 (63, 69). In Sweden, a decline in breastfeeding rates, both exclusive and any, has been seen since 2004. The reason behind the decline in exclusive breastfeeding rates in Sweden is, at least in part, due to a change to the more strict definition of exclusive breastfeeding given by the WHO. Rates of any breastfeeding have also declined in Sweden for reasons unknown at this time, but the frequency of breastfeeding in Sweden is still high compared to the rest of the world (67, 71). Considering the

decrease in breastfeeding prevalence seen in Sweden, and the decreasing prevalence of exclusive breastfeeding with infant age seen in the Nordic countries, it is deemed very important to further protect, promote, and support breastfeeding in all of the Nordic countries.

Recommendation for breastfeeding

Exclusive breastfeeding is recommended until the infant is about 6 months old. This is in accordance with the latest recommendation from the World Health Assembly and the WHO and is not changed from the NNR 2004 (8, 72–75). Exclusive breastfeeding means that the child only receives breast milk but, if necessary, can be supplemented with vitamins, minerals, and medications. The WHO recommendation applies to all countries and populations regardless of economic status or developmental level. In the Nordic countries, breastfed infants only need to be supplemented with vitamin D in the form of drops or as cod liver oil. If for some reason breastfeeding is not possible during the first 6 months of life, the infant should be given expressed breast milk, the mother's own or from others, or commercial infant formula formulated according to relevant regulations to serve as the only food for infants. Parents should when required be given guidance on how to prepare and feed formula to their babies. Some infants will need complementary feeding before 6 months of age, but experts agree that solid food should not be introduced before the age of 4 months.

Exclusive breastfeeding for about 6 months is recommended by most official bodies, including the AAP in 2008 and 2012 (47, 76), EFSA in 2009 (33), ESPGHAN in 2008 and 2009 (43, 77), SACN in 2011 (25), and the WHO (73, 74). At the same time, EFSA (33) and ESPGHAN (43) do not find any disadvantages with starting to give complementary foods in addition to breastfeeding in the age range of 4 to 6 months in Europe. But there is also no evidence that giving complementary foods between 4–6 months provides any health benefits beyond those of exclusive breastfeeding for 6 months. From 6 months of age, gradual introduction of a diversified diet is recommended. Breast milk as part of the diet is recommended throughout the child's first year, and partial breastfeeding can be continued for as long as it suits the mother and child.

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5 Food, food patterns and health outcomes – Guidelines for a healthy diet

Guidelines for a healthy diet
The current scientific evidence indicates that a micronutrient-and fibre dense dietary pattern should be adopted in order to promote the future health and wellbeing in Nordic populations.
The dietary pattern should include natural fibre-rich foods such as vegetables (e.g. dark-green leaves, fresh peas and beans, cabbage, onions, root vegetables, and fruiting vegetables), pulses, fruits, berries, nuts, seeds, and whole grains as well as fish and seafood, vegetable oils, vegetable oil-based fat spreads, and low-fat dairy products.
Such dietary patterns, especially if low in energy density and combined with physically active lifestyles, will reduce the risk of weight gain in the population. In contrast, dietary patterns characterized by high intakes of processed meat, red meat, and food products made from refined grains and sifted flour as well as those high in sugar, salt, and saturated and *trans*-fatty acids are associated with adverse health effects and chronic disease.

Introduction

Nutrition research has traditionally strived to identify the specific mechanisms, imbalances, and health impacts of single nutrients, but the 5th edition of the Nordic Nutrition Recommendations (NNR 2012) puts the whole diet in focus. Similar to previous editions, the 5th edition sets dietary reference values (DRVs) for individual nutrients, which are intended as a tool when planning diets for various population groups, assessing dietary intakes in the population, and formulating public health nutrition programs and policies. Most food items, however, contain many nutrients that interact with each other. Therefore, the concept of *food-based dietary guidelines* (FBDGs) was introduced by the FAO. FBDGs are defined as advice expressed at the food level that represents a 'translation' of energy and nutrient intake recommendations into foods and is aimed at the general population or specific population groups (1).

Non-communicable diseases are not simply caused by single nutrient imbalances, but are diseases with multifaceted aetiologies (2, 3). The search

for preventive measures against chronic disease, therefore, needs to take a broad approach. Over the past 15 to 20 years, a large number of observational studies and experimental trials have recognized the complexity of the diet and thus have focused on the impact of whole diets and of patterns of food consumption when examining diet-disease associations. Such an approach has resulted in a significant amount of new and original data.

The dietary habits in the Nordic countries have several common features, and food consumption trends tend to be similar. Some characteristics of these diets are an ample supply of milk and dairy products, moderate to high consumption of meat, and moderate consumption of vegetables and fruit. Consumption of fish is moderate to high overall, but lower in Denmark. Potatoes and cereal products are also consumed in moderate to high amounts. Cultural and culinary traditions differ, however, in terms of meal patterns, food choices, and traditional dishes and each Nordic country has developed and formulated national FBDGs.

Reports with a focus on the impact of food consumption on health that are relevant for Nordic countries include the extensive and systematic reviews (SRs) of the World Cancer Research Foundation/American Institute of Cancer Research WCRF/AICR (4, 5), the Norwegian comprehensive review of dietary guidelines for health (6), Danish reports on the consumption of fruits and vegetables, whole grains, and milk (7–9), a report on meat consumption from the Nordic council of Ministers (10), and the new Danish Dietary Guidelines (11). In addition, several systematic reviews (SRs) were undertaken to provide information on the health impact of food groups and food patterns in preparation for the 5th edition of the NNR (12–15).

Food sources of nutrients and other bioactive substances

Most foods contain a broad range of nutrients, with some exceptions such as refined sugar and household salt, and the distribution of nutrients differs across foods and food groups. Foods also contain a multitude of bioactive constituents other than nutrients that can affect the bioavailability, uptake, and metabolic response of nutrients. Diets are planned with the aim of promoting and maintaining optimal body function. A variety of common foods should be used in order to ensure that essential nutrients are provided as well as other food components for which human requirements have been less well defined. The descriptions of major food groups and their nutrient contributions given below are largely based on information provided in the Norwegian report of dietary guidelines for health (6).

Vegetables, fruits, and berries usually contain plenty of dietary fibre; vitamins such as ascorbic acid (vitamin C), carotenoids (pre-vitamin A), folate, tocopherol (vitamin E), and vitamin K; and minerals such as potassium and magnesium. Beans and peas are good sources of protein, minerals (iron, zinc, magnesium, and potassium), B-vitamins (except B_{12}), fibre, and starch. Nuts and seeds contain significant amounts of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) as well as protein, magnesium, zinc, copper, potassium, vitamin E, vitamin B_6, niacin, and several antioxidants. Although the energy density of many plant foods is low, others such as nuts and seeds, olives, root vegetables, legumes, and cereals are comparatively energy dense. The nutrient concentration per weight unit might be comparatively low when the water content of vegetables, fruits, or berries is high.

Potatoes are comparatively rich in carbohydrates (starch), several minerals (such as potassium and magnesium), and vitamins such as vitamin C. Potatoes have traditionally been important sources of vitamin C and protein, but today fruits and vegetables are the most important sources of vitamin C and animal products provide most of our protein.

Whole grain is defined as intact grain (or cereal), and in processed whole grains the fractions of endosperm, bran, and germ are present in the same proportions as in the intact grain. Cereals are good sources of carbohydrates, such as the starch concentrated in the endosperm, and, therefore, are major sources of dietary energy. Whole grains also provide fibre, resistant starch, minerals (iron, zinc, phosphorous, and magnesium), vitamins (vitamin E, thiamine, riboflavin, niacin, and vitamin B_6), and phytochemicals (see below). Phytic acid in cereals can reduce the absorption of both iron and zinc. Prolonged fermentation of bread (e.g. sourdough) and germination of seeds can reduce this negative effect of phytic acid, and vitamin C (ascorbic acid) enhances the absorption of iron from plant foods.

Cereals are processed and manufactured into a variety of products including many different types of flour, breads, and pasta and in mixed and complex products such as breakfast cereals, baked goods and bread. Because micronutrients and other bioactive compounds are mostly found in the germ and bran fractions, refined cereal products (made from sifted flour) generally have lower nutrient content and also often contain higher amounts of added sugar, fat, and salt (see below).

All plant foods (including vegetables, beans and peas, root vegetables, fruits, berries, nuts and seeds, and whole grains) naturally contain a wide variety of phytochemicals such as polyphenols, salicylates, phytosterols, saponines, glucosinolates, monoterpenes, phytoeostrogens, sulphides, terpenes, and lectins. Most of these have important functions in the plant cells and can also influence biological functions in the human body via a wide variety of mechanisms. Many are antioxidants with the potential to reduce oxidative stress, and others can influence signalling systems, cell cycles, repair systems, and inflammation reactions. The currently estimated number of bioactive phytochemicals is around 100,000 (6) and a single plant-based meal might provide around 25,000 different phytochemicals – albeit with comparatively small amounts of each. The observed health effects associated with vegetable, fruit, berry, and whole grain consumption can likely be explained by the combined action of many different phytochemicals and other nutrients.

Vegetable oils, margarine, vegetable oil-based fat spreads, and butter are used in cooking and with bread and by the food industry to produce foods such as mayonnaise, dressings, baked goods, and soups. Vegetable oils are manufactured by pressing oil from seeds or plants such as rapeseeds, sunflower seeds, flaxseeds, soya beans, olives, maize kernels, palm fruit, and coconuts. Margarine and fat spreads are mixtures of different vegetable oils and fats, and butter is made from the fat of cow's milk. Vegetable oils, vegetable oil-based fat spreads, and butter contain fat, and thus dietary energy, and fat-soluble vitamins such as vitamins A, D, E, and K. Vegetable oils and vegetable oil-based fat spreads also contain essential fatty acids. Vitamins A and D are usually added (regulated by legislation) to vegetable oil-based fat spreads. Vegetable oils contain 100% fat, but margarines and spreads contain varying amounts of fat. The fatty acids composition can vary considerably depending on the fat source used in manufacturing. Soybean, maize, and sunflower seed oils are rich in PUFA, and rapeseed oil and especially olive oil are rich in MUFA. Rapeseed and soybean oils have comparatively high content of omega-3 fatty acids. Vegetable oils and fats from marine sources, e.g. fish oils, contain more unsaturated fatty acids than fat from land-living animals, e.g. lard and tallow. However, palm and coconut oils have high contents of saturated fatty acids (SFA). Fish oils are generally rich in very long omega-3 PUFA. Butter and fat from ruminants (e.g. tallow) tend to have high contents of SFA and contain cholesterol. Butter and ruminant fat naturally contain 3% to 5% trans-fatty acids (TFA).

In the Nordic countries, the TFA content of margarines and vegetable oil-based fat spreads has decreased considerably during the last decades (to less than 1%) due to changes in raw materials and processing methods.

Fish and seafood contain 20%–35% protein. Lean fish such as cod, haddock, saithe, plaice, and pike contain less than 2 g of fat per 100 g, medium-fat fish such as winter-mackerel, halibut, catfish, and tuna contain 2–8 g of fat per 100 g, and fatty fish such as herring, summer-mackerel, trout, salmon, and eel contain more than 8 g of fat per 100 g. Medium-fat and fatty fish are the major dietary sources of the marine omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Fish also contain MUFA and SFA including odd-chain fatty acids (e.g. C15:0 and C17:0) (17, 18). Fatty fish are a major source of dietary vitamin D, and some lean fresh-water fish (e.g. pike-perch) also contain high amounts of vitamin D (19, 20). Fatty fish, and especially cod liver, contain high amounts of vitamin A (retinol). Fish and seafood are also good sources of vitamin B_{12}, iodine, and selenium. However, the nutrient content might vary between wild fish and farmed fish depending on the feed.

Fish and seafood can contain environmental toxins. In general, fish captured in the open sea have lower concentrations of pollutants than fish from the Baltic Sea or Norwegian fjords. Some marine fish (e.g. large tuna and halibut) and freshwater fish from certain areas might contain elevated levels of methyl mercury. Lean fish generally contain low levels of persistent organic pollutants (POPs). As a consequence the national food agencies of the Nordic countries have issued specific advice on fish consumption for specific population groups (i.e. children and women of fertile age).

Milk from ruminants is both a food in itself and a raw material for different dairy products such as cheese, butter, fermented milk, yoghurt, and cream. Milk and milk products are good sources of protein, fat, vitamin A, riboflavin, vitamin B_{12}, calcium, and iodine. Fat-soluble vitamins are often added to skim and low-fat milk. Two thirds of the fat in whole milk consists of SFA, and the major unsaturated fatty acid is oleic acid (C18:1). Milk also contains short-chain fatty acids and the odd-chain fatty acids C15:0 and C17:0 (21). The fat content varies from 0.1 g to around 4 g per 100 g, the protein content is about 3.0–3.5 g per 100 g, and the carbohydrate content (lactose) is about 4–5 g per 100 g. Whole milk and low-fat milk contain about the same amounts of calcium (120 mg per 100 g) and have the same proportions of fatty acids. Cheese has a high content of cal-

cium (750–940 mg per 100 g). Although milk products are generally good mineral sources, they usually contain very little iron (exceptions are whey products). Currently, several plant-based "milks" (e.g. those based on soy or rice) enriched with calcium, vitamin B_{12}, and vitamin D are available.

Eggs are high in protein, fat, riboflavin, vitamin A, and vitamin D relative to their energy content. The egg yolk contributes together with dairy products, meat, and fish to the dietary intake of cholesterol.

Meat from beef, pork, mutton, and game (e.g. reindeer and moose) is generally defined as "red" meat, and meat from chicken and turkey is defined as "white" meat. The term "processed meat" is defined by the WCRF/AICR as meats (usually red meats) preserved by smoking, curing, or salting or by the addition of preservatives (e.g. nitrites). Examples of such processed meats are ham, bacon, salami, different kinds of sausages, and smoked meat. Meat that is boiled, fried, dried, fermented, or frozen is usually not categorized as processed (4).

Meat and meat products contain 20%–35% protein and are usually good sources of vitamin B_6, vitamin B_{12}, iron, zinc, and selenium. The content of energy, fat, fatty acids, and salt can vary considerably between different types of meat. Fat content can vary from less than 1% to more than 40%. Also, the types of fatty acids vary between different animals depending both on species and feed; the typical proportion of SFA is 30% in chicken, 35%–40% in pork, and 40%–55% in beef and mutton. The level of TFA is less than 1% in chicken and pork, but 3%–5% in the meat of ruminants such as beef and mutton. The salt content is low in raw, unprocessed meat, but can be much higher in processed meat. Game meat usually has a lower fat content.

Alcohol (ethanol) is a toxic substance that is rapidly absorbed and distributed in the body and can influence all organs. Since the weight of alcohol is lighter than water (i.e., 1 litre of water equals 1000 grams, but 1 litre alcohol weighs 789 grams), the alcohol content of beverages is expressed in volume per cent (vol%). Alcoholic beverages have varied alcohol contents that range from 2–10vol% for beer to 10–15 vol% for wine to 30–60 vol% for liquor. In addition, alcoholic beverages can contain a wide variety of phytochemicals.

Non-alcoholic beverages

Coffee and tea contain stimulants such as caffeine but no macronutrients and, therefore, no energy. Pure juice made from fruits and berries is comparatively high in natural sugars (fructose) and contains most of the nutrients found in raw fruits and berries. Such juices, however, lack dietary fibre.

Breast milk

Breast milk provides infants with all nutrients, except vitamin D, in a combination that is efficiently absorbed. Breast milk also contains immune-related factors and hormonal factors that are important for infant health and growth. If breastfeeding is not possible or is not chosen, commercial infant formula prepared according to Codex standards is recommended (22). (For influences on health please see the chapter on breastfeeding).

Dietary supplements

Dietary supplements providing vitamins, minerals, protein, fatty acids, or non-essential nutritional factors derived from food can be purchased in all Nordic countries. These often include nutrients at doses similar to the recommended intake (RI), or even higher doses. A high intake of one nutrient, however, might disturb the bioavailability of other nutrients or be associated with other complications. Modern preparations of fish oil and fish liver oil are cleansed of high doses of vitamin A and pollutants. In Norway and Iceland, fish oil is classified as a food, not a supplement, and is a recommended source of the marine omega-3-fatty acids EPA and DHA and of vitamin D. It is not uncommon in the Nordic countries to advise the use of specific supplements at specific periods in life such as during pregnancy or for the frail elderly.

Characteristics of dietary patterns

Westernized dietary patterns (DP) are typically dense in energy and are characterized by high intakes of fat and SFA and processed and red meats. There is also a greater use of food products manufactured from refined cereals (sifted flour) and with added refined sugars, fat, and salt such as soft drinks, candy bars, desserts, sweet bakery goods, some highly sugared breakfast cereals and milk-products, deep-fried potatoes, savoury snacks, etc. In such products, the salt, fat, and sugar content is often disproportionate to the natural content of essential vitamins and minerals and to other

bioactive substances important for health. Especially substances found in plant foods that are naturally rich in fibre tend to be low in Westernized DP.

In contrast, the traditional diet of the Mediterranean region typically includes plant foods in abundance, fresh fruit, olive oil as the principal source of fat, pulses, cheese, yoghurt, fish, poultry, and wine consumed in low to moderate amounts. Such diets also include only small amounts of red meat. Data-driven food pattern studies have identified "prudent dietary patterns" (23, 24) that typically include plenty of plant foods and have characteristics similar to the Mediterranean-like diets. Biomarker studies have demonstrated that Westernized DP are associated with lower concentrations of micronutrients than the prudent patterns (25, 26).

The traditional diets of Nordic countries have lately been advocated as healthy alternatives to the Mediterranean-like diets (27, 28). Foods common across Nordic countries include whole-grain rye, oats, and barley, berries, fruits such as apples, pears, and plums, root vegetables, cabbages, onions, peas, beans, fish (e.g. herring), boiled potatoes, and dairy products and the use of rapeseed oil (29, 30). Although traditional Mediterranean and healthy Nordic diets exist in many varieties, both include large amounts of unrefined plant foods and are dense in micronutrients.

Most individuals today depend on food products supplied by the food industry, which over time has evolved into a complex global food production system. Food products are largely safe, tasty, nutritious, diverse, convenient, inexpensive, and readily accessible (31), but the identification of so-called unhealthy commodities (e.g. sugar-sweetened beverages) as major culprits in the worldwide spread of non-communicable diseases is of increasing concern (32). The imbalance of essential micronutrients in these foods is also a concern along with the potentially adverse health effects of other substances found in these foods. For instance, the health effects of TFA in processed foods have been recognized and documented over the last 10 to 15 years. In response, the food industry in the Nordic countries has changed raw materials and processing methods, and this has resulted in very low concentrations of TFA (close to zero) in most food products (33–38). Substances that still could be a concern are those added during the manufacturing process (e.g. nitrites in processed meat) or those formed during prolonged treatment at very high temperatures (e.g. deep-frying) such as heterocyclic amines, acryl amide, and advanced glycation/lipidoxidation end products.

Interestingly, studies within the EPIC (European Prospective Investigation into Cancer and Nutrition) cohorts report that the use of moderately

processed and non-processed foods is lower in Northern and Central European study centres compared to Mediterranean EPIC centres (39, 40). In these studies, the mean food intakes (from 24 hour recall data) were computed according to their degree of food processing (highly, moderately, or non-processed foods) using a specifically designed classification system (39). These studies also examined a biomarker of food processing (40).

The health impact of specific food groups

Because of the complexity of the diet, a search for the health effect of single nutrients might be misleading (41–43), and, therefore, an increasing number of studies are examining the link between food consumption (rather than nutrient intakes) and health outcomes. This section summarizes conclusions from comprehensive literature reviews regarding associations between food group intakes and the risk of major chronic diseases – including cardiovascular disease (CVD), type-2 diabetes, and cancer – and weight gain.

Vegetables, fruits, berries, and nuts

Prospective studies consistently conclude that high vegetable, fruit, and berry intakes are associated with reduced risk of CVD and lower levels of risk markers of CVD (6, 7). The comprehensive review by Mente et al (44). concluded that higher intake of vegetables and nuts was associated with strong evidence for protection against coronary heart disease (CHD) and myocardial infarction (MI) (44). Although the scientific evidence regarding different cancer types is less clear, the WCRF/AICR concludes that vegetables, fruits, and berries probably protect against most cancers in the gastric system and against lung cancer (4). Very few studies have examined the specific health influence of potato consumption (15). For instance, the evidence linking potato consumption to weight change is limited (13).

Whole grain

Prospective cohort studies indicate significant inverse associations between whole grain intakes and total risk of CVD, CHD, and stroke (6, 8). Prospective cohort studies also indicate protective associations between whole grain intakes and the risk of weight gain or obesity (13), and several larger cohort studies show convincing, protective associations between intake of whole-grain products and type-2 diabetes (6, 8).

The WCRF/AICR report of 2007 and the update report of 2011 (4, 5) both conclude that there is convincing evidence for a protective effect

of dietary fibre from plant foods on colorectal cancer risk. So far there is insufficient evidence for a direct link between whole grains and cancer.

Fish

Many reports indicate that there is convincing evidence for health benefits of replacing dietary SFA with unsaturated fat and PUFA from fish, nuts, seeds, vegetable oils, and vegetable oil-based fat spreads (6, 11). Several prospective cohort studies examining the direct health impact of fish consumption have concluded that fish reduce the risk of cardiovascular mortality, especially of MI and stroke (6, 11). The evidence seems clearer for secondary rather than for primary prevention (8, 45). A multicentre European randomized trial of young overweight adults found that fatty fish consumption was associated with reduced blood pressure (46) as well as improved insulin sensitivity (47). There is also possible evidence that fish consumption is related to reduced risks for type-2 diabetes, impaired cognitive function, and age-related macular degeneration (6).

A recent SR and meta-analysis of 21 cohort studies concluded that dietary marine n-3 PUFA was associated with reduced breast cancer risk (48). The WCRF/AICR concludes that there is limited-suggestive evidence that fish and foods containing vitamin D protect against colorectal cancer (4).

Milk

There is no convincing evidence that consumption of milk or dairy products is related to increased risk of CVD (6, 9, 15) }. Some reports indicate that milk consumption is related to a reduced risk of metabolic syndrome, type-2 diabetes, hypertension, and stroke (6, 9). However, a meta-analysis of long-term randomised controlled trials (RCTs) indicates that there is no beneficial effect on body weight and body fat loss by increasing dairy consumption without concomitant energy restriction (49).

The WCRF/AICR report (4) and the update report (5) concluded that milk consumption and high calcium intake probably reduce the risk of colorectal cancer. However, the 2007 report concluded that the consumption of diets high in calcium probably increases the risk for prostate cancer, while the evidence is weaker (limited-suggestive) for an association between milk and dairy products and increased risk of prostate cancer. No conclusion can be made on the link between milk and breast cancer. There is limited-suggestive evidence linking butter consumption to increased lung cancer risk.

Although nutrients important for bone health come from many foods,

there is probable evidence for an increased risk of osteoporosis with insufficient intakes of calcium and vitamin D, high alcohol intakes, low levels of physical activity, and low BMI (6, 11, 50).

Meat

Population studies consistently report that high consumption of processed meat is associated with an increased risk of type II diabetes and CHD (51–53). Similar but weaker associations were observed in a meta-analysis of red meat consumption (53). Replacing processed and red meat with vegetarian alternatives such as pulses or with fish and poultry was associated with a reduced risk.

The WCRF/AICR report of 2007 and the update report of 2011 (4, 5) both concluded that there is convincing evidence that high consumption of processed meat and red meat increases the risk of colorectal cancer. There is limited-suggestive evidence that foods containing animal fats are associated with increased colorectal cancer risk (4). There is also limited-suggestive evidence that processed and red meats are linked to other cancers (e.g. lung cancer). As a consequence, the WCRF has recommended that the consumption of processed meats should be reduced considerably, or avoided altogether, and that the consumption of red meat should be limited to an average intake of 500 g/week. A recent Nordic study examined the consequences on micro- and macronutrient intakes associated with reduction in processed and red meat according to the WCRF/AICR guidelines (10). That study concluded that the average consumption of red meat in the Nordic countries is currently at the comparatively low level recommended by the WCRF. However, in order to fulfil the WCRF recommendation for processed meat, a considerable reduction would be needed. The conclusion from the Nordic study was that a reduction of meat consumption would not have a detrimental impact on essential nutrient intakes in Nordic populations (10).

Alcohol

Light to moderate alcohol consumption has been associated with reduced risk of CVD and all-cause mortality in middle-aged and older subjects, whereas alcohol consumption among young adults is detrimental. High alcohol consumption is associated with increased risk of hypertension and stroke (11). High alcohol consumption is also convincingly associated with increased risks of several cancers such as those of the mouth, pharynx, larynx, and oesophagus (4). In women, there is convincing evidence for

an association between high alcohol consumption and increased breast cancer risk and probable evidence for increased colorectal cancer risk. In men, alcohol consumption is convincingly linked to increased colorectal cancer risk (4).

Sugar-sweetened beverages

A recent SR and meta-analysis of 30 RCT and 38 prospective cohort studies concluded that intake of free sugars and sugar-sweetened beverages (SSB) is a determinant of body weight in individuals with selfselected diets and that this effect is likely mediated via energy intake (54). Another SR and meta-analysis of 24 controlled intervention studies concluded that low to moderate doses (i.e. ≤ 100 g per day) of iso-caloric fructose in exchange for carbohydrates had no effect on cholesterol levels, but at high doses (> 100 g per day) blood levels of total and LDL cholesterol were significantly increased (55). In addition, a meta-analysis of eight prospective cohort studies concluded that high consumption of SSB was associated with increased risk of type 2 diabetes (56).

Energy density of food

There is limited-suggestive evidence linking total fat intake per se to increased risk of postmenopausal breast cancer and lung cancer (4). However, high fat intake as well as refined carbohydrates and sugars contribute to higher energy density. The WCRF/AICR report points out that because obesity and excessive body fat are major risk enhancers of many cancer types (including breast cancer), the low energy density of plant foods will likely have an indirect protective effect (4).

Three systematic reviews for the 5th edition of the NNR

Three SRs using the guidelines specifically prepared for the revision of the NNR (NNR5 working group (57)) were conducted and provided information on the health impacts of certain food choices relevant for the Nordic situation and health outcomes (12, 13, 15).

Five food groups

The SR of Nordic foods examined papers published from 2000 to 2010 to evaluate the scientific basis of dietary guidelines in relation to five food groups: potatoes, berries, whole grains, milk and dairy products, and red and processed meat (15). Out of the eligible abstracts, a total of 86 pub-

lished papers were extracted and quality graded and 64 papers were of sufficient quality for evidence grading. There was insufficient evidence to draw any conclusions regarding the health impact of potatoes and berries. Very few studies had examined the health impact of potatoes, especially boiled potatoes. Most of the identified studies of berries were conducted in North America and did not examine the types of berries consumed in Nordic countries. Also, there were still too few studies to draw a conclusion regarding red meat and processed meat intake and CVD risk. The end-point diversity in the reviewed studies contributed to the conclusion of insufficient evidence.

The review concluded that there was probable evidence (with a moderate evidence grade) for whole grains to be associated with protection against type-2 diabetes and against CVD, but only limited evidence for whole grains to protect against colorectal cancer. There was limited-suggestive evidence for total dairy consumption to be associated with decreased risk of type-2 diabetes. In contrast, there was suggestive evidence (with a low evidence grade) for total dairy consumption to be associated with increased risk of prostate cancer.

The papers identified regarding the association between red and processed meat and colorectal cancer were all reviewed in the WCRF/AICR report (4) and the update report in 2011(5). In line with these very detailed SRs, the NNR SR concluded that a high consumption of red and processed meat is a convincing cause of colorectal cancer. Because meat consumption is an important contributor to iron intake in Nordic populations, there is a concern that certain population groups might be at higher risk of iron deficiency if meat is not replaced by plant foods with sufficient mineral content (e.g. pulses/legumes). The NNR SR search identified only one relevant RCT. This study indicated an improvement in iron status among 12 to 20-month-old toddlers with increased intake of red meat (58), but more studies are needed to draw any conclusions.

Sugar

The second SR for the 5th edition of the NNR examined the effect of sugar intakes (SSB, sucrose, and fructose) on metabolic risk factors and related diseases (12). This review selected studies of adults from 2,743 potential abstracts. Out of 17 extracted studies of sufficient quality, 15 were prospective cohort studies and two were randomised controlled crossover trials. It was concluded from prospective cohort studies published in the years 2000 to 2011 that SSB probably increase the risk of type-2 diabetes.

However, too few studies were available to draw conclusions on other types of sugars or foods and on the links with related metabolic risk factors, CVD, or all-cause mortality. With respect to the incidence of type 2 diabetes, four of six prospective cohort studies found a significant positive association with SSB intake. Larger cohort studies with longer follow-up more often reported positive associations, and BMI seemed to mediate part of the increased risk.

Macronutrients, food, and weight maintenance

The third NNR SR examined prospective cohort, case-control, and intervention studies on the role of dietary macronutrient composition in predicting change in body weight or waist circumference in adults (13). This review also included comprehensive, albeit non-systematic, data on the associations between food consumption, dietary patterns, and weight change. The literature search covered studies published between the years 2000 and 2012. Out of 1,517 abstracts, 50 papers were extracted and quality graded. All data on food consumption and weight gain were taken from the 21 prospective cohort studies that were identified in this search. No conclusion could be made regarding the preventive role of the dietary proportion of macronutrients on weight regain after prior weight loss. Currently there is not enough evidence linking potato consumption to weight change (13). However, probable evidence was found for high intake of dietary fibre and nuts to predict less weight gain, and for high meat intake to predict more weight gain. Limited-suggestive evidence was found for whole grains, cereal fibre, high-fat dairy products, and prudent dietary patterns to protect against weight increase. Evidence was also limited-suggestive for dietary fibre and fruit intake to protect against larger increases in waist circumference. Similarly, plenty of fibre-rich foods and dairy products, and less refined grains, meat, and sugar-rich foods and beverages, were associated with less weight gain in prospective cohort studies. In contrast, there was limited-suggestive evidence for high intakes of refined grains, sweets, and desserts to predict weight gain, and for refined (white) bread and high energy density foods to predict larger increases in waist circumference.

Conclusions

These three NNR SRs concluded that red and processed meat is a convincing cause of colorectal cancer, but there is too little evidence to make a conclusion regarding red and processed meat and CVD (15). High intakes

of SSB probably increase the risk of type-2 diabetes (12), and whole grains probably protect against type-2 diabetes and CVD (15). There is limited-suggestive evidence that total dairy protects against type-2 diabetes but increases the risk of prostate cancer (both with low evidence grade) (15). No effect was seen for total dairy consumption and CHD risk, and there was no evidence for dairy consumption to increase the risk of breast cancer (15). There is probable-suggestive evidence that "prudent dietary patterns" rich in plants foods, fibre-rich foods such as whole grains, nuts, and dairy products protect against weight gain and a larger waist circumference, and that diets with large amounts of meat, refined grains, sweets, SSB, and desserts predict more weight gain and larger waist circumference (13).

Scientific evidence from Whole Diet Trials – "The power of food"

Nordic studies

In the late 1980s, a Danish trial was launched to examine the direct influence of the whole diet on risk markers of cardiovascular health (59). Young adults (18 men and 12 women) consumed a diet for eight months that was planned according to the NNR (3rd edition, 1989). The results indicated that changing diets from an average Danish diet to one in accordance with the NNR was associated with favourable changes in a range of CVD risk markers including continuous decreases in blood lipids and blood pressure, unintended decreases in body weight and fat mass, and favourable changes in the haemostatic system (59–61).

In later years, a range of experimental whole-diet trials, including multicentre collaborative projects (e.g. the SYSDIET and DiOGenes studies) have been launched. These are intervention trials to examine the health impact of dietary components commonly consumed in Nordic countries (e.g. the NORDIET and SYSDIET studies) (62) or of combinations of dietary components with specific biological activities (63). The DiOGenes study is a Pan-European study targeting issues related to the macronutrient composition of the diet in relation to obesity that takes genetic predisposition into account (64).

The SYSDIET study, which was one of three projects in the Nordic Centre of Excellence Programme on Food Nutrition and Health, was launched in 2007 (65, 66). This randomized controlled dietary trial examined the impact on insulin sensitivity, lipid profile, blood pressure, and inflammatory markers in adults over a period of 18 or 24 weeks (66). The experimental

diet was based on the NNR 2004 and included whole-grain products, berries, fruits, vegetables, rapeseed oil, vegetable oil-based margarines (i.e. > 2/3 of fat in the diet was unsaturated fatty acids), three fish meals per week, and low-fat dairy products. Key dietary components were provided to the participants, and an average Nordic diet was served as a control diet. Favourable and significant changes between the groups were found in blood lipid profiles and in markers of low-grade inflammation. With the iso-caloric diets, body weight remained stable and no changes were observed in insulin sensitivity or blood pressure.

Thus a range of intervention studies suggest that changing from an average diet to one planned according to the NNR and/or using healthy foods commonly found in Nordic countries is clearly associated with health benefits (59–66). Similarly, several prospective epidemiological studies have concluded that healthy Nordic dietary patterns are associated with important health benefits (29, 30, 67).

Two international trials

In preparation for the 5th edition of the NNR, an exploratory literature search was conducted to identify review articles of studies that had examined food or dietary patterns in relation to chronic disease that were published from 2000 to January 2011 (14). This search identified several review articles that described and discussed two large secondary prevention trials, both of which have received much international attention. An important design aspect of these two trials was that foods were provided to the study participants ensuring internal validity of the exposure and treatment (68).

The Lyon Heart Study – conducted in France in the late 1980s – was a randomized dietary trial in survivors of a first MI (69). Participants, men and women younger than 70 years of age, were carefully instructed to adopt a Mediterranean-like diet including more bread, more root and green vegetables, more fish, less meat (i.e. replace red meat like beef, lamb, and pork with poultry), and no days without fruit. Butter and margarine were replaced by margarine based on rapeseed oil, which was supplied by the study. The margarine content of SFA and MUFA was similar to that of olive oil (i.e. SFA made up 15% and MUFA made up 48% of the total fatty acids), and the content of linoleic acid (LA) was 2-fold (16.4%) higher and α-linolenic acid (ALA) was 8-fold (4.8%) higher. After 2 years, the experimental group had significantly less heart disease (in terms of both the number of MIs and deaths) compared to the control group, and after 4 years

the experimental group showed a 50%–70% reduction in heart disease. Thus the data confirmed the preventive effect of the Mediterranean-like diet on heart disease (69).

These observations were recently supported by a large (n = 7447) intervention study that examined the effects of different Mediterranean diets on cardiovascular disease (70). The participants were randomized into three groups: a Mediterranean diet supplemented with extra-virgin olive oil (i.e. enriched with MUFA and polyphenols), a Mediterranean diet supplemented with mixed nuts (i.e. enriched with different PUFAs and polyphenols), or a low-fat control diet. Total fat was close to 40% in the Mediterranean diets, whereas the control diet had both poorer quality (especially in terms of type of fatty acids) and a slightly lower proportion of total fat (37%). This resulted in similar total mortality in all three groups, but the incidence of cardiovascular events was significantly reduced (by about 28%–30%) with the Mediterranean diets compared to the control diet.

The Dietary Approaches to Stop Hypertension (DASH) feeding studies were a series of controlled trials carried out in the 1990s among US men and women aged 22 years or older. DASH was designed to test the effect of a whole-diet modification on blood pressure (BP) (43, 71–73). The DASH diet emphasized fruits, vegetables, and low-fat dairy products and included whole grains, poultry, fish, and nuts. The diet was also reduced in dietary fats (especially SFA), red meat, sweets, and SSB (74). The most effective diet was the reduced-salt DASH diet (74). This diet was not only rich in minerals such as potassium, magnesium, and calcium and in dietary fibre, but also reduced in both SFA and sodium. The result was a clear reduction in systolic BP both in normotensives and in hypertensives. Because each dietary factor only has a modest effect, the best interpretation of the impressive reduction is that multiple dietary factors influence BP and that the influence of a combination of factors can be substantial (72).

Since the time of the DASH studies, researchers in the US have designed and conducted several similar trials (75, 76). The conclusion from these studies is that well-balanced diets that meet the recommended intakes of minerals, vitamins, macronutrients, and micronutrients (as recommended by the US Food and Nutrition Board of the National Research Council, and US national health organizations (77, 78)) can improve risk factors of CVD (79). In addition, two recent SRs on prospective cohort studies have concluded that a diet following the DASH principles is associated with reduced incidence of type 2 diabetes (80) and CVD (81).

Systematic reviews of Food and Dietary Pattern studies

Epidemiological studies that construct food patterns or DPs have been designed to examine the impact of the whole diet on health. These studies include a combination of many food items, nutrients, and other food factors and have the potential to capture dietary factors that would be hard to detect in studies focusing on single components. The number of epidemiological studies that use DPs as the exposure variable to estimate disease risks has increased rapidly in the last 15 to 20 years. DPs are typically constructed either using data-driven statistical (*a posteriori*) or index (*a priori*) methodologies.

Data-driven statistical (a posteriori) methodologies

Factor analysis, principal component analysis, and cluster analysis are examples of data-driven methodologies that were originally developed in the social sciences to handle large datasets. When using these statistical methods with dietary data in epidemiological studies, researchers will obtain DPs that reflect the diets reported by the study participants. These patterns are typically a mix of many different foods and can contain foods both with and without health benefits.

Researchers conducting DP studies tend to label emerging patterns similarly, e.g. "prudent" and "Western" patterns. It should be noted, however, that even if the chosen labels are similar across studies, the food habits that exist in the examined populations, the methodologies used to assess diets, and the specific methodologies used to construct the patterns will all influence the emerging food patterns. Thus even if DPs largely appear similar across populations, details within the patterns might still vary considerably.

Index (a priori) methodologies

Dietary indices are typically constructed using the general dietary recommendations as a base. High scores of a dietary index will, therefore, reflect how well the examined individuals adhere to the recommendations. Because the basis of the *a posteriori* and *a priori* methodologies differ, the emerging patterns might share some characteristics but also show dissimilar features.

The Mediterranean diet index has been used in many studies. However, the index typically needs to be adjusted to every new population examined due to population-specific differences in food habits. Also, it should be noted that the scores obtained for the separate components of the index

commonly use the population medians as cut-offs to indicate adherence or non-adherence to the diet. Several food consumption differences exist between Northern European and Mediterranean countries, and these could influence the ability and efficiency of the Mediterranean diet index to rank individuals. For instance, because the population median, and the index cut-off, of vegetables and fruits is considerably lower in Northern European countries compared to the Mediterranean populations, it can be argued that this index is not able to assess adherence to a Mediterranean diet in Northern European populations. At best, a "Mediterranean-like diet" is reflected.

Three systematic reviews

The exploratory literature search of food patterns studies (14) identified three SRs that used independent reviewers and strict inclusion and quality assessment criteria in line with those issued for the revision of the NNR (NNR5 working group (57)).

Breast cancer. One SR and meta-analysis by Brennan et al. (82) examined DP studies using either factor analysis or principal component analysis in relation to the risk of breast cancer. This SR identified 16 articles published between 2001 and 2009 that defined and labelled DPs as "prudent/healthy", "Western/unhealthy", and/or "drinker" (i.e., DPs characterised by high/frequent consumption of alcoholic beverages). This review concluded that the prudent DP was associated with a significantly decreased risk of breast cancer. There was more heterogeneity among case-control studies with non-significant risk estimates, but less heterogeneity among prospective cohort studies with significant protective associations with the prudent DP. The drinker DP was significantly associated with increased risk of breast cancer, and no evidence of heterogeneity across studies was seen. The Western DP was associated with increased breast cancer risk in case-control studies, but no significant associations were seen in cohort studies. However, one cohort study using a diet-history methodology to assess diet (as opposed to a less extensive food-frequency questionnaire) showed significantly increased risk with the Western DP and decreased risk with the prudent DP (82).

CHD. The SR and meta-analyses of cohort studies and RCT on the associations between diet and CHD and MI by Mente et al. (44) evaluated studies according to four of the Bradford Hill criteria for causality: strength,

consistency, temporality, and coherence (44). This SR indicated strong evidence for a causal link (i.e., support from all four criteria) between DPs and CHD. Protective associations were observed with Mediterranean-like and high-quality DPs, but it should be noted that "high-quality" was not defined in the paper. In studies of high methodological quality, the evidence was strong both for protection of prudent DPs and for adverse effects of Western DPs. Beneficial effects of the Mediterranean-like diet were observed in RCTs (44). In addition, this SR found that some separate dietary factors were associated with strong evidence for protection, including higher intakes of vegetables, nuts, and MUFA. The evidence for harmful effects of higher intakes of TFA and of foods with high glycaemic index or glycaemic load was also strong.

Mediterranean-like diet patterns. A third SR and meta-analysis of prospective cohort studies by Sofi et al. (83) evaluated the effects of adherence to the Mediterranean-like diet (as assessed with population-specific index scores) on several health outcomes. Previous observations of convincing protective effects of the Mediterranean-like diet on all-cause mortality, mortality from and incidence of CVD, the risk of neoplastic diseases, and the occurrence of neurodegenerative diseases were confirmed, and no significant heterogeneity was observed across studies (83).

These SRs of prospective epidemiological studies that used independent reviewers and strict inclusion and quality assessment criteria indicate consistently that DPs high in vegetables, fruits, nuts, legumes, fish, vegetable oil, and low-fat dairy products (such as the prudent DP or the Mediterranean-like diets) are associated with decreased risk of chronic diseases such as breast cancer, CHD, and MI and of all-cause mortality. In contrast, Westernized DPs characterized by high fat (especially SFA), processed meats, refined grains, sifted flour, and sugar-rich products – and low in plants foods, whole grains, fish, and vegetable oils – are linked to increased risks of these diseases.

Implications of documented diet-disease risks

Based on the scientific evidence documented in the 5th edition of the NNR regarding associations between food and food patterns and risk of chronic disease, and the current situation in the Nordic countries, an overall micronutrient-dense DP can be identified with the potential to promote future health and wellbeing in Nordic populations. A combination of food

selection changes should be implemented to fulfil all aspects of dietary improvement.

Decrease energy density, increase micronutrient density, and improve carbohydrate quality
Diets dominated by naturally fibre-rich plant food (e.g. vegetables, pulses, fruits and berries, nuts and seeds, and whole grains) will generally be lower in energy and higher in micronutrients compared to diets dominated by animal food. The energy density is generally higher in food products high in fat and sugar (e.g. desserts, sweets, candy bars, cakes and biscuits, savoury snacks, some breakfast cereals, ice-cream, and some dairy products). Whole grains and whole-grain flour are rich in dietary fibre and have lower energy density compared to refined grains and sifted flour.

Limit sugar-sweetened beverages.
A limited consumption of SSB will contribute to an increased micronutrient density and a reduced intake of added sugars.

Improve dietary fat quality by balancing the fatty acid proportions
Fatty fish, nuts and seeds, avocados, olives, vegetable oils and vegetable oil-based fat spreads high in unsaturated fat should largely replace butter, high-fat meat, and meat products. A switch from high-fat to low-fat dairy will also improve the dietary fat quality while sustaining micronutrient density.

Replace processed and red meat with vegetarian alternatives such as pulses or with fish and poultry
A limited consumption of processed meat and red meat, and a switch from high-fat to low-fat red meat, will contribute both to an improvement of dietary fat quality and to lower energy density of the diet.

Limit the use of salt in food production and food preparation
Manufactured food products provide a large proportion of the total salt intake. A reduced salt intake can be achieved by choosing low-salt varieties and limiting the salt added during food preparation.

Table 5.1. Dietary changes that potentially promote energy balance and health in Nordic populations

Increase	Exchange		Limit
Vegetables Pulses	Refined cereals →	Wholegrain cereals	Processed meat Red meat
Fruits and berries	Butter Butter based spreads →	Vegetable oils Vegetable oil based fat spreads	Beverages and foods with added sugar
Fish and seafood	High-fat dairy →	Low-fat dairy	Salt
Nuts and seeds			Alcohol

Vegetarian diets

Modern vegetarian diets come in many varieties (See Tables 5.2. and 5.4.). A vegan diet consists only of plant foods, and avoids all food products of animal origin. A vegetarian diet might include foods from living animals such as dairy and eggs. Other diets that exclude meat and meat products, but include fish and/or poultry are not strictly speaking vegetarian diets.

Individuals adopt a vegetarian diet for several different reasons including health, nutritional, ethical, religious, philosophical, environmental and economic concerns (84–86). However, there is a concern that modern vegetarian diets are not always selected with care. If so, and if certain food groups are consistently excluded from the diet, dietary imbalances can result that can lead to health problems.

A well planned vegetarian diet includes a variety of plant foods such as vegetables, fruits and berries, pulses, nuts and seeds, and whole grain cereals and generally provides high amounts of dietary fibre, folate, potassium, magnesium and antioxidants such as vitamin C, vitamin E, and β-carotene. Well planned vegetarian diets also include other health enhancing bioactive substances including phytochemicals such as phytoestrogens. A well-balanced lacto-ovo-vegetarian or lacto-vegetarian diet provides sufficient amounts of energy and essential nutrients for adults, including pregnant and lactating women, as well as children. The brief review *below* is mainly based on a report by the Swedish National Food Agency (87).

Table 5.2. Vegetarian diets can include, or exclude certain animal foods

	Plant foods	Dairy	Egg	Fish	Poultry
Lacto-vegetarian	•	•			
Ovo-vegetarian	•		•		
Pescitarian	•			•	
Pollotarian	•		•		•
Lacto-Ovo-vegetarian	•	•	•		
Lacto-Ovo-Pesci-vegetarian	•	•	•	•	

Health effects

Research studies have most often examined the health effects of the common lacto-ovo-vegetarian diet that is based on plant foods and includes both dairy products and eggs (87). In general, research indicates that vegetarian diets are associated with lower risk of chronic diseases such as CVD, type 2-diabetes, and obesity (88–92). In addition, vegetarians often have lower blood-lipid levels and lower blood pressure (90, 93), and are likely to live longer (89). Besides the dietary influence, it is probable that the overall lifestyle also contributes to a better health status among vegetarians because they often tend to be more health conscious and physically active, and less likely to smoke than non-vegetarians (89).

Nutritional considerations

If certain foods are consistently excluded from the diet, some nutrient intakes might be systematically lower compared to a mixed, conventional diet (Table 5.3.). This could result in deficient or inadequate intakes of essential micro-nutrients and other food components that are important for health. The content of some nutrients or bioactive constituents might, on the other hand, be higher or closer to current recommendations in vegetarian diets.

Protein

Pulses, whole grain cereals, nuts and seeds are good and Important sources of vegetable protein in all vegetarian diets. Other plant foods also provide protein, although in lower amounts. All essential amino acids are found

in plant foods, but the proportions are not as optimal as in animal foods. Protein is not a problem among vegetarian adults consuming varied diets, as long as energy needs are met and a variety of foods providing vegetable proteins are consumed. However, because the digestibility of vegetable protein is slightly lower compared to animal protein, individuals adopting vegan diets might require somewhat higher protein intakes.

Also, lectins found in many varieties of pulses could cause unfavourable health effects such as nausea, vomiting, bowel pain and diarrhoea if beans and peas are improperly cooked, or are consumed uncooked. Dried beans and peas should be soaked in water overnight, and boiled until soft (94).

Fat and fatty acids

Although, the content of SFA is usually lower in vegetarian diets compared to regular Westernized mixed diets, lacto-ovo-vegetarian diets can contain high amounts of SFA and cholesterol if high fat dairy products are used (89).

There are two essential fatty acids; α-linolenic (ALA) and linoleic acid (LA). Vegetarian diets often provide only limited amounts of long-chain omega-3 fatty acids. Therefore, a sufficient amount of the essential short chain omega-3 fatty acid ALA from plant foods needs to be included in the diet. The most important dietary source of ALA is rapeseed oil, and vegetable oil-based fat spreads made from rapeseed oil. Flax seed oil and camelina oil have a high content of ALA. Other good sources are also soybean oil, hempseed oil and walnuts. Eggs might contain some long-chain omega-3, depending on the feed content. The other essential omega-6 fatty acid LA is the most common fatty acid in nuts and seeds, and is usually included in sufficient amounts in most vegetarian diets.

Dietary fibre

A vegetarian diet based on naturally fibre-rich foods such as whole grain cereals, vegetables, pulses, nuts, fruits and berries, generally has a high and adequate content of dietary fibre. In contrast, with mixed diets based on animal foods an insufficient intake of dietary fibre is often a concern.

Vitamin D

Because vitamin D is produced in the skin when exposed to UV-light from the sun, the dietary supply is especially important at Nordic latitudes during the winter season. The vitamin is mainly found in fish, eggs (the yolk), and dairy products. It can also be found in some mushrooms. Vegan diets

need to be complemented with supplemental vitamin D all year round, whereas individuals following a vegetarian diet might need supplemental vitamin D in the winter season. Vegetable oil-based spreads are often enriched with vitamin D, and in Finland, Norway and Sweden fat-free and low-fat milk is enriched with the vitamin. This is not the case in Denmark and Iceland, although, some low-fat milk available is enriched with vitamin D. Some other food products might also contain added vitamin D since the introduction of voluntary fortification as per EU legislation in 2006.

Vitamin B_{12}

Vitamin B_{12} is only found in animal foods. Thus; vegan diets need to be complemented with supplemental vitamin B_{12}. Studies have, however, shown that low vitamin B_{12} status is not uncommon even among vegetarians with less strict diets (95). Therefore, all individuals consuming vegetarian diets should consider the use of vitamin B_{12} supplements (see the chapter on vitamin B_{12}).

Riboflavin

Animal foods, especially dairy products are the major riboflavin sources in Nordic diets. If dairy products are excluded from vegetarian diets plenty of pulses, dark green leaves and wholegrain cereals should be included to provide sufficient riboflavin intake. Also, many plant milks (e.g. soy bean or rice based) are fortified with calcium and riboflavin.

Vitamin B_6

Meat, potatoes, fish and dairy products are major sources of vitamin B_6 in mixed conventional diets. In vegan diets dark green leaves, pulses, whole grain cereals, almonds, sesame seeds, wheat germs and yeast are important sources (see the chapter on vitamin B_6).

Calcium

Dairy products are major sources of calcium, but in vegan diets whole grain cereals, pulses, nuts, seeds and dark-green leaves are major contributors. Because the oxalic acid found in some dark green leaves can inhibit calcium absorption, a good variety of plants foods should be included in the diet.

Iron

The iron content of plants foods such as pulses, whole grain cereals, nuts, seeds and dark green leaves is comparatively high. Iron absorption is gen-

erally good when eating varied vegetarian diets, but less is absorbed compared to the iron ingested from meat (i.e., heme iron). Because vitamin C enhances the absorption of iron ingested from plants foods, a sufficient intake of vitamin C might ensure sufficient iron absorption (89).

Zinc

Wholegrain cereals, pulses, nuts and seeds are good sources of zinc, but as with iron absorption, zinc absorption from animal foods is better than from plant foods. Phytic acid in cereals can reduce both iron and zinc absorption. However, prolonged fermentation of bread (*e.g.* sour-dough) and germination of beans and seeds can potentially reduce the negative effect of phytic acid on absorption.

Selenium

The major sources of selenium in the Nordic countries are fish, meat, eggs and milk. Although, lentils, peas, chick peas and mushrooms are important plant food sources of selenium, excluding one or several animal product categories from the diet might lead to low selenium intake. In addition, the soil content of selenium is generally low in Nordic countries, and plant foods grown on such soils have low selenium contents. The selenium content of imported plant foods vary due to varying selenium levels in soil around the world. In Finland, selenium is added to fertilizers, and cereals grown there are, therefore, a good source of the mineral. It is also added to animal feed, which means that dairy products and eggs generally are good sources. However, this might not be the case for all organically produced products.

Iodine

Iodized salt, sea salt, fish, shell-fish, eggs and dairy products are important sources of iodine in the Nordic countries. Algae are often suggested as a vegetarian source of iodine, especially in vegan diets. However, because the content of iodine in algae vary considerably (some varieties might even contain toxic amounts), the iodine content of algae should be known before the food is consumed.

Infants and children

A vegetarian diet including dairy has generally been associated with adequate growth, and a well-balanced lacto-ovo-vegetarian diet is nutritionally adequate for the growing child (96). There are few studies on children adopting vegan diets, although the results of the available studies indicate a somewhat slower growth among some of the children (96, 97). Vitamin B_{12}-deficiency has been observed in breastfed infants born to mothers consuming vegan diets, and in children from families following such a DP. This emphasises the need for adequate supplementation in both mothers and children (98, 99). Thus, vegan, lacto-vegetarian and lacto-ovo-vegetarian diets should be able to satisfy the nutrient needs of infants, children, and adolescents and promote normal growth if they are appropriately planned (89), but vegan diets always need to be supplemented with vitamin B_{12} and vitamin D.

Table 5.3. Nutritional recommendations in vegetarian diets

Type of diet	Critical nutrients	Recommendation
Vegan	Vitamin B_{12} Vitamin D	Supplements are needed
	Protein	Careful combination of pulses, whole grain, nuts and seeds
	Essential fatty acids; ALA	Search for sources of ALA
	Riboflavin Calcium, iron, zinc, selenium and iodine	Search for appropriate sources
Lacto-ovo vegetarian	Vitamin B_{12} Vitamin D Fat quality; ALA Iron, zinc, and selenium	Search for appropriate sources

Table 5.4. Modern diets can be defined in many different ways[1]

	General principles
Vegan – veganism	"...a way of living that seeks to exclude, as far as possible and practicable, all forms of exploitation of, and cruelty to, animals for food, clothing and any other purpose".[2] Diets exclude all animal products and animal-derived substances and are based on fruits, legumes, grains and vegetables.
Macrobiotic[3]	These diets typically consist of 50%-60% organically grown whole grains; 20%-25% locally, organically grown fruits and vegetables; and 5%-10% soups with vegetables, seaweed, grains, beans, and miso (fermented soy); The diets allow the occasional consumption of fresh white fish, nuts, seeds, pickles, Asian condiments, and non-stimulating and non-aromatic teas. These diets exclude all other animal products. The diets discourage consumption of coffee, sugar, stimulant and aromatic herbs and processed foods, some vegetables (potatoes, tomatoes, eggplants, peppers, asparagus, spinach, beets, zucchini, and avocados) and fruits not grown locally.
Fruitarian[4]	Diet includes only dried or raw fruits, berries, nuts, seeds (e.g. cereals) and fruit vegetables (e.g. tomatoes, cucumbers, olives and avocados).
Live-Raw foodism[4]	Diet consists of uncooked, unprocessed, often organic or wild foods and might include raw fruits, vegetables, nuts, seeds, sprouted whole grains, eggs, fish (e.g. sashimi), meat (e.g. carpaccio), and non-pasteurized/non-homogenized dairy products (e.g. raw milk, or cheese and yogurt made from raw milk).

1 Depending on the specific restriction the impact on health and well-being can vary.
2 The Vegan Society (http://www.vegansociety.com).
3 Source: the American Cancer Society (http://www.cancer.org/).
4 Information from Wikipedia.

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6 Sustainable food consumption – Environmental issues

Introduction

For food consumption to be sustainable it has to be safe and healthy in both amount and quality, and this has to be achieved through means that are economically, socially, culturally, and environmentally sustainable. In addition, waste and pollution need to be reduced, and the changes in food consumption at e.g. individual, national or regional level, should not jeopardize the needs of others (1). According to the international Susfood project (2), the changes need to operate within the biological limits of natural resources, especially with regard to soil, water, and biodiversity. The way we choose to consume food has an effect on the environment as measured in terms of climate change, toxic impact, biodiversity, eutrophication, acidification, land use and change, and water use.

This chapter gives a short overview of the major issues recognized in connection with food consumption and its environmental impact. This field is new, the measurement tools are not always agreed upon, and new aspects are continuously being added. In this overview, the literature search has not been systematic and the discussion is more exploratory.

Among all dietary guidelines, the following are pivotal: Eat a varied diet! Choose food from a variety of food groups over the day and do not overeat. This advice ensures that diet that covers the necessary nutrients and maintains a healthy body weight. The question, however, is whether this will still be true when the diet is altered to a more environmentally sustainable one. Is it possible to eat a nutritionally adequate diet in a sustainable way? This overview seeks to describe some of the issues around such dietary changes.

Environmental factors

Planetary boundaries

In general, current sustainable food consumption issues have been focused on climate impact, i.e. in terms of greenhouse gas emission (carbon dioxide equivalents), and less on the effect of toxic impact, biodiversity, eutrophication, acidification, land use, land use change, and water use. Rockström et al. (3) propose a set of nine planetary boundaries within which humanity can continue to develop and thrive for generations to come. Crossing these boundaries, however, could generate abrupt or irreversible environmental changes, and respecting the boundaries reduces the risks to human society of crossing these thresholds. (3). The authors' analysis suggest that three areas are already beyond safe planetary boundaries; the nitrogen cycle, climate change, and biodiversity.

The Millennium Ecosystem Assessment of 2005 (4) concluded that changes in *biodiversity* due to human activities were more rapid in the past 50 years than at any time in human history and that this has increased the risks of abrupt and irreversible changes to ecosystems.

Nitrogen and phosphorus are both essential elements for plant growth so fertilizer production and application is the main concern. Much of this nitrogen is emitted into the atmosphere in various forms rather than being taken up by plants. When nitrogen is washed out of the soil by rain, it pollutes waterways and coastal zones or accumulates in the terrestrial biosphere. Similarly, only a relatively small proportion of phosphorus fertilizers applied to food production systems is taken up by plants, and much of the phosphorus ends up in aquatic systems. These systems can then become oxygen-starved in the process of eutrophication in which bacteria consume the blooms of algae that grow in response to the high nutrient supply. A significant fraction of the nitrogen and phosphorus applied as fertilizer makes its way to the sea and can push marine and aquatic systems across ecological thresholds of their own.

Land is converted to human use across the planet. Forests, wetlands, and other vegetation types have primarily been converted to agricultural land. This *land-use change* is one driving force behind the serious reductions in biodiversity, and it has impacts on water flows and on the cycling of carbon, nitrogen, phosphorus, and other important elements.

Fresh water is becoming increasingly scarce – by 2050 about half a billion people are estimated to be subject to water-stress increasing the pressure to intervene in water systems.

Emissions of *toxic compounds* represent some of the key human-driven changes to the planetary environment. Many of these compounds can persist in the environment for a very long time, and their effects are potentially irreversible. The effects of reduced fertility and the potential of permanent genetic damage can have severe effects on ecosystems.

Recent evidence suggests that the Earth, now passing 387 ppm CO_2 in the atmosphere, has already transgressed the planetary boundary and is approaching several Earth system thresholds. We have reached a point at which the loss of summer polar sea ice is almost certainly irreversible. The weakening or reversal of terrestrial carbon sinks, for example, through the on-going destruction of the world's rainforests, is a primary cause of increased CO_2 levels (3).

Greenhouse emissions

The most widely used measure describing environmental impact is the effect on the climate. The impact on climate is estimated by computing and converting the greenhouse gases into carbon dioxide equivalents (CO_2e) which is the summary measurement of the emissions of carbon dioxide (CO_2), methane (CH_4), nitrous oxide (N_2O), and the extremely powerful refrigerants used to keep fish cold on ships at sea. Greenhouse gases trap global heat and increase the temperature in the planet's atmosphere, and the ability of certain gases to trap this heat is referred to as the compound's global warming potential. Food systems, including food production, food consumption, export, import, transport, storage, and retail, account for about 20%–25% of all greenhouse gas emissions in European countries (5, 6). Emissions of CO_2 are tied to the use of fossil fuels in the production and transport of food. Lately, CO_2 emissions generated from land-use change are an emerging issue (7, 8).

Emissions of CH_4 are tied to production of meat, milk, and rice. CH_4 is generated by decomposing organic material under anaerobic conditions such as digestion by ruminant livestock, storage of manures, and cultivation of rice under flooded conditions. Emissions of N_2O are tied to all crops and animal products. N_2O is generated by the microbial transformation

of nitrogen in soils and manures, and emissions also occur during the production of synthetic fertilizers.

In northern European countries, each person currently contributes an average of at least 10 tonnes of greenhouse gas emissions per year through their food consumption, housing, transport, and shopping habits. Food consumption is estimated to account for approximately 2 tonnes in the Nordic countries (9, 10). The transition toward a competitive low-carbon emission economy means that the EU should prepare for reductions in its domestic emissions by 80% by 2050 compared to 1990. The global increase in temperature might then stay below 2°C. In short, total climate impact should not exceed 2 tonnes of greenhouse gas emissions per person per year (11).

A complex web

Environmental impact is a complex web in which each factor is related to the others in a complicated arrangement of positive and negative effects. Rearing ruminant livestock adds to the production of CH_4 and N_2O emissions and eutrophication (excess nitrogen and/or phosphorous in the water). However, grazing livestock contribute to the maintenance of a rich biodiversity in countries with an abundance of land. It is calculated that greenhouse gas emissions in the European Union from the livestock sector correspond to close to 13% of the total greenhouse gases emitted, including the effects of land use and land-use change. Approximately half of the emissions originate from enteric fermentation (CH_4). Corresponding global emissions from livestock amount to 18% of all the greenhouse gases (12, 13).

Promotion of biodiversity is connected to reduced use of pesticides in agriculture and, when land is abundant, to the grazing of animals. In countries with less land, however, overgrazing threatens biodiversity. When biodiversity is rich, fluctuations and stress are absorbed in the ecosystem – the resilience is good – and biodiversity is a crucial endpoint in many of the environmental measurements. Globally, around 30% of the total human-induced biodiversity loss is related to livestock production. Cropland and grassland areas are expected to expand by 10%–20% over the coming decades in low-income countries leading to significant losses of terrestrial biodiversity (4). Globally, 80% of commercial fish populations are being fully exploited or overexploited (14).

Food consumption and climate impact

A balanced diet is achieved by choosing foods from several different food groups and not overeating. Foods in the same food group have certain nutritional and other characteristics in common. From a nutritional point of view, this gives many options for choosing similar products within the same food group. However, from the viewpoint of sustainability the choice can have a marked impact.

The value of CO_2e generated during the production-cycle of a food differs widely between foodstuffs but also within each food depending on how it is produced and what energy mix is used. For example, the climate impact of milk varies from 1 kg CO_2e per kg milk in the Nordic countries up to 7 kg CO_2e per kg milk in sub-Saharan Africa (15). Thus milk production is more efficient in the Nordic countries and a larger volume of milk can be produced per the same amount of greenhouse gases emitted from the cows. In Table 1, foods are roughly divided into three groups depending on their climate impact in terms of its CO_2e value or carbon footprint.

The climate impact of food can be related to other units than per weight, for example, per MJ, per gram protein, or per unit of weight of any other nutrient. Combinations of several key nutrients can be added together in an index as illustrated by the comparison between milk and other beverages by Smedman et al. (16).

Food waste

Globally, food waste accounts for roughly one third of the food produced for human consumption (17). The per capita food waste by consumers in Europe and North America is estimated to 95–115 kg per year, but this figure in Sub-Saharan Africa and South/Southeast Asia is only 6–11 kg per year. The average household food waste per person is estimated to about 95 kg in Denmark (18) and to about 75 kg in Sweden (19). Approximately one third of the Swedish waste in the household is potentially edible, unnecessary waste, and the rest of the waste is inedible (banana skins, trimmings, bones, potato peels). A larger proportion of vegetables, fruits, and bread is wasted in comparison to other food groups (WRAP 2008). The climate impact of the 25 kg of unnecessary waste corresponds to approximately 50 kg CO_2e per year or 2.5% of the climate impact of the food used in the household (19).

All values are combined estimates based on Macdiarmid et al (20); Carlsson et al (8); Cederberg et al (13); and various Life Chain Analyses reports on food items (21–24).

Nutritional benefits from a sustainable diet

It has been shown that no food group affects the environment as much as the production of meat and dairy products (25), and their effect on the climate contributes to almost half of the present climate impact from food consumption in the Nordic countries. This is seen in Denmark where calculations on the average diet show that combined meat and dairy products contribute to 53% of the climate impact from the diet (10). The corresponding figure for Sweden is 40% from the national calculations by the Environmental Protection Agency (9). Meat and dairy contribute to almost 2/3 of the intake of protein among adults in the Nordic countries according to recent dietary surveys (26, 34), and the average EU consumption of animal protein per capita is about twice the global average (50).

One way to measure the climate efficiency of protein production is to calculate how much protein is produced per kilogram CO_2e from various food sources. The most efficient protein source is wheat and legumes giving at least 160 g protein per kg CO_2e. Corresponding amounts of protein for other foods are 145 g/kg CO_2e for herring, 53 g/kg CO_2e from eggs, 50 g/kg CO_2e from chicken, and 10 g/CO_2e from beef. These calculations are based on data from life-cycle analyses performed by the Swedish Institute for Food and Biotechnology (SIK) and on nutritional data from the food database of the Swedish National Food Agency (NFA).

For health reasons, a limitation of the consumption of meat products and meat, especially red meat from cows, lambs, goats and pigs, is recommended by the World Cancer Research Fund (WCRF). Few countries achieve the population goal set by WCRF of a maximum of 300 g (400–450 g raw meat) of prepared red meat per week (27). The Nordic consumption of red meat amounts to an average of up to 400 g prepared meat per week. Women in all countries tend to have an average intake closer to the recommended amount than men (28). Red meat is a source of iron, and iron deficiency is estimated to be the most common cause of anaemia in all countries of the world (29). A British report on iron and health emphasizes the importance of a healthy, balanced diet that includes a variety of foods containing iron, and this is more important than focusing primarily on iron from meat sources (30). In a Dutch study, replacement of meat and dairy

by plant-based foods benefited the environment by decreasing land use. On average, total iron intake increased by 2–5 mg/d, although most of the iron intake was from less bioavailable sources (31). In a Nordic study, it was shown that reducing the intake of red meat to the recommended level of 300 g prepared red meat per week (27) did not reduce the intake of iron to any substantial degree. However, the bioavailability of iron in the diet may be affected with a decreased meat intake, depending on which foods replace the meat, an aspect that was not studied. The study also showed that there would be no significant nutritional consequences from reducing the intake of red meat or processed meat to the recommended levels (28).

A shift in the consumption of proteins from animal to vegetable sources would also likely result in reduced consumption of saturated fat. A study from the UK estimated that reducing the overall intake of meat, which also reduced the overall consumption of saturated fat, would lead to a 17% decrease in the number of premature deaths from heart disease among adults (32). Furthermore, it was calculated that a 30% reduction in meat production and subsequent decline in consumption would match nutritional guidelines. In Sweden, 40% of the saturated fat in the diet comes from animal sources excluding fish. In the UK, the intake of saturated fatty acids from meat is 40% higher than in the Nordic countries (26, 33–35).

An increased consumption of dried legumes increases the intake of dietary fibre, folate, carbohydrates (starch), and several other nutrients. The production of pulses has a low climate impact, they are beneficial in crop rotation systems, and they store well. The amino acid content in legumes is not fully balanced, but when combined with the amino acids in cereals or animal sources a satisfactory amino acid combination can be achieved.

Field and root vegetables contribute with vitamins and minerals and are rich in dietary fibre. They tend to store well and their climate impact is low, around 100 g CO_2e or less per kilogram of vegetable. Vegetables grown in heated greenhouses have a higher climate impact and are often more perishable, but positive developments in greenhouse heating technology have been seen, for example, in the Netherlands, Sweden (36), and Finland (37). The climate impact from producing peppers and tomatoes has dramatically declined with the introduction of residual heat use from nearby industries and the use of renewable energy sources. In Iceland, a substantial portion of the tomatoes consumed comes from greenhouses heated by geothermal power.

The climate impacts of reducing body weight and of the extra burden of obesity on the climate have been calculated. A reduction of ten kilogram in

all obese and overweight people would result in a decrease in CO_2 production equal to 0.2% of the CO_2 emitted globally in 2007 (38). Compared with a normal population distribution of BMI, a population with 40% obese requires 19% more food energy for its total energy expenditure (39). Greenhouse gas emission from food production and car travel due to increases in obesity in a population of one billion are estimated to be between 0.4 gigatonnes (GT) and 1.0 GT of CO_2e per year (39).

Healthy and sustainable diets – potential conflicts

Presently there are some areas of potential conflict concerning dietary recommendations and sustainability. One concerns the recommendation of increased fish consumption, the second the restriction of butter, and the third concerns iodine.

An increase in *fish* consumption is recommended because fish in general is a valuable source of vitamin D, selenium, iodine, and long-chain n-3 fatty acids. There are several nutritional reasons to promote increased fish consumption, but from a sustainability point of view there are doubts. Wild fish in general are overexploited, and currently 80% of the fish populations are fully exploited or overexploited (14). Aquaculture is steadily compensating for wild fish, but to an increasing degree plant-based feed is added to the feed given to farmed fish, including predatory fish. Eutrophication is a significant environmental problem associated with aquaculture, and in tropical waters coastal deforestation is a growing issue. In addition, some populations of wild fish, such as herring, are contaminated and restricted consumption is advised despite the availability of strong stocks.

There are few nutritional benefits to the use of butter. The use of palm oil as an ingredient in industrial food products instead of butter or hydrogenated oils has increased but is generally not a sustainable solution. Actors in the Norwegian government and food industries in Nordic countries have taken a firm position against the use of palm oil in ice creams, cookies, spreads, and for frying and this has resulted in a considerably reduced consumption of the oil (40). Other fat sources could be considered and use of more sustainably produced palm oil should be prioritised.

In the Nordic countries, milk and milk products contribute substantially to the intake of *iodine*. Over half of the iodine intake comes from the current intake of milk and milk products in Norway (41), and milk contributes 40% of the daily intake of iodine in Finnish adults (33). To compensate for a lower intake of dairy products, an increased consumption of fish

and shellfish is an option, which is in line with dietary guidelines. Other management options, including fortification, could also be considered.

Experiences of healthy and sustainable diets and potential positive climate impact

How low can we go in terms of climate impact by changing our consumption and still eat a nutritionally adequate diet? Substantial decreases in climate impact – by up to a factor of 10 – have been seen when comparing single meals (8), but more realistic differences are shown when whole diets are compared over time. In Denmark, a diet following the Danish dietary guidelines showed a 4% decrease in climate impact compared to the average diet. If foods with low carbon footprint were chosen from the meat, vegetable, and fruit food groups, the climate impact was reduced by up to 23% in comparison to the average diet, including beverages (10). The total household food waste was estimated to be around 20% and accounted for 12% of the climate impact of food production. The authors of that study concluded that there is a potential synergy between the goal of a healthier diet and the goal of reduced carbon footprint.

In a similar Swedish calculation, a diet including 86 different food items over one week and fulfilling all dietary guidelines would lead to a reduction in climate impact from approximately 1.7–2 tonnes CO_2e for the average diet to 1.4–1.7 tonnes CO_2e per person per year. In addition, choosing foods with a lower climate impact from all food groups and eating less meat and dairy would lead to a climate impact of 0.9–1.3 tonnes CO_2e per person per year. This diet was based on a one-week menu in March containing 110 food items (42). A Dutch study showed that if diets became more plant based it would be possible to achieve a 25% to 50% reduction in climate impact from the diet. In addition, reducing all food waste would lower the climate burden of food by 15% (43). Furthermore, a 25% reduction in climate impact was seen when theoretically shifting the entire Dutch population to a diet with reduced consumption of meat, fish, and eggs. Only a 13% reduction in climate impact was seen when consumption of beef and pork was cut by about half in the entire population (43). In another Dutch study, the potential reduction in climate impact of changing to a healthy diet was greater than that of having a meat-free day. The reduction potential was three times higher if the only meat consumed was chicken and six times higher for a switch to a vegan diet (44).

A 36% reduction in climate impact was seen when a British seven-day

sample menu for adult women meeting the dietary requirements was set (20). The diet contained 52 food items and included meat products in smaller quantities than in the current UK diet. High-fat and sweetened foods were also included, but no alcoholic beverages.

The climate impact from a vegan diet was almost half that of the average German diet, and an ovo-lacto vegetarian diet had 25% lower impact compared to the average diet. The vegan and the lacto-ovo diets followed the dietary patterns issued by US Department of Agriculture/Department of Health and Human Services. A diet that met German recommendations reduced climate impact by 16% compared to the average German diet (45). Participants following a diet with lower climate impact tended to have intakes closer to the Nordic nutrition recommendations than those with a higher climate impact diet. These were results from a 7-day weighed food record from 177 Swedish participants linked to life-cycle assessment data on greenhouse gas emissions for 80 food groups or products (46).

The European Commission's Roadmap 2050 outlines various paths to a decarbonised Europe by 2050 (11). A Swedish study investigated predicted food consumption in the year 2050 in a society not using fossil fuels and calculated that the climate impact of food consumption would be 30% lower than with fossil fuels (47). Further calculations showed that very low meat consumption or a vegan diet together with further improvements in agricultural efficiency could reach a climate impact of 0.3–0.4 tonnes CO_2e per person per year.

Conclusions

Environmental and public health scientists agree that a predominantly plant-based diet is preferable to one largely based on animal sources. The above calculations show that if the climate impact from food production could be reduced by 40%–50% in combination with changes in consumption and production then each individual's contribution could be reduced to as low as 0.5 tonnes CO_2e per year. However, the uncertainty in the calculations is large and comparisons between the studies should be undertaken with caution.

The question, then, becomes whether people will be able to maintain nutritional balance if they alter their diet to a more sustainable one. The change must be made to the entire diet to reflect increases in some foods in response to decreases in others (6). Studies have shown that those following a diet close to the dietary guidelines had a diet with a lower climate

impact. Those who choose a diet with less meat and dairy products have even less of an impact on the climate than those eating the present average diet. With a general vegan diet, it is possible to halve the climate impact from what we eat.

The food choices necessary to reach a more sustainable diet are summarized in Table 1. Existing official dietary guidelines almost all coincide with the dietary changes necessary to achieve an environmentally sustainable diet. However, to reach a more sustainable diet requires more plant-based foods and less animal-based food; choosing primarily meat and fish with low environmental impact; eating more dried beans, peas, lentils, and cereals; choosing mainly field vegetables, root vegetables, potatoes, fruits, and berries that store well; choosing perishable products when they are in season; and minimizing waste. There could be a conflict between nutritionally and environmentally sustainable diets regarding the advice for fish and seafood and for the use of dairy fat in the food industry. The overall conclusion is that there are promising possibilities to eat nutritionally adequate and varied diets in a sustainable way.

Table 1. Possible dietary changes from present average consumption to reach a sustainable diet: Health and environmental impact (10, 48, 49)

Consumption challenges. Change in present average consumption	Health effects		Environmental effects		Comments
	Positive	Negative	Positive	Negative	
Meat and eggs					
Less Meat – Ruminants (beef, sheep, game)	Less saturated fat Decreased cancer risk	Less iron and zinc	Less GHG* Less eutrophication	Lack of grazing animals where land is in abundance results in difficulty keeping the landscape open and varied. This might have a negative impact on biodiversity.	2/3 of all grain produced goes to animal feed. Demand for soy drives deforestation in the Amazon. Combined meat and milk production is more efficient than only meat production.
Less Meat – Pork, poultry	Less saturated fat Decreased cancer risk	Less iron and zinc	Less GHG	Pork and fowl production does not affect biodiversity.	2/3 of grain produced used in animal feed. Demand for soy drives deforestation in the Amazon. Fowl production is very efficient
More eggs	Source of many nutrients		Climate effective	Soy in feed drives deforestation in Amazonas.	Soy can be replaced by domestic legumes.
Dairy products					
Less Dairy Milk	Less saturated fat (if consumption of high-fat dairy is reduced)	Less calcium Less iodine	Less GHG* Less eutrophication	Lack of grazing animals where land is in abun-dance results in difficulty keeping the landscape open and varied. This might have a negative impact on biodiversity.	Difficult to meet calcium recommendations without milk and dairy products.
Less Dairy Cheese	Less saturated fat Less salt	Less calcium Less iodine	Less GHG* Less eutrophication	Lack of grazing animals where land is in abun-dance results in difficulty keeping the landscape open and varied. This might have a negative impact on biodiversity.	Difficult to meet calcium recommendations without milk and dairy products.

Fish and shellfish					
More fish and seafood Wild	More unsaturated long-chain fatty acids More vitamin D More selenium More iodine	Risk of being exposed to contam-inants		Increased pressure on fish stocks if not handled with caution following scientific advice. Leaking refrigerants on fishing vessels are strong greenhouse gases. Some fishing methods damage the ocean floor. Fishing methods are not always selective and large amounts of unwanted fish are caught and discarded.	Overexploitation of fish populations is a concern. Scientific advice and policies need to be followed.
More fish and seafood Farmed	More unsaturated long-chain fatty acids More vitamin D More selenium More iodine		More vegetable-based fodder is used, including for predatory fish	Farmed predators need large amount of fodder based on fish. Farmed fish that escape might weaken the wild population's genetic pool. Disease might spread to wild fish. Eutrophication from concentration of fish.	Aquaculture is rapidly increasing. Herbivorous fish species and filtering organisms are interesting options. Microalgae oil with DHA and EPA could be an alternative to consuming fish, but supplements have not been shown to perform as well as the naturally occurring nutrients in fish.
Plant food					
More fruits and berries	More dietary fibre More folate More nutrients overall		Low climate impact	Many fruits and berries are treated with pesticides. Large amounts are imported and transported long distances under climatised conditions.	Numerous foods in this category are transported by air.
More field vegetables including root vegetables	More dietary fibre More folate More nutrients overall		Low climate impact	Many field vegetables are treated with pesticides	Choose those that store well. Many of these vegetables store well.

Consumption challenges. Change in present average consumption	Health effects		Environmental effects		Comments
	Positive	Negative	Positive	Negative	
More, but less fossil fuelled greenhouse-grown, vegetables	More dietary fibre More folate More nutrients overall		Fewer pesticides are used and are often replaced with biological methods in greenhouses.	Fossil fuel is used for heating and cooling greenhouses.	Many greenhouse-grown vegetables are sensitive and require care-ful handling and certain tem-pe-ra-tures during transport. Many do not store well. More fossil free greenhouses are seen.
More potatoes	More dietary fibre More vitamins and minerals		Low climate impact	Potatoes are exposed to many diseases and pesticides are often used.	Store well
More dried legumes	Protein-dense plant food Low fat More dietary fibre More nutrients Overall health-promoting benefits	Might contain anti-nutritional substances and flatulence-promoting oligosaccharides	Nitrogen fixator Beneficial for crop rotation	Pesticide use	Store well Acceptability problems among some consumers
More nuts and seeds	Unsaturated fat Dietary fibre Protein Vitamins and minerals	Prone to mould.			Toxins, e.g. aflatoxins
More cereals and grains	More dietary fibre/ whole grain (if the intake of whole-grain cereals is increased) More vitamins and minerals	Increased intake of rapidly absorbed starch, with only minimal amounts of fibre and nutrients (if the intake of refined grain is increased). Prone to mold	Low climate impact for cereals, higher impact for rice.	Production of fertilizers causes emission of N_2O. Fertilizer used on fields cause eutrophication and emission of N_2O. Pesticide use	Rice production leads to CH_4 emissions due to anaerobic fermentation under water. Toxins, e.g. DON in cereals.
More organic	None	None	Less or no pesticide is used		Lower production per hectare

		Beneficial for soil conditions Promotes biodiversity		
Dietary fats				
More vegetable oils	More unsaturated fats	Rapeseed production is part of agricultural rotation	Pesticide use	
Less butter	Less saturated fat	Less GHG* Less eutrophication	Lack of grazing animals where land is in abundance results in difficulty keeping the landscape open and varied. This might have a negative impact on biodiversity.	
Less palm oil	Less saturated fat	Less pesticide use Less deforestation Biodiversity increases		Palm oil production is very efficient per hectare. Land use change from deforestation is not included in the evaluation. Production of certified (sustainable production) palm oil is small but increasing. Trans fatty acid intake decreased dramatically when palm oil replaced partially hydrogenated fats.
Other				
Less savoury snacks	Less salt and fat			
Less sweets	Less energy (sugar and fat)		Some sweets have high climate impact	This is a large group consisting of a variety of sugary and fatty foods. The nutritional benefit is very low.
More water as drink	Contains no extra energy		The packaging and transport of bottled water has a significant climate impact.	

GHG = greenhouse gases.

Table 2. Climate impact from primary production of food: Low, Medium, and High CO2e values per kg edible weight

Low < 1 kg CO_2e/kg	Medium 1–4 kg CO_2e/kg	High > 4 kg CO_2e/kg
Field vegetables	Poultry	Beef
Root vegetables	Greenhouse vegetables (heated with fossil fuels)	Lamb
Greenhouse vegetables (heated with renewable resources)	Rice	Pork
Potatoes	Fish	Cheese
Beans, peas, lentils	Vegetable oil (olive, rape)	Tropical fruits and vegetables transported by air
Cereals	Sweets	Butter
Pasta	Snacks	
Bread	Fruits (bananas, melons)	
Fruits, local (apples, pears)	Vegetables imported from a far distance	
Vegetable oil (palm, coconut)	Wine	
Sugar	Eggs	
	Milk, yoghurt	

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7 Fluid and water balance

	Adults and children > 14 y	Children 2–13 y
Guiding value*	1–1.5 L/d	1 L/d

* From water and fluids. In addition to water from foods.

Introduction

Safe water for drinking and sanitation is critical to maintaining good health. This pivotal role of water is described in several human rights provisions, including the Convention of the Rights of the Child (Article 24) and the International Convention on Economic, Social, and Cultural Rights (elaborated on in General Comment 15), and is highlighted in Voluntary Guideline 8c on the Right to Adequate Food as adopted by the Food Agricultural Organisation (FAO). According to the World Health Organisation (WHO), 2.5 million children suffer annually from diarrhoea and malnutrition due to unsafe water, and improvement in water standard in large parts of the world could have a profound impact on the incidence of many infectious diseases that currently affect millions of people of all ages.

Dietary intake

The usual volume of ingested water and other fluids amounts to 1,000–2,000 mL per day in the Nordic countries. Foods contain on average 1,000 to 1,500 mL water per day. This brings the total amount of available water to 2,000–3,500 mL per day, which is about 10% of total water content of the body.

Physiology and metabolism

Water is the main component of the human body and is vital for organ functions and for thermoregulation. Water content as a fraction of body weight is usually lower in women than in men. It also varies with age and is about 75% in new-borns and about 50% in the elderly. Approximately two thirds of the total body water is confined to the intracellular compartment and the remaining third is located extracellularly. In the extracellular compartment, about 75% of the water is in the interstitium and 25% is a component of blood plasma (1).

The regulation of fluid balance is closely linked to the regulation of electrolyte balance. In the kidneys, the excretion of water and electrolytes is regulated by hormones, in particular the antidiuretic hormone and aldosterone. When there is excess water in the body, diluted urine is excreted. If the concentration of electrolytes in body fluids becomes too high, the thirst centre in the brain is stimulated and this leads to a feeling of thirst and reduced excretion of water by the kidneys.

Foods provide an average of 1,000 mL to 1,500 mL of water per day. The water content in food items varies considerably and ranges from about 5% in nuts to 90% in fruits and vegetables. Intake of drinking water and beverages also provide varying amounts of water, and the oxidation of fat, carbohydrates, and protein yields an additional 300 mL to 350 mL of water per day. Loss occurs by through urinary output, the water in the stools, and evaporation from the respiratory tract and the skin. The daily urinary output exceeds 600 mL in healthy adults and is normally between 1,000 and 2,500 mL. The water content of stools is generally 100 mL to 200 mL per day, but this amount can increase considerably when a person suffers from diarrhoea. The daily insensible losses by evaporation are on average 300 mL to 500 ml per square meter of body surface in a temperate climate. Losses by sweating are generally small, but they can increase to several litres per day in a warm and humid environment or with heavy exercise in temperate conditions.

During total parenteral nutrition, the daily requirement for total water is generally considered to be 30 mL per kg body weight and this corresponds to 2,250 mL for a 75 kg healthy person living in temperate conditions and performing moderate physical activity.

Requirement and recommended intake

The vast majority of healthy people meet their daily hydration needs by letting thirst be their guide. It is virtually impossible to give exact recommendations on daily water intake for healthy subjects because the requirement for fluids shows considerable inter-individual variations, and it is confounded by physical activity patterns and the ambient climate. Moreover, the evidence is insufficient to establish water intake recommendations as a means to reduce the risk of chronic diseases such as cancer and cardiovascular and metabolic disorders (2, 3).

The U.S. Institute of Medicine has set general recommendations for adequate intake (AI) of approximately 2.7 litres and 3.7 litres of total water from all beverages and foods daily for women and men, respectively, but has not set an upper level for total water intake (3). Moreover, in the U.S. the AI for total water was set to 1.3 litres per day for children 1–3 years old, 1.7 litres per day for children 4–8 years old, 2.4 and 2.1 litres per day for 9–13-year-old boys and girls, respectively, and 3.3 and 2.3 litres per day for 14–18-year-old boys and girls, respectively (3).

The European Food Safety Authority (EFSA) set the AI of total water to 2.0 and 2.5 litres per day for adult women and men, respectively (4). The AI for total water per day was set to 0.8–1.0, 1.1–1.2, 1.3, and 1.6 litres per day for children aged 0.5–1, 1–2, 2–3, and 4–8 years, respectively. Furthermore, the daily AI for 9–13-year-olds was set to 2.1 litres for boys and 1.9 litres for girls. The recommended AI for children aged 14 years and older is similar to that of adults.

The EFSA also recommends an additional 0.3 litres of water per day for pregnant women (4). Lactating women increase their fluid intake in relation to the volume of breast milk that they produce. A volume of 750 mL per day of breast milk during the first six months increases the requirement for fluid by about 600–700 mL per day. This is generally compensated for by a self-regulatory increase in fluid intake of about 12–16% (6). The EFSA recommends that lactating women have the same daily AI of total water as non-lactating women plus an extra 0.7 litres (4). For elderly people whose capacity to concentrate the urine is limited and who often have impaired feelings of thirst, a broader safety margin might be needed. The EFSA, however, does not recommend a specific AI for total water intake among the elderly (4).

In NNR 2004 guiding values for daily intake of water and fluids, in addition to water derived from foods, were set to 1 litre for adults and children

and 1.5 litre for elderly. In NNR 2012 the guiding value for daily intake of drinking fluids for adults and children performing moderate physical activity and living under moderate temperate conditions is 1–1.5 litres of water in addition to the water derived from foods. Lactating women increase their fluid intake in relation to the volume of breast milk. A volume of 750 ml per day of breast milk during the first six months increases the requirement for fluid by about 600–700 ml per day. This is generally compensated for by a self-regulatory increase in fluid intake.

Lower and upper limits of intake

Mild dehydration – defined as a 1% to 2% loss of body weight due to fluid losses – can result in headache, fatigue, loss of appetite, and vertigo. Dehydration in excess of 3% to 5% of body weight can decrease endurance and strength and contribute to heat exhaustion (5, 6). Dehydration of 15% to 25% of body weight lost as water is fatal (7).

Acute water toxicity has been reported (8) due to rapid consumption of large quantities of fluids that greatly exceed the kidney's maximal excretion rate of 0.7–1.0 L/hour (4). Excessive ingestion of water can increase the risk of water intoxication and hyponatraemia during pregnancy (9). However, it is not possible to define a maximum daily amount of water that can be tolerated by a population group without taking into account individual and environmental factors (4).

Hydration status in relation to coffee and alcohol

Coffee is reported to increase 24-hour urine excretion in subjects with no habitual intake (10), while hydration status seemed unaffected in habitual coffee drinkers (11). Because the main diuretic compound in coffee and tea is caffeine, it appears that caffeine tolerance develops after habitual consumption but there is reportedly no basis for restricting caffeine consumption to avoid either dehydration or overhydration (12).

Alcohol (ethanol) has a diuretic effect by inhibiting the secretion of antidiuretic hormone, but moderate amounts of alcohol such as beer and wine appear to have little or no effect on hydration status (13).

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8 Energy

Components of daily energy expenditure

Definitions of energy requirement

The basic principle behind the formulation of energy requirement reference values is energy balance, i.e. the physiological state in which daily energy intake equals energy expenditure and both body weight and energy content (defined by body composition) are constant. For some people, especially those who are over- or underweight, the recommended energy intake might be lower or higher than energy expenditure for a prescribed time period, but long-term energy balance is the ultimate goal even in treatment of undernourishment and obesity. Therefore, the NNR defines the energy requirement in adults *as "the energy intake needed to cover energy expenditure in individuals with body weight, body composition and physical activity compatible with good health. In addition, energy requirement is affected by the energy needed for growth in children, for deposition of tissues during pregnancy and for milk production during lactation*" (1). However, because body energy stores are very large (at least 30 times the daily energy energy expenditure, there is no need for energy intake and energy expenditure to be equal over short periods of around 1 to 4 days (2).

The daily energy expenditure can be divided into the following components:

- Basal (or resting) energy expenditure (BEE or REE)
- Diet-induced thermogenesis (DIT)
- Energy expenditure caused by physical activity

Energy expenditure is measured in kJ (1000 kJ = 1 MJ) per time unit (usually MJ/d). One kilojoule equals 0.24 kcal (or 1 kcal = 4.184 kJ), a unit that is still often used in the literature.

On average, daily energy expenditure is higher in men than in women but the difference disappears after adjustment for the difference in body

size and body composition between the sexes. Very cold or hot environments, genetic differences, hormonal status (e.g. serum concentrations of thyroid and growth hormones), sympathetic nerve activity, psychological state, pharmacological agents, and several disease states have been shown to increase or decrease energy expenditure, mainly by affecting REE (3, 4).

Basal (resting) energy expenditure

BEE, or basal metabolic rate (BMR), is defined as the energy expenditure of an individual at physical and mental rest in a thermoneutral environment and about 12 hours after the previous meal. REE is measured under less rigorous conditions than BEE and is considered, therefore, to be approximately 5% higher than BEE. The mean energy expenditure is slightly lower during sleep than during waking hours (3). Therefore, sleeping energy expenditure (SEE) is about 10% lower than BEE. Despite small systematic differences, SEE, BEE, and REE are very strongly inter-correlated and they are often used interchangeably.

In individuals with approximately equal physical activity levels, daily energy expenditure is strongly related to body weight and particularly to fat free mass (FFM = body weight – fat mass) (5). Fat mass (FM) also shows a positive correlation with energy expenditure. However, the increase in energy expenditure per unit FM is much smaller than for unit FFM (5). Hence, the inter-individual variations in FFM explain much more of the REE compared to variations in FM. FFM consists of skeletal muscle and organ tissue. When expressed per kg, the metabolic rate in the organs is much higher than in skeletal muscle. In adults, 70%–80% of BEE is derived from organs that comprise only 5% of the total body weight (5). Thus there is an association between total FFM and REE such that when FFM (and hence muscle mass) is low, the slope of BEE against FFM is lower than when FFM (and muscle mass) is high (4). In other words, when the organs make up a higher proportion of the FFM, increases in skeletal muscle mass has less influence on REE.

The inter-individual variation at a given FFM is about 2.1 MJ per day, and this indicates the possible magnitude of the difference in REE between two individuals with similar FFM. Variations in genetic makeup, body composition, hormone concentrations, energy balance, and physical fitness have been found to explain the variation in REE after adjustment for FFM (3, 4, 6, 7).

Diet-induced thermogenesis

DIT, or diet-induced energy expenditure, is defined as the increase above REE in energy expenditure after food intake divided by the energy content of the food ingested (8). The postprandial rise in energy expenditure lasts for several hours, but about 90% of DIT is observed within 4 h of the meal. DIT is assumed to be 10% of the daily energy expenditure in individuals in energy balance who consume a mixed diet with an average composition (9, 10). The DIT of fat is only about 5% of its energy content, but the DIT of protein is approximately 20% of its energy content. The DIT of carbohydrate is around 10% of its energy content, but this figure might be as high as 20% if glucose is directly converted to fat (de novo lipogenesis). However, this process requires an excess of energy from carbohydrates and this situation occurs rarely in healthy individuals consuming diets typical for the Nordic countries (11).

Physical activity

Physical activity (at work or leisure time) is defined as any bodily movement produced by skeletal muscle that results in energy expenditure (12). *Exercise* is a subcategory of physical activity and is a voluntary, deliberate physical activity performed because of anticipated positive effects on physical, psychological, and/or social well-being.

The daily physical activity level (PAL) is defined as total energy expenditure divided by REE (or BEE). This way of quantifying physical activity is based on the assumption that the variation in daily energy expenditure is based on physical activity and body size.

The metabolic equivalent of task (MET = energy expenditure during an activity divided by REE) is a measure of instant physical activity level, and PAL is the daily average of the METs weighted by the time each task was performed (see, for example, Table 8.8.) (13, 14). The inter-individual variation in PAL (roughly 1.4 to 2.0) is much more restricted than for MET, which can range, for example, from 1.2 when sitting to as high as 15 for riding a bicycle at a speed of 30 km/h.

Daily physical activity (and physical activity-induced energy expenditure) can be divided into occupational and leisure activities. The latter can be further divided into exercise and non-exercise activities that have different grades of intensity. Occupational activity can also vary in intensity. Inactivity refers to a state where energy expenditure is close to REE, and

this usually includes sitting or lying down while awake. The associations between physical activity, sedentary lifestyle, and health are described in detail in chapter on physical activity.

Energy balance and health

Body mass index

In obesity, the amount (in kg or as a percentage of body weight) or anatomical distribution (subcutaneous/visceral or abdominal/truncal) of body fat leads to an increased risk for adverse health effects, particularly type 2 diabetes, cardiovascular diseases, musculo-skeletal disorders, and some forms of cancer. Regardless of whether the amount of body fat or the distribution of body fat is used, it is not possible to determine a single point separating normal and healthy body weight from obesity. Moreover, health risks increase with increasing severity of obesity (15–17).

The simplest and probably most common way of assessing the status of obesity is by using body mass index (BMI), that is, body weight (kg) divided by the square of the height (m^2). BMI has a U or J shaped association with total mortality and morbidity (15, 17, 18). In general, the BMI compatible with the lowest mortality (and morbidity) in adults is approximately 22–23. According to the WHO definition (15), the normal (or recommended) BMI is between 18.5 and 24.9 (Table 8.1.). The term overweight describes a slightly elevated BMI, and a BMI of 30 or more is considered to be obesity.

Table 8.1. Body mass index; definitions of underweight, overweight, and obesity; and health risks for adults 18–64 years of age

Body mass index	Definition	Morbidity and mortality
<18.5	Underweight	Slightly increased
18.5–24.9	Normal weight	Low
25.0–29.9	Overweight	Slightly increased
30.0–34.9	Grade I obesity	Increased
35.0–39.9	Grade II obesity	Much increased
≥40.0	Grade III obesity	Very much increased

The categories in Table 8.1. are, in principle, applicable in all Nordic countries. However, it should be kept in mind that BMI might represent different

levels of fatness and body fat distribution depending on age, sex, ethnicity, athletic training, and race (26, 27). For instance, the healthy BMI range might be higher for Inuits (19) and lower for individuals of Asian descent (20). Therefore, BMI on the individual level should be used with great caution. Other simple measures, such as waist circumference (see heading *Abdominal obesity*) might help to assess obesity-related health risks.

In a meta-analysis (21), the sensitivity of BMI for detecting high adiposity was 0.50 (95% confidence interval (CI): 0.43–0.57) and its specificity was 0.90 (CI: 0.86–0.94). These data indicate that using BMI leads to both type I errors (true obesity is not detected) and type II errors (obesity is detected even when it is not true) and that type I errors seem to be more common. Okorodudu et al. (21) compared BMI against measures of body fat from body composition analyses and showed that BMI is more prone to underestimate than to overestimate body fatness. In other words, many individuals with a BMI just below a cut-off limit (e.g. 25 or 30) should in reality have been classified as overweight or obese, respectively. Despite a common belief, it is less typical that BMI overestimates fatness (although it certainly does, for example, in people such as bodybuilders).

Obesity in children and adolescents can be defined using BMI, but the cut-off points differ from those presented in Table 8.1. Cole et al. (22) have published international age- and sex-specific BMI cut-off points for overweight (85th percentile) and obesity (95th percentile) for children and adolescents between 2 and 18 years. Many countries also use specific age-adjusted growth charts (weight-to-height for a given age) to assess overweight and obesity.

Studies have found that ageing is associated with decreasing height, weight, and BMI (23, 24) along with a loss of muscle mass and a gain of body fat (30). These changes imply that optimal BMI might be different in older people compared to younger people. Several studies have found the BMI associated with the lowest age-adjusted mortality to be higher in elderly people when compared to recommendations for younger subjects (25–30). Unfortunately the data are inadequate to make any precise recommendations for optimal BMI among the elderly. Studies that relate BMI to functional ability have found both a high and a low BMI to be related to disability (31, 32). However, marked obesity is clearly associated with physical disability and difficulties in performing activities of daily living (33, 34).

The prevalence of adult obesity in the Nordic countries is shown in Table 8.2. These data were obtained from nationally representative surveys, but

the values themselves were self-reported. The prevalence of overweight (BMI between 25 and 29.9) is even higher than the prevalence for obesity. This means that roughly half of the adult population in Nordic countries is either overweight or obese. Because individuals tend to underreport their body weight, the actual prevalence of overweight and obesity is likely to be somewhat higher than shown in the table. Compared to the prevalence of obesity reported in NNR 2004, this condition has become more common in all Nordic countries.

Table 8.2. Prevalence (%) of adult obesity (approximately 25–64 years of age, BMI >30.0) in the Nordic countries as assessed from self-reported body weight

	Women	Men	Reference
Denmark	14.8	15.6	(21)
Finland	19.3	18.2	(22)
Iceland	19.4	19.4	(23)
Norway	22.1	21.0	(24)
Sweden	14	13	(25)

Abdominal obesity

Abdominal fat distribution is an indicator of intra-abdominal fat mass and can also be used as an indicator of obesity (35). Table 8.3. presents cut-off points for waist circumference as suggested by the National Institute of Health (36) and the WHO (15). Intra-abdominal fat mass, or abdominal fat distribution, can be even more strongly associated with metabolic disturbances than the total amount of body fat. The cut-off points are probably higher for elderly subjects (37, 38), but BMI values are interpreted without any age adjustments in all adults older than 18 years.

Table 8.3. Waist circumference (cm) and the risk of metabolic complications in adults (18–64 years)

Risk level	Women	Men
Low	≤79	≤93
Increased	80–87	94–101
High	≥88	≥102

Obesity, weight stability and health

Obesity, and to a smaller extent overweight, is associated with an increased incidence of several diseases (16). This meta-analysis found statistically significant associations between obesity and overweight and the incidence of type 2 diabetes, several types of cancers (breast, endometrial, colorectal, and kidney), cardiovascular diseases, asthma, gallbladder disease, osteoarthritis, and chronic back pain. The strongest association was found between obesity and type 2 diabetes.

According to epidemiological studies, stable weight is related to the lowest total mortality and weight gain is clearly related to increased mortality (39). Many epidemiological studies indicate that weight loss is also associated with increased mortality (e.g. (39–42). However, these data should be interpreted with caution because of difficulties in separating voluntary and involuntary (due to pre-existing disease) weight reduction. Moreover, epidemiological studies do not separate different techniques or rates of weight reduction or composition of lost body weight (43). Nevertheless, even a modest (5%–10% of body weight) weight reduction in high-risk individuals improves health (15). Weight cycling (weight reduction then increasing to previous weight) might have adverse effects on mortality and morbidity (44, 45), but the data do not provide compelling evidence for this (46) A 25-year study in Gothenburg, Sweden, has found an age-related decrease in body weight from the age of 70 years to 95 years of approximately 0.5–1.0 kg for every 5 years, and this effect is more pronounced in the highest quintiles of body weight (24).

Determinants of obesity and weight control

Weight gain is caused by a positive energy balance. Several retrospective and prospective population-based studies have evaluated factors related to obesity or weight gain. A systematic literature review examining the role of dietary macronutrient composition was carried out as part of the NNR 2012 process (47). The literature search covered the year 2000 to the present, and prospective cohort studies, case-control studies, and interventions were included. The literature search also provided the opportunity to review the role of food consumption and dietary patterns in predicting changes in weight or waist circumference.

The review (47) found probable evidence that high intake of dietary fibre and nuts predicted less weight gain and that high intake of meat predicted more weight gain. Suggestive evidence was found for a protective role against increased weight for whole grains, cereal fibre, high-fat

dairy products, and high scores on an index describing a prudent dietary pattern. Likewise, there was suggestive evidence for both fibre and fruit intake as a protection against increases in waist circumference. Suggestive evidence was found for high intake of refined grains, sweets, and desserts in predicting weight gain, and for refined (white) bread and a high energy density diet in predicting increases in waist circumference. The results of the literature search suggested that the proportion of macronutrients in the diet was not important in predicting changes in weight or waist circumference. In contrast, prospective cohort studies have shown that increased intake of fibre-rich foods and dairy products and a reduction in refined grains, meat, and sugar-rich foods and drinks are associated with a reduction in weight gain.

In a very recent meta-analysis, Te Morenga et al. (48) concluded that the intake of free sugars or sugar-sweetened beverages is a determinant of increasing body weight. These results give additional support for restricting sugar intake as a means to prevent obesity. In another meta-analysis from the same year, Chen et al. (49) did not find evidence that intake of dairy products prevented weight gain. These results are somewhat in contrast to the review by Fogelholm et al. (47). The discrepancies in the results might be related to different selection of studies; Chen et al. (49) scrutinized randomized trials, but Fogelholm et al. (47) examined cohort studies.

A major problem in assessing the grade of evidence was that similar combinations of exposure and outcome variables were quite rare in the literature making comparisons difficult (47). It was decided, therefore, to perform a *post hoc* evidence analysis by first combining the outcome variables (BMI and waist circumference). To increase the number of studies used for evidence grading, foods were grouped by their closeness in terms of nutrient composition. The results of these *post hoc* analyses are shown in Figure 8.1. These analyses suggest that a healthy diet in general (assessed using indices that describe the healthiness of dietary patterns) and fibre-rich foods are clearly associated with less weight gain. Dairy products are only to some extent associated with reduced weight gain. In contrast, meat, refined grains, and sugar-rich foods and drinks are associated with more weight gain.

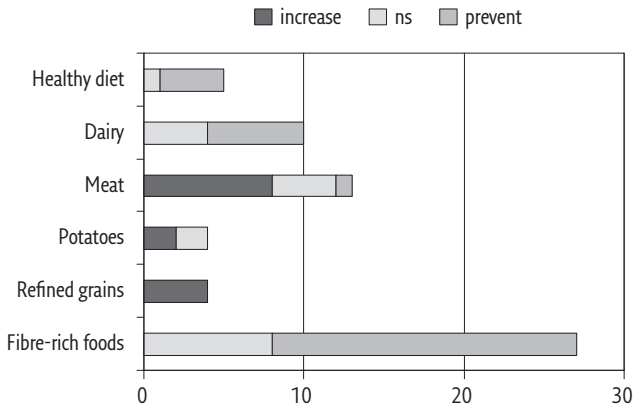


Figure 8.1. Evidence for association between grouped exposure variables against grouped outcome variables (BMI and waist circumference not separated) (47)

Low levels of physical activity are positively associated with obesity and age-related weight gain. Most studies have examined leisure activity, and data on occupational energy expenditure that have been adjusted, for example, to socioeconomic factors in relation to obesity are lacking. High levels of physical activity are also associated with less weight being regained after weight reduction (50). However, most of the above findings are observational and retrospective and the studies are still inconclusive as to whether physical activity can be regarded as a single predictor of weight control. Spontaneous physical activity corresponds to small, involuntary muscle movements, such as fidgeting, and might be related to weight control (51), but the data to support this are limited. Obesity is also associated with education level and socioeconomic status. The general trend is that higher social classes have a lower prevalence of obesity compared with lower social classes (52, 53).

Estimation of energy requirements

There are two main approaches to estimate total energy requirements. The first approach is the doubly labelled water (DLW) technique (54, 55) in which stable isotopes (^{2}H and ^{18}O) are administered orally. The isotopes are gradually eliminated from the body, ^{2}H through water and ^{18}O through water and CO_2. The difference between the elimination rates of ^{2}H and ^{18}O is related to CO_2 production and, therefore, to energy expenditure. This estimation of total energy expenditure is quite accurate provided that the

experimental and analytical conditions are appropriate. In theory, a large number of DLW measurements could be used as the basis to predict total energy expenditure by deriving equations that describe how total energy expenditure varies as a function of, for example, age, sex, and various anthropometric measures such as weight and body fat. There are several data sets with energy expenditures for a total of several hundred individuals assessed by DLW (56, 57) and pooled analyses (81). However, the populations in these studies were selected and the representativeness of these data cannot be guaranteed.

The second main approach to assess energy expenditure is the factorial method in which total energy expenditure is calculated from the resting (or basal) energy expenditure (REE) and a factor indicating PAL. DLW is more accurate in assessing individuals, but the factorial method provides more opportunity to generalize the results. Therefore, estimates of average energy requirements in NNR 2012 were determined using the factorial method.

Because of technical constraints on REE measurements, determinations of energy requirements are usually based on predicted REE. Table 8.4. shows prediction equations for REE as given by Henry (58). In the previous version of the NNR, the equations of Schofield et al. (59), WHO/FAO/UNU (60), and the Commission of the European Communities (61) were used. However, because a recent validation study has shown that the Schofield equations tend to overestimate REE (62, 63), the new and more accurate equations by Henry (58) have been used in this version of the NNR. The same decision was also made by EFSA in 2013 when formulating reference values for energy (64).

Table 8.4. Equations for calculating the average resting energy expenditure (REE, MJ/d) based on either body weight (W, kg) or a combination of weight and height (H, m) (58)

Age Year	REE MJ/d based on weight	REE MJ/d based on weight and height
Girls		
<3	0.246 W – 0.0965	0.127 W + 2.94 H – 1.20
3–10	0.0842 W + 2.12	0.0666 W + 0.878 H + 1.46
11–8	0.0465 W + 3.18	0.0393 W + 1.04 H + 1.93
Women		
19–30	0.0546 W + 2.33	
31–60	0.0407 W + 2.90	0.0433 W + 2.57 H – 1.180
61–70	0.0429 W + 2.39	0.0342W + 2.10 H – 0.0486
>70	0.0417 W + 2.41	0.0356 W + 1.76 H + 0.0448[a]
Boys		
<3	0.255 W – 0.141	0.118 W + 3.59 H – 1.55
3–10	0.0937 W + 2.15	0.0632 W + 1.31 H +1.28
11–18	0.0769 W + 2.43	0.0651 W + 1.11 H + 1.25
Men		
19–30	0.0669 W + 2.28	
31–60	0.0592 W + 2.48	0.0600 W + 1.31 H + 0.473
61–70	0.0543 W + 2.37	0.0476 W + 2.26 H – 0.574
>70	0.0573 W + 2.01	0.0478 W 0+ 2.26 H – 1.070[a]

[a] This equation covers all ages above 60 years.

Reference values for energy requirements in children and adolescents

Part of the energy intake of children and adolescents is used for growth, and their energy requirement per kg body weight is, therefore, higher than for adults. During the first four months of life, approximately 27% of the energy intake is used for growth. At the end of the first year of life, this amount decreases to approximately 5%; at age 1–3 years it decreases to approximately 3%; and in older children this value is less than 2% (65).

Reference values for energy requirements of children and adolescents should be based on their REE, their energy expenditure in response to physical activity, and their energy requirements for growth. These values should be consistent with the attainment and maintenance of long-term good health, including recommended levels of physical activity (66).

Age 1–12 months

The estimated energy requirement for infants is based upon the approach of FAO/WHO/UNU (1) where daily energy expenditure is calculated using DLW-derived equations (67) (Table 8.5.).

Table 8.5. Estimated average daily energy requirements (per kg body weight) for children 1–12 months assuming a mixture of breastfeeding and complementary foods (67)

Age months	Average daily energy requirements kJ/kg body weight	
	Boys	Girls
1	486	469
3	411	404
6	339	342
12	337	333

Some studies have shown that breast-fed infants have a lower energy intake than formula-fed infants (68–70), especially infants breast-fed for more than seven months, and that this results in less body weight gain from 6 to 10 months than in infants breast-fed for a shorter period (71, 72). The effect of the infant's food source on energy requirements was found to persist throughout the second year of life in one of the studies used as a basis for the estimated energy requirement (65). This was primarily because of a higher REE in formula-fed than in breast-fed infants (65) although varying digestibility might also play a role (73). However, the differences between feeding groups in terms of energy expenditure never exceeded 20 kJ/kg, and the current NNR gives a single energy requirement that is valid for both breast-fed and formula-fed infants.

Estimated average reference values for children and adolescents

The estimated daily energy requirements according to age for children and adolescents (Table 8.6.) are based on the factorial method. Thus, REE is first estimated using the equations of Henry (58) and daily energy expenditure is then calculated by multiplying REE by an appropriate PAL. Values for body weight related to age in the group aged 0–5 years are based on the mean of the reference values from Denmark (93), Norway (94), Sweden (74), and Finland (75). No values were available for 2–5 year olds in Finland so data for 3–5 year olds in Norway and the other Nordic values were used. Values for growth at school age show increasing weight-to-height ratios and an increased prevalence of overweight (76). This means that using current weight data would base the recommendations on an increasing prevalence of excess body weight. Therefore, values for 6–17 year olds are based on mean values from 1973–1977 (77). The situation is similar for

adults in which the energy requirements are based on a theoretical BMI of 23, not actual BMI data. In the US, the estimated energy requirements for children are based on the median weight and this is slightly higher than the reference weights used in the current NNR (78).

The increase in obesity over the past 30 years in Nordic countries might be leveling off. There are indications showing a decreasing, or at least a stable, prevalence of overweight and obesity among school children in the Nordic countries (79). However, the prevalence of these conditions among young children and adolescents is still high.

Children of the same age vary widely in body weight, particularly in the age groups where only a small fraction of the children have started puberty. The body weight of children of the same age and sex can differ by a factor of two. Therefore, the estimated energy requirement in a certain age group, as illustrated in Table 8.8., must be used with caution. Moreover, the calculated energy requirement for overweight children (>2 SD weight-to-height ratio) is too high when based on body weight because such children have a comparatively high body fat content and the energy requirement is primarily determined by the size of the FFM. Therefore, it is recommended that the energy requirement in overweight children should be based on the weight one SD above normal weight for height or on the weight corresponding to the cut-off value of overweight according to the International Obesity Task Force (15).

PAL values in the NNR2012 are based on a systematic review of the DLW studies that was carried out for the SACN (80) recommendations. The analysis showed no significant differences between the sexes, but did show an increased PAL with age. We have used the first quartile (25^{th} percentile) value as a cut-off for low vs. average activity, and the third quartile (75^{th} percentile) as the cut-off for average vs. high activity (Table 8.6.).

Table 8.6. Estimated daily energy requirements (MJ/d) for children and adolescents (from 2 to 17 years) using the Henry (2005) equations for REE and the physical activity levels from SACN (80)

Age years	Body weight kg	REE	Physical activity level[1]		
			Low	Average	High
Girls					
2	12.5	2.98	4.02	4.14	4.26
3	14.9	3.57	4.82	4.96	5.10
4	16.8	3.53	5.02	5.55	5.97
5	19.2	3.74	5.31	5.87	6.31
6	21.1	3.90	5.53	6.12	6.59
7	23.7	4.12	5.84	6.46	6.96
8	26.1	4.32	6.13	6.78	7.30
9	28.7	4.54	6.44	7.12	7.67
10	31.8	4.80	7.96	8.30	8.88
11	35.5	4.83	8.02	8.36	8.94
12	40.4	5.06	8.40	8.75	9.36
13	45.6	5.30	8.80	9.17	9.81
14	49.9	5.50	9.13	9.52	10.18
15	53.2	5.65	9.39	9.78	10.46
16	54.8	5.73	9.51	9.91	10.60
17	56.0	5.78	9.60	10.01	10.70
Boys					
2	13.2	3.23	4.35	4.48	4.61
3	15.4	3.79	5.11	5.26	5.41
4	17.3	3.77	5.35	5.92	6.37
5	19.4	3.97	5.63	6.23	6.71
6	21.4	4.16	5.90	6.52	7.02
7	24.8	4.47	6.35	7.02	7.56
8	26.5	4.63	6.58	7.27	7.83
9	29.1	4.88	6.92	7.66	8.24
10	32.2	5.17	8.58	8.94	9.56
11	35.3	5.14	8.54	8.90	9.52
12	39.1	5.44	9.03	9.41	10.06

13	43.5	5.78	9.59	9.99	10.68
14	49.2	6.21	10.31	10.75	11.49
15	55.1	6.67	11.07	11.53	12.33
16	60.0	7.04	11.69	12.19	13.03
17	63.6	7.32	12.15	12.67	13.54

[1] Physical activity levels (low, average, high) by age group. 1–3 y: 1.35, 1.39, and 1.43; 4–9 y: 1.42, 1.57, and 1.69; 10–18 y: 1.66, 1.73, and 1.85.

Reference values for energy requirements in adults

The reference values for energy requirements in adults are based on estimates of REE and PAL. Energy requirement is equivalent to the product of REE and PAL. RMR can be calculated from the prediction equations that are presented in Table 8.1., and the PAL values (Table 8.4.) are estimated generalisations (average values) based on studies using DLW. By using more detailed information on daily physical activity (time spent in different activities) and the respective MET values (14), PAL can be approximated for an individual as the daily time-weighted average MET value (Tables 8.7.and 8.8.). For instance, in Table 8.8., an active day is assumed to consist of 8 h rest (mostly sleep), 10 h very light activity (mostly sitting, sometimes standing), and 2 h light activity (e.g. slow walking, cooking, etc.). In addition, the day consists of 1 h moderate activity (e.g. brisk walking) and 1 h vigorous activity (e.g. playing football). To calculate PAL, the MET values of different activity levels are multiplied by the time spent in the corresponding activity divided by 24. Daily energy expenditure is calculated by multiplying PAL by the REE.

Table 8.7. Physical activity level expressed as multiples of the resting energy expenditure according to different levels of occupational and leisure activity (modified from Black et al. (81))

	PAL
Bed-bound or chair-bound (not wheelchair)	1.1–1.2
Seated work with no option of moving around and little or no leisure activity	1.3–1.5
Seated work with some requirement to move around, and with some leisure activity	1.6–1.7
Work including both standing and moving around (e.g. housework, shop assistant) OR seated work with some requirement to move around with regular, almost daily, leisure activity	1.8–1.9
Very strenuous work or daily competitive athletic training	2.0–2.4

Note 1 Moderate leisure physical activity (e.g. brisk walking): 0.025 PAL unit increase for each hour per week.
Note 2 Strenuous leisure physical activity (e.g. running, competitive football): 0.05 PAL unit increase for each hour per week.

Table 8.8. Two examples of how to estimate daily physical activity levels from data on physical activity

		Very inactive day		Active day	
Intensity of Activity (MET)		Time, h	MET × h	Time, h	MET × h
Rest	(1.0)	10	10	8	8
Very light	(1.5)	12	18	10	15
Light	(2.0)	2	4	4	8
Moderate	(5.0)	0	0	1	5
Strenuous	(10.0)	0	0	1	10
Total		24	32	24	46
PAL			1.33		1.92

Explanation. The time spent in different activities is multiplied by the respective metabolic equivalent value (MET value). To obtain the daily physical activity level (PAL), the sum of daily MET × h is divided by 24. Hence, PAL is the weighted average of daily MET × h. Daily energy expenditure is calculated by multiplying PAL by the resting (or basal) energy expenditure.

An average PAL for adults in Nordic countries is assumed to be around 1.6, which is compatible with sedentary work and some physical activity (56, 57). A totally sedentary lifestyle (PAL 1.4–1.5) is associated with health risks that might be equal to the risk associated with marked obesity (BMI 30–35) or regular smoking. These health risks are offset by approximately 3–4 hours per week moderate physical activity or 2 hours per week of more strenuous leisure-time physical activity (82), which would mean an increase of only 0.1 PAL units. However, it is likely that a PAL of roughly

1.8 would be more optimal for overall health. This level was close to the 75th percentile in the large data sets of Tooze et al. (56) and Mosghfegh et al. (57). This PAL is approximately the same as that observed in moderately active prepubertal children (83). Strenuous athletic training can increase energy requirements to PAL 2.0–2.5 and in extreme cases even up to 4.0 (84, 85). However, it is rare for physical exercise to increase energy requirements by more than 20% compared to energy expenditure during normal daily living. PAL 1.4 is used as the level indicating physical inactivity, and this level is close to the 15th percentile in larger population samples (56, 57).

Table 8.9. shows reference weights based on population data in Denmark, Finland, Iceland, and Sweden. Because of the high prevalence of overweight and obesity, population weights cannot be used directly to estimate reference weights because then the reference energy needs would support the maintenance of overweight and obesity. Therefore, the reference weight needs to be adjusted to a theoretical situation in which all individuals are at normal weight. In the NNR 2012, the reference weight was calculated by using population-based data on height to estimate an age-adjusted weight corresponding to BMI 23. This arbitrary BMI was used to indicate healthy weight. The precise mean point within the WHO normal body weight range (BMI 18.5 to 24.9) would have been BMI 21.7. Because the actual mean BMIs of the populations in all Nordic countries are clearly higher, BMI 23 was chosen as more realistic but still within the normal BMI range. The principle difference in the new recommendations compared to the previous NNR is that in the previous NNR the weight for all overweight and obese individuals was reduced to correspond to BMI 25. The new reference weight is slightly higher for the youngest age group and lower for the oldest age group.

Table 8.9. Reference weights (kg) from Nordic countries calculated as the weight for height corresponding to BMI 23

	Denmark[a]	Finland[b]	Iceland[c]	Sweden[d]	Mean
Men, age in years					
18–30	77.5	73.2	77.2	73.7	75.4
31–60	75.2	72.2	75.5	74.8	74.4
61+	72.0	69.1	74.1	73.0	72.1
Women, age in years					
18–30	65.5	63.1	64.2	65.0	64.4
31–60	64.6	61.7	64.5	63.8	63.7
61+	62.2	58.9	63.3	62.7	61.8

Data sources: [a] (86); [b] (87); [c] (88) [d] (89).

Table 8.10. shows the average estimates of daily energy requirements for men and women with respect to age, different activity levels, and reference weight (Table 8.9.). The values in Table 9.10. are estimations assuming that all individuals have BMI 23. It should be noted that these estimations have a large standard error due to imprecision in both estimation of REE and of PAL. Therefore, the results should be used only for estimations on the group level. In particular, the data for the oldest age group in Tables 8.9. and 8.10. should be used with special caution. Compared to the reference energy requirements in the previous version of the NNR, the new values are lower because the REE equation uses a slightly lower predicted REE and the reference weights have been calculated differently. Due to the age-related weight changes among healthy elderly individuals, 0.5–1.0 kg should be subtracted from the average weights in Table 8.9. for every 5 years above the age of 75.

Table 8.10. Reference energy requirements (MJ/d) in adults based on Nordic reference weights (Table 8.9.) and different activity levels

Age, years	Reference weight, kg[a]	REE, MJ/d[b]	Sedentary PAL[c] 1.4	Average PAL 1.6	Active PAL 1.8
Men					
18–30	75.4	7.3	10.3	11.7	13.2
31–60	74.4	6.9	9.6	11.0	12.4
61–74[d]	72.1	6.1	8.5	9.7	10.9
Women					
18–30	64.4	5.8	8.2	9.4	10.5
31–60	63.7	5.5	7.7	8.8	9.9
61–74[d]	61.8	5.0	7.1	8.1	9.1

[a] Reference weight corresponds to BMI 23.
[b] REE = Resting Energy Expenditure, estimated from the equations of Henry (2005).
[c] PAL = Physical Activity Level.
[d] The REE for 61–74 year olds was calculated with the equation for 61–70 year olds.

Reference values for energy requirements are based on assumptions regarding weight stability, normal (healthy) weight, and energy balance. However, these assumptions are not always valid. For instance, a negative energy balance is needed for the treatment of obesity. If energy intake is 2.1 MJ/d below the requirement for energy balance, the estimated weight reduction during the first month is approximately 500 g/week. This rate of weight loss is often recommended although a larger negative energy balance (up to 4.2 MJ/d) leading to a weight loss of 1000 g/week still seems to be compatible with a healthy weight reduction (8, 90). The long-term estimation (several months to years) of weight loss due to a fixed reduction in energy intake is much more complicated (91). The reason for this is that energy expenditure decreases with weight loss. Hence, with increasing weight reduction the energy deficit decreases (same intake but less expenditure). Therefore, the 500 g/week weight loss for each 2.1 MJ (500 kcal) reduction in energy intake cannot be used for anything other than predicting initial weight reduction.

The energy requirement for an individual with weight and physical activity different from the values presented in Tables 8.9. and 8.10. can be calculated as follows. First, the RMR is estimated using the appropriate equation in Table 8.4. PAL is then estimated either from Table 8.7. or using the calculation shown in Table 8.8. Finally, the energy requirement

is calculated as RMR × PAL. It should be noted, however, that RMR as well as PAL tend to be imprecise and it is indeed possible to misjudge the daily energy requirement by at least 2 MJ.

Energy requirement during pregnancy

The requirement for energy during pregnancy is based on estimates of weight gain during gestation and the composition of that gain in terms of fat and protein. Hytten and Chamberlain (92) studied reproductive outcomes in healthy women and concluded that a weight gain of 12.5 kg was associated with the best reproductive outcome in mother and infant (92) This value is lower than average values for weight gain in pregnancy in the Nordic countries, and the US Institute of Medicine (IOM) (93) has extended the recommendation of weight gain in pregnancy by taking varying pre-pregnancy weight into consideration.

Pregnant women are in an anabolic dynamic state throughout gestation, and this creates additional needs for energy. Forsum and Löf described the partitioning of energy metabolism in the pregnant versus the non-pregnant state (94). According to Butte and King (67), "The energy requirement of a pregnant woman is the level of energy intake from food that will balance her energy expenditure when the woman has a body size and composition and level of physical activity consistent with good health". The energy requirement of pregnant women includes the energy needs associated with the deposition of tissues consistent with optimal pregnancy outcome (67). The energy cost in pregnancy is due to the foetus, placenta, and amniotic fluid as well as the weight gain of the uterus and breasts and increased volumes of blood, extracellular water, and adipose tissue (95).

In 2004, FAO/WHO/UNU published recommendations for energy intake by pregnant women based on a 12.0 kg weight gain during gestation (3). Butte and King (67) modified these figures for women gaining 13.8 kg, a figure in better agreement with values observed for Scandinavian women. The calculations were based on two approaches (1, 67). The first was a factorial approach using estimates of the energy costs due to changes in the resting energy expenditure (REE) and the cost of tissue deposition along with separate estimates for the amount of energy retained and the cost of synthesis associated with this retention. The second approach was based on the increment in total energy expenditure (TEE) and estimates of the amount of energy retained. The two calculations gave similar results for the complete pregnancy (374 and 369 MJ for the first and second alterna-

tive, respectively) but differed with respect to the increase in requirements during the three individual trimesters. The average of the two calculations (430, 1375, and 2245 kJ/24 hours during the first, second, and third trimester, respectively) is considered to represent the additional need for energy during the three pregnancy trimesters, and these are the recommended energy intake values during the three trimesters. A comparison between NNR 2004 and the new recommendations is shown in Table 8.11.

Table 8.11. Additional daily energy requirement during pregnancy: comparison between NNR-2004 and the new recommendations

	NNR 2004	NNR 2012
1st trimester	Value not given	430 kJ (103 kcal)
2nd trimester	350 kcal	1375 kJ (329 kcal)
3rd trimester	500 kcal	2245 kJ (537 kcal)

An additional aspect that should be considered is the potential decrease in energy needs due to a decrease in physical activity during pregnancy. This is a complicated issue where definite answers cannot be provided. Studies have shown that Swedish pregnant women do (96) or do not (97) "save energy" by such a decrease. Thus, as stated by Prentice et al. (98), it cannot be assumed that a high proportion of the energy costs of pregnancy are normally or automatically met by reductions in physical activity.

There is great variation among women regarding the amount of weight gained during pregnancy. Positive associations between this gain and the health of both baby and mother have been observed. However, a very large weight gain is a health risk both for mother and child, especially among women who were overweight or obese prior to pregnancy (e.g. an increased risk for breast cancer in the mother, spontaneous abortion, gestational diabetes, and gestational hypertension) (99, 100). If weight gain during pregnancy is too small, the risk for a low birth weight baby is increased because weight gain in pregnancy is positively correlated to infant size at birth (100). Low birth weight increases the risk for health complications in early life and has been found to be related to increased risks of adult diseases such as coronary heart disease, hypertension, and type 2 diabetes (100–103).

Weight gain during pregnancy among women in the Nordic countries is, on average, 14–16.5 kg (100, 104–107). The average birth size in the

Nordic countries is high (>3500 g), the highest is in Iceland and the Faeroe Islands, and has been increasing for full-term babies in all the Nordic countries in recent years (108). Values on weight gain during pregnancy have been reviewed, and in 2009 the IOM published guidelines with recommended gestational weight gains for women having different BMIs before conception (109). These are the values now recommended by NNR for Nordic women (Table 8.12.). The median value of the recommended weight gain range for women who were normal weight before pregnancy (11.5–16 kg) is the same asthe value of 13.8 kg used by Butte and King (67) when calculating energy requirements during pregnancy.

Table 8.12. Weight gain during pregnancy as recommended by the Institute of Medicine (109)

BMI (kg/m_2) before conception	Recommended weight gain (kg)
<18.5 (underweight)	12.5–18
18.5–24.9 (normal weight)	11.5–16
25.0–29.9 (overweight)	7–11.5
>30.0 (obese)	5–9

In recent years the importance of foetal nutrition has attracted a significant amount of interest. Studies in humans as well as in experimental animals suggest that the supply of energy and nutrients during this very first part of life is related to health later in life. Furthermore, studies have shown that the nutritional situation of the woman before conception is also important and, as indicated above, in the US the recommended weight gain during pregnancy varies according to the pre-pregnancy BMI of the woman. In fact, recent recommendations, also from the US (109), emphasize that "all women should start pregnancy with a healthy weight", i.e. with a BMI between 18.5 and 24.9. A recent systematic literature review (110) shows that insufficient data are available regarding health outcomes of intended weight loss as a result of dieting prior to conception. It is conceivable that such weight loss might be associated with harmful effects, for example impaired iron and folate status during subsequent pregnancies and a risk for developing eating disorders.

Overweight and obesity is common among Scandinavian women of reproductive age, and this is a serious concern because the pre-pregnancy BMI is a strong predictor of many adverse outcomes of pregnancy (109).

Therefore, it is important that every effort is made to avoid overweight and obesity in women of reproductive age. However, although overweight and obesity are presently the most common nutritional problems in Scandinavian women it should be emphasized that low BMI and insufficient weight gain do occur in some women and are associated with increased health risks for their offspring.

Energy requirement during lactation

The additional energy requirement during lactation is based on estimates of the energy costs for milk production and an estimate of the amount of energy mobilized from the body's energy stores. During pregnancy there is a physiological retention of body fat that, to some extent, can be mobilized postpartum. Thus the energy needs during lactation are dependent on the nutritional status of the mother during pregnancy. According to Butte and King (67), "The energy requirement of a lactating woman is the level of energy intake from food that will balance her energy expenditure when the woman has a body size and composition and a breast milk production which is consistent with good health for herself and her child and that will allow for desirable physical activity".

According to international recommendations (1, 67), energy requirements during lactation for women in developed countries are based on an average milk production of 749 g every 24 hours. Breast milk is considered to contain 2.8 kJ/g and to be produced with an energy efficiency of 80% (95). For partial lactation, the breast milk production is assumed to be 492 g every 24 hours. Table 8.13. shows the energy cost of lactation for women in developed countries during different time periods postpartum (1, 67). These costs should be added to the energy requirement of the non-pregnant and non-lactating woman, and they can be covered by an increased intake of dietary energy or partly covered by mobilized body fat. This contribution of body fat to the energy costs of lactation has been estimated to be, on average, 0.72 MJ every 24 hours during the first six months of lactation. However, the variation between individual women is considerable. A large individual variation is certainly also present with respect to the milk production figures given above. There are no data showing that lactating women decrease their physical activity to "save energy" for milk production. However, because of a risk for weight gain after pregnancy (111), it is recommended that lactating women increase rather than decrease their amount of physical activity.

Table 8.13. Energy cost of milk production (MJ/24 hours) for women in developed countries during exclusive and partial breastfeeding (67)[1]

Months post partum[2]	0–2	3–5	6–8	9–11	12–23
Exclusive breastfeeding	2.49	2.75	2.81	3.15	–
Partial breastfeeding	2.24	2.40	2.07	1.53	1.57

1 These costs can be covered by an increased intake of energy from food or by mobilized body fat (0.72 MJ/24 hours on average) during the first six months of lactation.
2 Scandinavian women are recommended to breastfeed exclusively during the first six months postpartum and then breastfeed partially at least until the child is one year old.

The increased prevalence of overweight and obesity among Scandinavian women is also a potential problem during lactation because it has been shown that obese and overweight women tend to have a less successful lactation than normal-weight women (112). Furthermore, there are data from Danish women showing that breastfeeding promotes postpartum weight loss (113). However, this effect is rather weak and it is quite possible to gain weight during lactation if the energy balance is positive, i.e. too much energy from food and/or too little physical activity. A Swedish study showed that dietary advice to overweight and obese lactating women could effectively promote weight loss after pregnancy (114). It is important to stress, however, that breastfeeding is an energy-demanding process and for many lactating women a considerably increased energy intake is recommended.

Energy requirements in the elderly

Daily energy expenditure tends to decline with age (115, 116) mainly due to decreased FFM (117, 118) and decreased physical activity (119, 120). REE is strongly related to FFM, which consists mainly of muscle and organ mass (121). The decrease in REE is not fully explained by the age-related decrease in FFM (122), and Pannemans et al. (115) found that 80% of the variation in REE in elderly subjects was explained by FFM.

Longitudinal (123–125) and cross-sectional (82, 126, 127) studies have found an age-related decrease in REE, but knowledge about daily energy expenditure in the elderly (>75 years) is limited (82). A Swedish study found that the REE among 91–96 year olds was not different from the REE among 70–80 year olds (128), and a US study found a 27% lower REE in very old individuals compared to 60–74 year olds (129). However, a longitudinal follow-up of the 73 year olds at age 78 showed a decrease

in REE as well as TEE but not in active energy expenditure (AEE) (130). The PAL values in the above individuals averaged 1.74 at both ages (73 years and 78 years) indicating a physically active lifestyle for this age group (130). DIT does not seem to be affected by age (127).

A review including 24 studies with measured REE in healthy elderly (mean age 70.6 ± 5.1 years, mean body weight 72.4 ± 6.0 kg, and mean BMI 25.6 ± 1.5) found the mean of the weight-adjusted REE to be about 80 kJ/kg body weight in both males and females, and this value was not significantly different from a group of sick elderly patients (131). The measured PAL obtained from 24 h TEE relative to the REE was 1.66 ± 0.11 among the healthy elderly.

Low energy intake

Lowenstein (132) has suggested a reference value of 1500 kcal/d – corresponding to approximately 6.5 MJ/d – as the minimum daily energy intake necessary for providing an adequate intake of micronutrients from an ordinary diet. In the NNR, *very low energy intake is defined as an energy intake below 6.5 MJ/d*, and an energy intake of 6.5–8 MJ is considered a *low energy intake* with increased risk of an insufficient intake of micronutrients.

A very low energy intake is related to a very low PAL and/or to a low body weight. Low body weight is related to low muscle mass and, therefore, to low energy expenditure. The age-related decrease in energy expenditure might result in a very low energy intake, and such low intakes are also found among people on slimming diets and among subjects with, for example, eating disorders or food intolerances.

Among healthy subjects, very low habitual energy intakes are probably rare – even among sedentary elderly subjects the estimated daily energy requirement is only 7–8 MJ, see Table 8.12. However, with lower body weight among the sedentary elderly, energy intake might become critically low.

Intake of most micronutrients is positively associated with energy intake and, consequently, habitually low energy intake is associated with low nutrient intake. In dietary surveys, the reporting of energy intake is often biased by a widespread underreporting that is independent of age, especially among women and overweight/obese subjects. Thus, it is difficult to explore the consequences of low energy intake on nutritional status based on low-energy *reporters*.

Among elderly subjects, low reported energy intakes were not associated with biochemical signs of nutritional deficiencies (133, 134). This

somewhat surprising result might be explained by underreporting (thus true intakes are higher) or that recommended biochemical levels are already reached at lower intakes than expected. Among elderly Europeans (133), it was not possible to establish a level of reported energy intake that ensured an adequate supply of iron, thiamine, riboflavin, or pyridoxine. At a reported intake of 8 MJ per day, 13% of men and 16% of women still had an inadequate intake of at least one of these four micronutrients.

Energy content of foods

Calculation of energy content

The energy in foods available for metabolism – i.e. the metabolizable energy – is determined by the energy content of the food as assessed in the laboratory by measuring the heat produced when its organic components are fully oxidized. Not all energy in a food item is available to humans, and its energy value must be corrected for losses due to insufficient absorption and, in the case of protein, also for incomplete oxidation and for losses as urea in urine. Accurate calculation of the metabolizable energy content in foods requires knowledge of the foods' macronutrient content as well as of the digestibility of these macronutrients. Because the energy content and the digestibility of each macronutrient vary between foods, it is convenient to use standardised factors based on the energy content and digestibility of macronutrients representing the composition of an average mixed diet.

Due mainly to historical background and tradition, there are different standard factors that differ slightly from each other. In the NNR, the energy content of a mixed diet is calculated based on 17 kJ/g protein and available (glycaemic) carbohydrate and 37 kJ/g fat. Alcohol (ethanol) is considered to yield 29 kJ/g. In kcal, these standard factors are 4 kcal/g protein and carbohydrate, 9 kcal/g fat, and 7 kcal/g alcohol. Note that these numbers include some errors caused by rounding off from kilojoules. To transform values between the two systems of units, the following relationships are used: 1 kcal = 4.2 (or 4.184) kJ and 1 kJ = 0.24 (or 0.239) kcal. These standard factors are not intended for calculating the metabolizable energy content in individual food items because the heat of combustion as well as the digestibility vary slightly between macronutrients from different foods. In a mixed diet, however, these variations balance each other and the standard factors have been shown to be accurate. Specific factors for calculating energy content in individual food items have been presented (135, 136).

As pointed out in chapter 9.1.3, the energy content of foods is not fully available to cover human energy requirements. Large differences exist in the amounts of energy available from different macronutrients because their metabolism *per se* requires different amounts of energy. The postprandial rise in energy expenditure is highest for proteins (about 20% of the energy content), lower for carbohydrates (about 10%), and lowest for fat (about 5%) (9, 10). In addition, the absorption of macronutrients varies among individuals and is dependent on the specific foods eaten, how they are prepared, and intestinal factors (91).

Carbohydrates and fibre

The values for carbohydrate that are shown in food composition tables are in many cases determined by means of the 'difference method' that defines total carbohydrate as the difference between the total dry matter and the sum of protein, fat, and ash. These values include digestible mono-, di-, and polysaccharides (starch) as well as non-digestible carbohydrates such as lignin and organic acids. The glycaemic or 'available' carbohydrates represent total carbohydrates minus dietary fibre, and are the sum of the total amounts of sugars and starch.

The heat of combustion of glycaemic carbohydrates is slightly lower for monosaccharides than for disaccharides and even higher for polysaccharides (136). However, these differences can be disregarded in most practical situations. When total carbohydrate is analysed 'by difference', available carbohydrate and dietary fibre are considered to contribute with the same amount of metabolizable energy. The energy content will, therefore, be overestimated in diets containing high amounts of dietary fibre if the calculation is based on a carbohydrate content assessed 'by difference'.

In diets containing up to 30 g fibre per day, standard energy factors can be used without significant consequences for the calculated metabolizable energy content of the diet (137). In fact, dietary fibre contributes only a small amount of such energy because its components are, to some extent, fermented in the colon. End products in this process are short-chain fatty acids that can be absorbed and metabolized and thus contribute to the metabolizable energy of the diet. The magnitude of this contribution depends on the type of fibre, but 8 kJ (2 kcal)/g has been suggested as an average value (135, 138). In regulations for specifying the nutritional content of foods, the energy content of fibre is considered to be zero, and dietary fibre is not considered to contribute to the metabolizable energy of diets in the NNR. However, the Codex Alimentarius Commission as well as current

suggestions for revisions of the European Nutrition Labelling Directive, propose that dietary fibre should be given an energy factor of 8 kJ/g.

The digestibility of carbohydrate varies from 90% in fruits to approximately 98% in cereals. The digestibility of flour depends on the fractions included, i.e. the digestibility decreases with a higher content of fibre.

Protein

Protein is not completely oxidized in the body. Therefore, when calculating the metabolizable energy content of protein incomplete digestibility as well as urea losses in the urine must be considered. The digestibility of protein is lowest in legumes (78%) and highest in animal products (97%) (135, 136).

Fat

The heat of combustion for dietary fat is a function of the fatty acid composition of the triglycerides in the diet and the proportion of other lipids in the diet. On average, the digestibility of dietary fat is considered to be 95% in most foods (135, 136).

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9 Physical activity

Recommended minimum physical activity in addition to normal daily activities.		
	Minutes per week	*Intensity*
Adults	150 or	Moderate
	75	Vigorous
	Minutes per day	
Children and adolescents	60	Moderate to vigorous
All	Reduce sedentary behaviour	

Introduction

There is a lack of data for making direct comparisons of past and present levels of energy expenditure and physical activity among different populations, and differences in definitions of physical activity across studies usually preclude meta-analyses of the existing data. However, both the average weight and the percentage of women and men in the Nordic countries who are overweight/obese have increased in recent decades (1–4) even though energy intake in the adult population has remained relatively stable from the mid-1970s until 1997 (5;6). However, many nutritional studies are affected by under-reporting of energy-dense foods that are high in fat and sugar. Nevertheless, this suggests that the level of physical activity among Nordic populations has been decreasing. Furthermore, Church et al estimated that the average daily occupational-related energy expenditure has decreased by more than 100 kcal (420 kJ) over the last 50 years, and they suggested that this could account for a significant proportion of the average weight gain over the same period (7). This trend is likely due to structural changes in society that might have resulted in a decrease in overall physical activity in daily life. As a result, large segments of the population can be characterized as physically inactive. Indeed, objective

measurements of physical activity in both Sweden and Norway show that adults and older people spend the vast majority of their time being sedentary and that adherence to physical activity recommendations is low (8). However, trend data from high-income countries indicate that leisure-time physical activity has increased among adults while occupational physical activity has decreased (9).

The understanding of how physical activity and insufficient physical activity is associated with health outcomes has increased considerably over the past decades. Epidemiologic research, clinical interventions, and mechanistic studies have contributed to the evidence that physical activity is essential to preventing disease, improving health, and improving quality of life. The reference list in this chapter includes several key references but does not intend to cover the entire body of literature regarding the effects of physical activity.

Physical activity in the prevention of various diseases

The effect of insufficient physical activity on the global burden of major communicable diseases has been quantified (13). According to conservative estimates, insufficient physical activity causes 9% of premature mortality and more than 5 million deaths a year worldwide. The risk factor of being inactive is, therefore, similar to established risk factors such as smoking and obesity (13).

Cardiovascular disease, metabolic syndrome, and type 2 diabetes

Several studies have shown an inverse relationship between physical activity (14–19) or physical fitness (20–23) and coronary heart disease (CHD) in both genders and in different age groups. People who are sedentary run twice as great a risk of developing CHD as those who are physically active (24). This is probably an underestimation due to the dilution of relative risk (25). A study from Norway (26;27) found that women and men below the median peak oxygen uptake (<35.1 mL $O2 \cdot kg^{-1} \cdot min^{-1}$ and <44.2 mL $O2 \cdot kg^{-1} \cdot min^{-1}$, respectively) were five and eight times more likely to have a cluster of cardiovascular risk factors compared to those in the highest quartile of peak oxygen uptake (≥40.8 mL $O2 \cdot kg^{-1} \cdot min^{-1}$ and ≥50.5 mL $O2 \cdot kg^{-1} \cdot min^{-1}$ in women and men, respectively). Each 5 mL $O2 \cdot kg^{-1} \cdot min^{-1}$ lower peak oxygen uptake corresponded to ~56% higher odds of cardiovascular risk factor clustering.

A study by Stensvold and colleagues (28) showed that individuals with

Box 9.1. Definitions

Physical activity is a comprehensive concept that encompasses many terms related to movement of the body. It is defined as any bodily movement achieved by contraction of skeletal muscles that increases energy expenditure (EE) above resting levels (10).

Physical inactivity is insufficient physical activity and is defined as a failure to meet the current recommendations.

Sedentary behaviour refers to any waking activity characterized by an energy expenditure ≤ 1.5 metabolic equivalents and a sitting or reclining posture (11). In general, this means that any time a person is sitting or lying down they are engaging in sedentary behaviour. Common sedentary behaviours include TV viewing, video game playing, computer use (collectively termed "screen time"), driving automobiles, and reading.

Exercise is any planned, structured, and repetitive bodily movement carried out to improve or maintain one or more components of physical fitness.

Physical fitness is a set of attributes related to the ability to perform physical activity and is something that people "have" or "strive to achieve" (12). The term includes cardiorespiratory fitness, strength, coordination, flexibility, etc.

Cardiorespiratory fitness relates to the ability of the circulatory and respiratory systems to supply and utilize oxygen during sustained physical activity (12).

MET (metabolic equivalent) is a unit used to estimate the metabolic cost (oxygen consumption) of physical activity. One MET equals the resting metabolic rate and corresponds to approximately 3.5 mL $O2 \cdot kg^{-1} \cdot min^{-1}$.

Light intensity activity is defined as activity corresponding to an EE between 1.5 to 3 METs such as standing or walking slowly (<3.5 km/h).

Moderate intensity physical activity is defined as activity that requires three to six METs.

Vigorous intensity physical activity is activity requiring more than 6 METs (8;12).

Muscle-strengthening/resistance training is exercise designed to increase strength and power.

Endurance training is repetitive, dynamic use of large muscles (e.g. swimming, walking, or bicycling).

the metabolic syndrome (a clustering of risk factors for cardiovascular disease) had an increased risk of premature mortality from cardiovascular causes (hazard ratio 1.78, 95% CI 1.39–2.29) compared with the risk in healthy counterparts. Additionally, those with the metabolic syndrome who reported being highly active had about a 50% reduced risk of cardiovascular mortality compared to inactive individuals with metabolic

syndrome. The study also showed that, compared to insufficient physical activity, even low levels of physical activity were associated with reduced cardiovascular mortality.

There is sufficient evidence to clearly establish a dose-response association between physical activity and fitness and CHD morbidity and mortality (29;30). Paffenbarger et al demonstrated that those who had an extra energy expenditure on activities of at least moderate intensity corresponding to approximately 500–1000 kcal per week had a 22% lower mortality compared to a group who were sedentary (31). Leon et al. showed that people who were regularly physically active for 30 minutes a day during their leisure time, corresponding to an energy expenditure of 150 kcal (630 kJ), had a 36% lower risk of dying from CHD after adjustment for other important CHD risk factors (17). One study found that a weekly energy expenditure of 2000 kcal might represent a threshold, at least for the risk of heart attack in men (32). Interestingly, Lee et al. (33) showed that apparently healthy elderly men who exercised one to two times per week (so-called "weekend warriors"), had a ~60% lower risk of all-cause mortality compared with sedentary, apparently healthy men. In addition, a dose-dependent association has been indicated, suggesting an additional benefit among those who attain an even higher activity level (29). A Norwegian study (34) found that a single weekly bout of exercise of high intensity reduced the risk of cardiovascular death, both in men (~40%) and women (~50%), compared with those who reported no activity. In contrast to studies of male college graduates, in which mortality from ischaemic heart disease was gradually reduced with increasing energy expenditure from 500 to 3500 kcal per week (35), no additional benefits were found to be associated with as many as four high-intensity sessions per week compared with a single weekly bout (34).

Some studies have suggested that physical activity and cardiovascular fitness have independent effects on overall mortality (36;37), but these associations appear to be complex. In one recent study, Lee et al (38) found that the preventive effect of following the guidelines for physical activity was completely attenuated when adjusting for fitness. This meant that the protective effect was confounded by high or low levels of fitness. In contrast, Hein and colleagues found that men who were inactive and highly fit had similar mortality rates from ischaemic heart disease as men who were inactive and unfit, while men who were active and unfit were protected compared to those who were inactive and unfit (20). Although further studies are needed to examine the combined effects of activity

and fitness on morbidity and mortality and whether fitness modifies the association between activity and mortality, the scientific evidence to date is consistent in suggesting that being physically active provides protection against all-cause mortality and cardiovascular disease regardless of fitness level.

Physical activity/physical fitness and metabolic risk factors

Regular physical activity and high levels of physical fitness are favourably associated with plasma lipid levels (triglycerides, HDL-, and LDL-cholesterol) (39) (40) blood pressure (41), insulin sensitivity (42), haemostasis/fibrinolysis (39;43), and endothelial function (44). Increased physical activity has the potential to influence all of these factors in a favourable manner at the same time. The "effect size" and the amount of physical activity needed to improve these factors are not fully understood, but some data in this regard are available for plasma lipids, blood pressure, and insulin sensitivity.

The average expected changes in lipids and lipoproteins following exercise are an increase in HDL-cholesterol of 4.6%, a reduction in LDL-cholesterol of 3.7%, and a reduction in triglycerides of 5% (45). There is also evidence of a beneficial effect on LDL sub-classes (40). The baseline levels of these metabolic risk markers strongly influence the effect of physical activity, and greater beneficial effects are seen in those with poor lipoprotein profiles. The improvements are probably more related to the amount of activity and not to the intensity of the activity or to improvement in cardiorespiratory fitness (40).

A meta-analysis of randomised controlled trials has shown that the effect of exercise on systolic/diastolic blood pressure reduction is on average 3/2 mm Hg in normotensive and 8/6 mmHg in hypertensive individuals (41). Engaging in moderate intensity physical activity 3 to 5 times per week with a duration of 30–60 minutes appears to be effective in reducing blood pressure. There is strong scientific evidence that regular physical activity has a beneficial effect on insulin sensitivity (42;46). Prospective studies have shown that regular physical activity brings about a linear decrease in the age-adjusted risk of developing type 2 diabetes (47–49). Importantly, the protective effect is also independent of general and central adiposity (50). The decrease in risk is on the order of 6% for each 500 kcal expended in physical activity during weekly leisure time (49). It appears that those who are at greatest risk of developing type 2 diabetes benefit the most from regular physical activity (48).

Overweight and obesity

Physical activity has profound effects on body composition and metabolism. It increases EE and helps to maintain and increase muscle mass, and this might result in an increased basal metabolism and an increased capacity for mobilising and burning fat both while using the muscles and while resting (51;52). Thus, regular physical activity is likely to be of importance in long-term regulation of body weight. However, there is limited evidence of a prospective association between physical activity and later body weight, and the association might be bi-directional. Regular physical activity is important for obese people because health benefits can be achieved through improved physical fitness regardless of whether or not weight loss occurs (53). The mortality and morbidity related to being overweight are substantially reduced in people who, despite being overweight, are physically fit (30;54;55). However, in a systematic review by Fogelholm it was concluded that having a high body mass index (BMI), even with high levels of physical activity, was a greater risk factor for the incidence of type 2 diabetes and the prevalence of cardiovascular and diabetes risk factors than having a normal BMI with low levels of physical activity (54). Only in short-term studies (16 weeks or shorter duration) is it possible to find evidence of a linear dose-response relationship between the amount of physical activity and the amount of weight loss when diet is controlled for. The amount of weight loss is consistent with the excess energy expended (56). In practice, a weight loss of around 3 kg, with large individual variations, might be expected following increased physical activity in obese persons (57). Even though there is a lack of conclusive data, it seems that the amount of activity needed to avoid weight gain is about 60 minutes of moderate-intensity activity per day or a shorter duration if the activity is of vigorous intensity (58;59).

Cancer

Physical activity is an essential modifiable lifestyle risk factor that has the potential to reduce the risk of some major forms of cancer (13;60). The risk reduction for active individuals is 10–70% for colon cancer, but this is dependent on intensity and duration (61). With respect to breast cancer, regular physical activity corresponding to an intensity of 6 METs and with a duration of four hours per week might reduce the risk by 30–50% (62;63). Physical activity might also prevent the development of endometrial cancer (62–64). The evidence is weaker for lung and prostate cancers and is generally either null or insufficient for all remaining cancers (63;64).

There are several possible biological mechanisms through which physi-

cal activity might prevent cancer. They include, among others, the effect of physical activity on body composition and energy metabolism, insulin resistance, sex steroid hormones, inflammation, and immune function. In a review by Fridenreich et al, it was estimated that between 9% and 19% of cancer cases in Europe can be attributed to lack of sufficient physical activity (64). They also found that public health recommendations for physical activity and cancer prevention generally suggest 30–60 min of moderate- or vigorous-intensity activity performed at least 5 days per week. Recently, several observational studies, as well as some randomised clinical trials, have found that physical activity might improve survival in breast and colon cancer patients. However, the effects of physical activity on site-specific cancer survival have not yet been fully established.

Musculo-skeletal disorders

Reversible risk factors for falls include weak lower limb muscle strength, poor balance, and a poor level of overall physical fitness, all of which can be improved by regular physical activity (65–68). Muscle strength and muscle endurance diminish with increasing age and decreasing activity level (69), and physical activity can counteract and reverse this trend to a substantial degree and keep older people independent in daily life longer (66;70).

Loss of calcium can lead to osteoporosis. This risk increases with age, particularly in post-menopausal women. Physical activity contributes to increased bone density and can counteract osteoporosis, and physical activity immediately before and during puberty seems to yield greater maximum bone density in adult life (71–74). For adults and the elderly, physical activity retards bone loss (75). To be beneficial for bone mass and structure, exercise should preferably be weight-bearing (76) and repeated weight-bearing and loading, such as walking and running, is more beneficial than activities such as swimming and cycling. Even better for bone health are activities with high impacts (e.g. tennis, squash, and aerobics) or high volume loading (weight training). However, there is a lack of information about the dose-response relationship between activity/exercise and osteoporosis (76).

Exercises that strengthen and stabilize the muscles of the back reduce the incidence of back problems. This is particularly true in people with a history of back problems, but these exercises are also effective to a certain degree among those who have not previously experienced such problems (77). Regular physical activity might have a preventive effect on lower back pain, but the type of the activity that has the most benefit has yet to be determined (76).

Mental health and quality of life

A positive association has been found between physical activity habits and both self-esteem and psychological well-being in children and young and middle-aged adults (12). There is also evidence that regular physical activity reduces symptoms of anxiety and poor sleep. Furthermore, observational studies have shown that those who are physically inactive are at greater risk of developing depression than those who are physically active (78;79). However, there is not enough data to determine clear-cut dose-response relationships between physical activity and depression and anxiety (80). There is evidence supporting the hypothesis that physical activity can prevent the development of vascular dementia (81) compared to a sedentary lifestyle. Further research is needed to study the volume and mode of physical activity that is most psychologically beneficial and to explore the mechanisms through which physical activity improves mental health. For more details see http://www.health.gov/paguidelines/Report/pdf/G8_mentalhealth.pdf

Sedentary behaviour

Knowledge regarding the importance of reducing the amount of time spent sitting and engaging in daily physical activities has grown significantly in recent years. Several cross-sectional and prospective studies have demonstrated a relationship between sedentary behaviours, especially during leisure time, and obesity (81;82). Recently, prospective studies have also demonstrated a dose-response relationship between TV viewing and cardiovascular mortality as well as total mortality (83). Although residual confounding by unmeasured or poorly measured confounders (e.g. unconscious or poorly reported diet intake while viewing TV) cannot be excluded, these studies suggest that the association might be independent of physical activity level and exercise habits (82). Even in individuals fulfilling the recommendations for physical activity, sitting for prolonged periods might compromise metabolic health (81).

The underlying mechanisms are yet not fully known, but substantially decreased lipoprotein lipase activity as well as an instantaneously insulin-resistant state during sitting might contribute to adverse health effects (81). Energy expenditure differs substantially when comparing sitting still with standing, walking, or light intensity indoor activity (84), and a study from Australia showed that the frequency of breaks during prolonged sitting is associated with a favourable metabolic profile (85). Reducing sedentary time should be considered as an additional strategy in combination with the promotion physical activity

as a means of improving public health. Recommendations regarding reduced sedentary time are now being incorporated along with recommendations on physical activity in various countries, for example, the UK (gov.uk/government/publications/UK-physical-activity-guidelines).

Recommendations on physical activity

There is strong evidence that vigorous intensity physical activity that is sufficient to improve cardiorespiratory fitness has a major impact on different health outcomes at all ages (12). In fact, previous recommendations on physical activity were equal to the quantity and quality of exercise sufficient to develop and maintain cardiorespiratory fitness. However, as previously described in this chapter, clinical and epidemiological studies have established that activity of a moderate intensity, even without associated improvements in cardiorespiratory fitness, also has favourable effects on several risk factors for CHD and type 2 diabetes (12;86). Therefore, it is important to emphasize that substantial health gains can be achieved through moderate intensity physical activity. Nevertheless, evidence from large population-based studies in healthy individuals (34, 87) demonstrates that physical activity with high intensity gives more robust risk reduction compared to that achieved by physical activity at low and moderate intensities. These observations are in line with the cardiovascular adaptations observed after high-intensity endurance training compared to those observed after low- to moderate-intensity activities in small-scale randomized studies (88). Interestingly, Stanaway et al followed 1,705 men aged 70 years or older for a mean of 59.3 months and observed that men who normally preferred to walk faster than 3 km/h were 23% less likely to die compared with those walking at a slower speed during the follow-up period (89).

Examples of energy requirements corresponding to 3–6 METs (moderate intensity activity) and > 6 METs (vigorous intensity activity) are given in Table 9.1. Cardiorespiratory fitness decreases as people age and also as a consequence of insufficient physical activity. Activity of a certain MET value, therefore, requires a greater percentage of a person's cardiorespiratory fitness (Table 9.1.) as he or she ages. Note that activity of a certain energy cost might be perceived differently by different groups. For instance, climbing stairs might be perceived as a light intensity activity for a 30-year-old but hard for a 70-year-old.

Table 9.1. Energy requirements for performing various activities in different age groups shown as METs and as percentages of cardio-respiratory fitness (≈ maximal oxygen uptake)

		Energy requirements as percentages of cardiorespiratory fitness (≈ maximal oxygen uptake) and corresponding rating of perceived exertion (Borg scale, raised and in bold) according to age group in years.*			
Activities	**Energy cost in METs**	**Young 20–39**	**Middle-aged 40–59**	**Old 60–79**	**Very old 80+**
Watching TV/reading	1.3	10 **<10**	13 **<10**	15 **<10**	18 **<10**
Light household chores	2.5	20 **<10**	25 **10–11**	29 **10–11**	35 **10–11**
Driving a car	1.5	12 **<10**	15 **<10**	18 **<10**	21 **<10**
Moderate physical activity					
Climbing stairs	5.5	42 **10–11**	55 **12–13**	64 **14–16**	77 **15–17**
Walking (4.8 km/h)	3.5	27 **10–11**	35 **10–11**	41 **10–11**	49 **12–13**
Walking (6.4 km/h)	5.0	39 **10–11**	50 **12–13**	59 **14–15**	70 **14–16**
Snow clearing (snow blower)	3.0	23 **<10**	30 **10–11**	35 **10–11**	42 **10–11**
Snow clearing (manual)	6.0	47 **12–13**	60 **14–16**	70 **14–16**	84 **15–17**
Lawn mowing (manual)	4.5	35 **10–11**	45 **12–13**	53 **12–13**	63 **14–16**
Vigorous					
Jogging 8.0 km/h	7.0	55 **12–13**	80 **14–16**	93 **17–19**	>100 **20**

* Activity of a certain energy cost might be perceived differently by people both as a function of age and of insufficient physical activity. For instance, climbing stairs might be perceived as light activity for a 30-year-old but hard for a 70-year-old. Rating of perceived exertion (Borg scale)(63): Very light <10; Light 10–11; Somewhat hard 12–13; Hard 14–16; Very hard; 17–19; Very, very hard 20.

The total amount of physical activity (the combination of intensity, duration, and frequency) is related to a number of health variables in a dose-response relationship. The preventive effect (the health gain) increases with increasing activity level, but the relationship is curve-linear (Figure 9.1.). Those who are physically inactive might achieve the greatest health gains by increasing their physical activity, and this applies even in old age (12;16;90). The health gain seems to be dependent on the amount of physical activity, but the intensity of the aerobic physical activity might compensate for duration or frequency and provide further health benefits than moderate intensity alone as described above. Another aspect is whether several short bouts of activity are as effective in influencing health outcome as one longer session of the same total duration (91). Although aerobic physical activity is the type primarily recommended, data also show

that resistance training also have a protective effect on the incidence of CHD (92) and also all-cause mortality and cancer in men (93). It is recommended that regular resistance training involving the major muscle groups of the upper and lower body two or three times a week is sufficient to have an impact on health (94).

The question of how much physical activity is needed to improve health depends on initial health status and the group of interest: the young, the elderly, overweight individuals, etc. It is important, however, to keep in mind that physical activity might have different dose-response relationships with different health outcomes and that these effects might also be dependent on the type of activity.

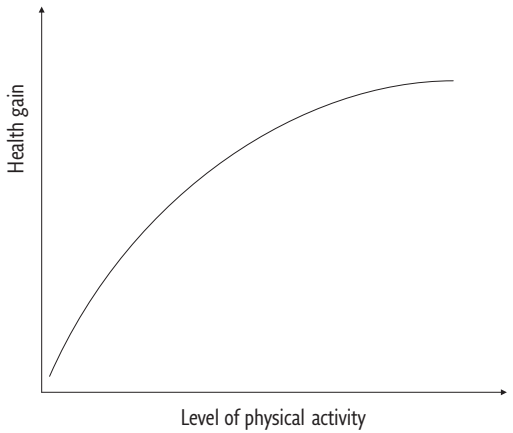


Figure 9.1. Dose-response curve for physical activity and health (95). Different health outcomes probably have different dose-response relationships

Children and adolescents

Regular physical activity is necessary for normal growth and the development of cardiorespiratory endurance, muscle strength, flexibility, motor skills, and agility (96–100). In addition, physical activity during the formative years strengthens the bones and connective tissues and yields greater maximum bone density in adult life (96;101;102). Physical activity that provides high impact loading on bones is important for bone development, particularly during early puberty (103). There is also evidence of an association between cardiorespiratory fitness and physical activity and cardiovascular disease risk factors in children and adolescents (27;61;104). Furthermore, risk factors such as fatness, insulin glucose ratio, and lipids

tend to cluster in children and adolescents with low cardiorespiratory fitness and low levels of physical activity (27;61;104).

Regular physical activity is associated with wellbeing and seems to promote self-esteem in children and adolescents. Furthermore, children and adolescents who are involved in physical activity seem to experience fewer mental health problems (105–108). There is no indication that increased physical activity in school represents any risk of impairing children's cognitive skills as a result of less time for theoretical school subjects (109). However, a higher fitness level in young adults is associated with better cognitive function and higher future educational level (110).

There is convincing evidence regarding the health effects of regular physical activity in children and adolescents (111). Recent literature reviews have prompted the WHO and the U.S. health authorities to refine their recommendations of physical activity guidelines for children (112–115). The following is recommended for children and adolescents:

1. *Children and adolescents should accumulate at least 60 minutes of moderate to vigorous-intensity physical activity daily.*
2. *Physical activity of amounts greater than 60 minutes daily will provide additional health benefits.*
3. *Vigorous-intensity activities should be incorporated, including those that strengthen muscle and bone, at least 3 times per week.*
4. *Reduce sedentary behaviour*

Activities should be as diverse as possible in order to provide optimal opportunities for developing all aspects of physical fitness including cardiorespiratory fitness, muscle strength, flexibility, speed, mobility, reaction time, and coordination. Varied physical activity provides opportunities to develop both fine-motor and gross-motor skills. Active children get the exercise they need while playing in the neighbourhood, at day-care, and on the school playground and by participating in children's sports.

In NNR 2012, recommendations for children and adolescents are identical to those of the WHO (112). The WHO also recommends that inactive children and youth undergo a progressive increase in activity to eventually achieve the recommendations mentioned above. Also, the WHO states that the recommended levels of physical activity for children and adolescents should be above and beyond the physical activity accumulated in the course of normal daily non-recreational activity.

Adults

The evidence in the literature suggests that adults who are insufficient physically active gain considerable health benefits from participating in moderate to vigorous intensity physical activity for about 30 min per day. The optimal health effects are likely to be achieved from the combination of two modalities including at least 75 minutes of vigorous intensity physical activity per week and daily moderate intensity physical activity (see Figure 9.2.). Based on those mentioned above and other international guidelines (112), (113), (116), the recommendations on physical activity for adults are the following:

1. Adults should engage in at least 150 minutes of moderate-intensity physical activity throughout the week or engage in at least 75 minutes of vigorous-intensity physical activity throughout the week or engage in an equivalent combination of moderate- and vigorous-intensity activity preferably spread out over most days during the week.

2. Physical activity should be performed in bouts of at least 10 minutes duration.

3. For additional health benefits, adults should increase their moderate-intensity physical activity to 300 minutes per week or engage in 150 minutes of vigorous-intensity physical activity per week or engage in an equivalent combination of moderate- and vigorous-intensity activity.

4. Muscle-strengthening activities should be performed involving major muscle groups on 2 or more days a week.

5. Reduce sedentary behaviour.

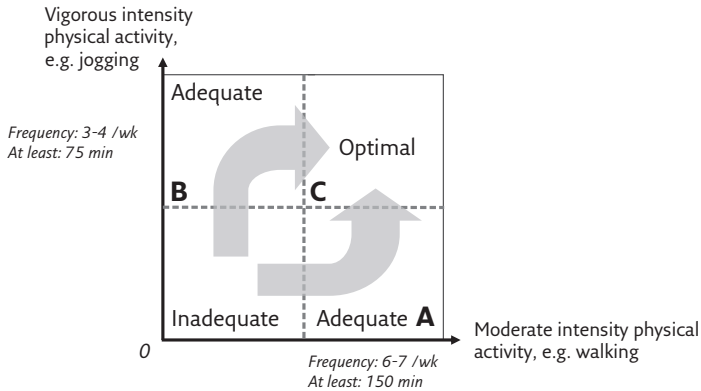


Figure 9.2. Three modalities of physical activity that are sufficient to provide health benefits:
A) Physical activity of moderate intensity – e.g. walking, household chores, and playing – 6 or 7 times per week and for a minimum of 150 min per week
B) Physical of vigorous intensity – e.g. jogging, swimming, tennis, resistance training, circuit training, and cross-country skiing – 3 or 4 times a week and for a total of 75 min per week
C) The *optimal* activity dose might be the combination of A) and B) (both moderate intensity physical activity and moderate to vigorous intensity exercise)

Elderly

Regular physical activity in elderly people is associated with improved strength and functional ability (117), is inversely related to mortality (118), and has been found to be strongly associated with maintaining mobility during a 4-year follow up study (119).

Endurance training in the elderly has been found to improve oxygen consumption (VO_2 max) by approximately 23% in a meta-analysis (120). Hard endurance training results in improved VO_2 max, increased muscle mass, unchanged body weight, and unchanged daily energy expenditure because of a compensatory decline in physical activity during the remainder of the day (121;122).

Resistance training increases basal energy expenditure, muscle mass, muscle strength (90;123), and daily energy expenditure in the elderly (124) and might counteract the age-related accumulation of fat (125). Even engaging in high-resistance training less than 3 times per week still provides beneficial outcomes in the elderly (126). Low-intensity and moderate-intensity physical activity might be beneficial for the institutionalised elderly (127), and positive effects of resistance training have been seen even in 85- to 97-year-old subjects (128). In general, healthy elderly people are advised to follow the recommendations for the adult population. This applies especially to the advice to become more physically active in daily life.

The following recommendations apply:

1. *The elderly should engage in at least 150 minutes of moderate-intensity physical activity throughout the week or at least 75 minutes of vigorous-intensity physical activity throughout the week or engage in an equivalent combination of moderate- and vigorous-intensity activity preferably spread out over most days during the week.*
2. *Physical activity should be performed in bouts of at least 10 minutes duration.*
3. *For additional health benefits, the elderly should increase their moderate intensity physical activity to 300 minutes per week or engage in 150 minutes of vigorous-intensity physical activity per week or engage in an equivalent combination of moderate- and vigorous-intensity activity.*
4. *Adults of this age group with poor mobility should perform balance exercises to enhance balance and prevent falls on 3 or more days per week.*
5. *Muscle-strengthening activities should be performed involving major muscle groups on 2 or more days per week.*
6. *Reduce sedentary behaviour.*

When adults of this age group are unable to participate in the recommended amounts of physical activity due to health conditions, they should be as physically active as their abilities and conditions allow. The intensity can be increased by climbing stairs or hills of increasing steepness, preferably on uneven terrain (which is an advantage for improving balance). Other forms of aerobic exercise that can be engaged in as an alternative to walking include swimming and other water activities, dancing, cycling, rowing, and the use of equipment such as exercise bicycles, rowing ergometers, etc.

Because resistance training is particularly valuable in maintaining muscle strength, a varied, progressive programme of weight training is recommended for older people. Strengthening exercises should be tailored to the needs of the individual with regard to types of exercises, number of sets, number of repetitions, and frequency of training sessions. Strengthening exercises should optimally be combined with aerobic, balance, and mobility training.

Pregnancy and lactation

Pregnancy is associated with extensive physiological and anatomical changes. Despite this, regular physical activity or exercise has minimal risk and has confirmed benefits for most women (129). Women who are moderately physically active during pregnancy experience easier pregnan-

cies and deliveries, have better self-esteem, gain less weight, have more normal deliveries, and have fewer perinatal complications than women who have not engaged in physical activity during their pregnancy (130–132). Except for complicated pregnancies and a few circumstances in which exercise is contraindicated (see (129) for details), the following recommendations apply:

1. *Women who have previously not been physically active should engage in moderate intensity physical activity during pregnancy with a gradual progression of up to at least 150 minutes per week*
2. *Women who were regular exercisers before pregnancy should continue to engage in physical activity at an appropriate level.*
3. *Training the muscles of the pelvic floor is particularly important during pregnancy and after giving birth.*
4. *Activities with a high risk of falling (such as horseback riding and downhill skiing) and contact sports (such as handball, basketball, and ice hockey) increase the risk of trauma and should be avoided. Scuba diving should be avoided throughout the pregnancy.*
5. *There are no restrictions regarding the kind of activities that can be carried out during lactation.*
6. *Lactating women should be encouraged to be physically active as much as possible. This is especially important for overweight and obese lactating women and for women having gained more weight than recommended during pregnancy.*

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10 Fat and fatty acids

Age	6–11 mo.	12–23 mo.	Adults and children from 2 years of age
Cis-MUFA	10–25 E%	10–20 E%	10–20 E%*
Cis-PUFA	5–10 E%	5–10 E%	5–10 E%*
- n-3	≥1 E%	≥1 E%	≥1 E%
SFA	<10 E%	<10 E%	<10 E%
TFA	As low as possible	As low as possible	As low as possible
Total fat	30–45 E%	30–40 E%	25–40 E%

* Cis-monounsaturated (cis-MUFA) and cis-polyunsaturated fat (cis-PUFA) should make up a minimum of 2/3 of the total fat intake.
SFA: saturated fatty acids; TFA: trans-fatty acids.
Fatty acids are expressed as triglycerides.

Introduction

Fat provides the body with energy in a concentrated form. In addition to energy, dietary fats provide essential fatty acids and fat-soluble vitamins. Lipids, mainly phospholipids and cholesterol, are included in cell membranes, and triglycerides are stored in adipose tissue as energy reserves. Certain fatty acids serve as a source of eicosanoids. In food items, fats are usually in the form of triglycerides.

Dietary sources and intake

The dietary content of fat and fatty acids in the Nordic countries has changed significantly in recent decades. The total fat content decreased from the 1970s to the 1990s. After being rather stable for several years, the dietary fat content has again increased in recent years in some Nordic countries, e.g. in Finland (1). The content of saturated fatty acids (SFA) has shown a similar trend as total fat, i.e. first it decreased, then levelled

off, and now is increasing in some countries. According to recent surveys, the proportion of SFA is above the recommendations and the ratio of unsaturated to saturated fatty acids is below the recommendations in Nordic countries. The dietary content of trans fatty acids (TFA) has decreased in all Nordic countries since the 1990s primarily through reduced use of partially hydrogenated fats in food production. The dietary content of TFA is currently below 1 E%. The dietary content of cis-polyunsaturated fatty acids (PUFA) increased from the 1960s to the 1980s and has been rather stable ever since. Table 10.1. shows the mean total fat and fatty acid intake in the Nordic countries according to recent surveys.

Table 10.1. The average dietary intake (E%) of total fat and fatty acid sub-categories in the Nordic countries in 2003–2012

	Denmark	Finland	Iceland	Norway	Sweden
	2003–08	2012*	2010- 2011	2010–2011	2010–11
Total fat	35	36.1/35.5	36.2	34	34
SFA	14	15.1/15.0	14.5	13	13
TFA	0.6	0.5/0.5	0.8	<1.0**	0.5***
MUFA	12	14.0/13.5	11.6	12	13
PUFA	4.9	6.7/6.7	5.9	6.2	5.6

* Men/Women.
** Household Consumption Survey 2005–2009.
*** Market Baskets 2010.

In Iceland, the intake of total fat decreased from 41 E% to 36 E% between 1990 and 2010/2011. In the same period, the intake of SFA decreased from 19 E% to 14.5 E% and TFA from 2 E% to 0.8 E% (2, 3). In Finland, the intake of SFA was reduced from 19 E% to 14 E% between 1982 and 2002, but it has increased between 2007 and 2012 from 12–13 E% to 15 E% in both women and men (1). In Norway, the dietary content of SFA decreased from 16 E% in 1980 to 14 E% in the 1990s, and it was 13 E% in 2010–11 (4, 5). The dietary content of TFA decreased from 4 E% in the 1970s to 1 E% around the year 2000, and it has been below 1 E% for the past decade. In Denmark, the intake of fat decreased during the period from 1985 to 2001 from 44 E% to 34 E%, mainly due to a decrease in consumption of butter and milk products but also from a decrease in meat consumption (6). However, fat intake in Denmark has increased recently (7). In Sweden, the mean total fat intake has remained stable from 1997

to 2011 (34 E%) and the intake of SFA has slightly decreased from around 14 E% to 13 E% (8, 9). The intake of PUFA has increased from a mean of 4.7 E% to 5.6 E%.

The most important sources of fat are 1) spreads, butter, and oils, 2) milk and milk products, and 3) meat and meat products. Fat-containing dairy products, butter, butter-based spreads, meat products, sweet bakery products, and confectionary are the main sources of SFA. Main sources of TFA are dairy and meat products. Soft margarines, vegetable oils, and fish are the main sources of PUFA, and cis-monounsaturated fatty acids (MUFA) are derived from several food groups.

Physiology and metabolism

Most of the naturally existing fats are mixtures of triglycerides composed of one molecule of glycerol esterified with three fatty acid molecules, mainly fatty acids with 16–18 carbon atoms. Fatty acids account for about 95% of the triglycerides by weight, and non-esterified fatty acids are uncommon in the diet. The effects of fatty acids depend on the length of the carbon chain, the degree of saturation, the number, position and structure of the double bonds, and, to some extent, on their position in the triglyceride molecule. The unsaturated fatty acids are characterised by the number of double bonds in the molecule: MUFA have only one double bond whereas PUFA have 2 to 6 double bonds. The positions of the double bonds are calculated either from the carboxy-terminal end of the carbon chain (D) or the methyl end (ω or n-). The human body is capable of synthesising SFA and MUFA – including n-7 and n-9 series MUFA – from acetate, but n-3 and n-6 series PUFA are required from the diet. Linoleic acid (n-6, LA) and α-linolenic acid (n-3, ALA) are metabolised (desaturated and elongated) further in the body by the same enzymes (Figure 10.1.). Naturally occurring unsaturated fatty acids in plants and wild fish are mainly cis-fatty acids.

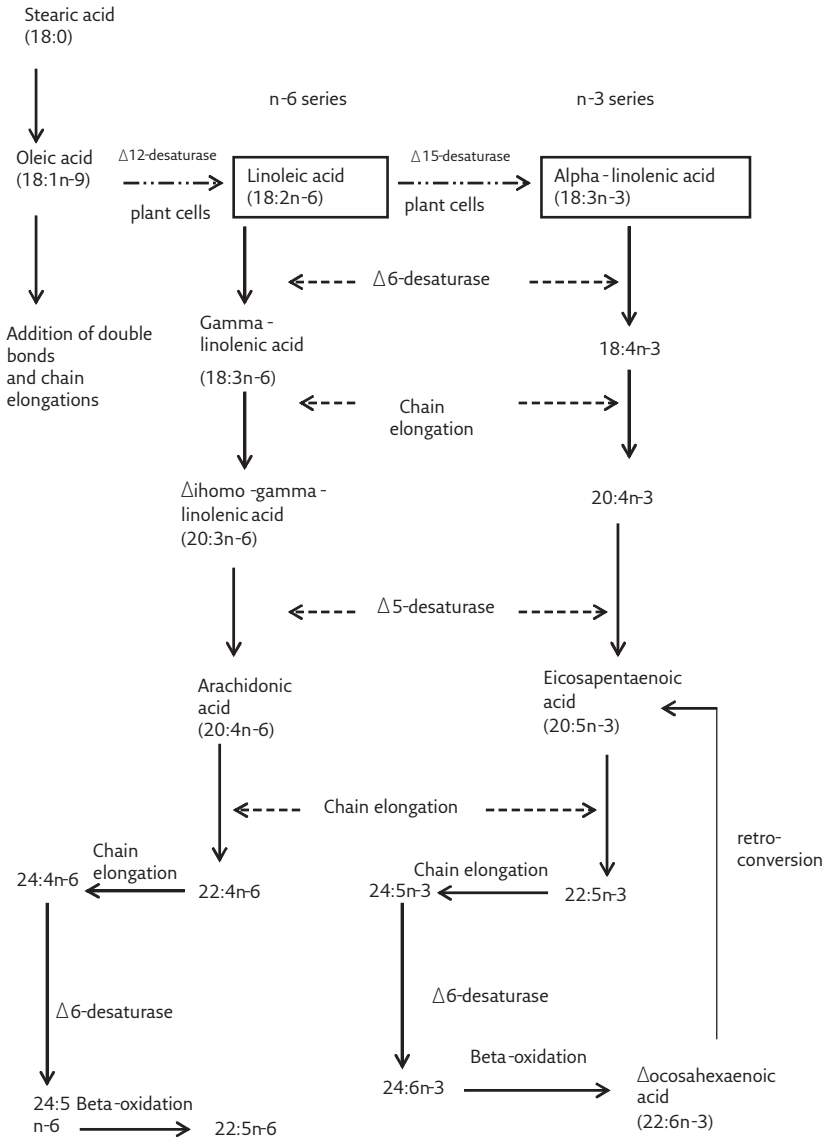


Figure 10.1. Metabolism of polyunsaturated fatty acids

In addition to triglycerides, dietary fats include phospholipids and cholesterol. The most common dietary phospholipid is phosphatidylcholine (lecithin), and cholesterol is found in foods of animal origin. Both phospholipids and cholesterol can be synthesised in the human body. Plants contain small amounts of plant sterols, mainly sitosterol and campesterol

and the corresponding saturated sterols sitostanol and campestanol that are poorly absorbed from the intestine and interfere with the absorption of cholesterol.

TFA are chemically formed by partial hydrogenation and deodorization of vegetable and fish oils (industrial TFA). They are also formed by natural biohydrogenation of fatty acids in the rumen of cattle, sheep, and goats (ruminant TFA) and, therefore, are present in milk and meat. Generally there are more than 10 different trans-18:1 isomers present in ruminant and partially hydrogenated fats (EFSA 2010). The fat of the milk and meat from cattle, sheep, and goats typically contains 3%–6% TFA (as the per cent weight of total fatty acids) of which D11-trans vaccenic acid (18:1t n-7) comprises 30%–50% of the total trans 18:1 isomers (10). There could also be TFA in pork and poultry fat, depending on the feed, but in lower amounts than in ruminant fat. Industrially, partially hydrogenated vegetable oils contain varying amounts of trans isomers with elaidic acid (18:1t n-9) accounting for 20%–30% and trans vaccenic acid accounting for 10%–20% of total trans 18:1 isomers. The TFA profiles of ruminant fat and hydrogenated vegetable oil show considerable overlap for many TFA isomers, but they are present in different proportions (10).

High intake of TFA has been associated with increased risk of coronary heart disease (CHD), sudden death, type 2 diabetes mellitus (T2DM), and increased circulating markers of systemic inflammation (11). The TFA found in partially hydrogenated oils has been associated with increased risk of CHD and appears to be more potent than SFA in the development of CHD (12). FAO recommends a mean population intake of less than 1 E% from both ruminant and industrially derived TFA (13).

One particularly important group of TFA are the conjugated linoleic acids (CLAs) that are formed by bacteria in the rumen and by desaturation of trans MUFA in the organism. The cis-9, trans-11 CLA that is the predominant isomer in milk fat has exhibited anti-carcinogenic properties in experimental animal studies. A chemically produced mixture of CLA isomers reduces fat mass and increases lean body mass in experimental animals. In humans, the effect has been less prominent (14). The trans-10, cis-12 CLA-isomer, which is industrially produced but also present in very low amounts in dairy fat, seems to be responsible for the adipose tissue effects. The same isomer has been found to increase insulin resistance (15) and C-reactive protein levels in humans (16).

Triglycerides are hydrolysed by lipases in the gut to mono-glycerides and fatty acids, which together with bile salts, lysophospholipids, and un-

esterified cholesterol form mixed micelles from which the digested lipids are absorbed in the small intestine. Fats are not soluble in water and are transported in the blood as lipoprotein particles. The core of the lipoprotein particles is formed by triglycerides and esterified cholesterol. The surface of the particles is composed of free cholesterol, phospholipids, and proteins. The lipoproteins are commonly divided into four classes according to density: chylomicrons, VLDL (very low-density lipoprotein), LDL (low-density lipoprotein), and HDL (high-density lipoprotein).

Essential fatty acids

LA (C18:2 n-6) and ALA (C18:3 n-3) are the essential fatty acids (EFA) that must be provided in the diet because the human body lacks the enzymes Δ12- and Δ15-desaturase that are capable of introducing double-bonds at the n-6 and n-3 positions (Figure 10.1.). These EFA serve important physiological functions. For example, LA, when incorporated into skin ceramides, is essential for maintaining the water-permeability barrier of the skin thereby avoiding excessive trans-epidermal water loss and the accompanying energy loss from water evaporation.

Physiology and metabolism

Both LA and ALA can be elongated and desaturated in the body (Figure 10.1.). LA is metabolised, for example, to γ-linolenic acid (C18:3 n-6), dihomo-γ-linolenic acid (C20:3 n-6, DHGLA), and arachidonic acid (C20:4 n-6, AA). Eicosapentaenoic acid (C20:5 n-3, EPA), docosapentaenoic acid (22:5 n-3, DPA) and docosahexaenoic acid (C22:6 n-3, DHA) are formed from ALA. There is considerable inter-individual variation in the formation of DHA from ALA related to common polymorphisms in the Δ-5 and Δ-6 desaturase genes FADS1 and FADS2 (17). DHGLA, AA, and EPA are further metabolised by other enzymes (e.g. cyclo-oxygenases and lipoxygenases) into eicosanoids, a group of biologically active substances including prostaglandins, prostacyclins, leukotrienes, and thromboxanes. These highly active substances modulate the regulation of blood pressure, renal function, blood coagulation, inflammatory and immunological reactions, the sensation of pain, and other tissue functions.

The n-6 and n-3 PUFA, particularly the long-chain metabolites, are important structural components of cell membranes. They are essential for various membrane characteristics and functions such as fluidity, permeability, activity of membrane-bound enzymes and receptors, and

signal transduction. DHA is necessary for growth of the brain and other membrane-rich tissues in foetal and early postnatal life and thus plays a significant role in neurological development and visual function.

The n-6 and n-3 PUFA compete for the same enzymes (e.g. desaturases, elongases, and cyclo-oxygenases), and the n-3 series fatty acids have a higher affinity for the enzymes. An imbalance between dietary intakes of LA and ALA might thus influence the further metabolism to more long-chain and unsaturated n-6 and n-3 fatty acids. However, the data from most human studies using radioactive tracers do not show any major impact on ALA conversion in diets with varying n-6:n-3 ratios (18, 19). Some feeding studies show an impact on EPA concentrations in serum phospholipids (20). The interpretation of the results from various studies is further complicated due to differences among studies in absolute intakes and ratios. The total intake of each of the n-6 and n-3 fatty acids is more important than the ratio, as long as basic dietary requirements are covered. This is supported by the FAO report (13) that concludes that the ratio is of limited relevance when dietary intakes are within the recommended reference intakes.

In humans, high intakes of PUFA can potentially result in adverse effects including increased lipid peroxidation, impaired immune function, and increased bleeding tendency (21). Intakes of n-6 fatty acids (LA) up to around 10 E% are considered safe (13, 21). The EFSA concluded that combined long-term supplemental intakes of EPA and DHA up to about 5 g/d did not appear to increase the risk of spontaneous bleeding episodes or bleeding complications or to affect glucose homeostasis, immune function, or lipid peroxidation provided that the oxidative stability of the n-3 long chain PUFA (LCPUFA) was guaranteed (22).

Deficiency

Clinical symptoms of EFA deficiency (skin changes and growth retardation) have been found in healthy, new-born babies fed for 2 to 3 months with a diet low (<1 E%) in LA. EFA deficiency in adults is rare. Reported cases have been associated with chronic diseases or prolonged parenteral or enteral nutrition either without fat or very low in fat. The minimum requirement for LA remains unknown. Combined deficiency of LA and ALA leads to increased formation of the PUFA C20:3 n-9 and an increased C20:3 n-9/C20:4 n-6 ratio. It has not been confirmed, however, that this ratio is a useful indicator of EFA deficiency in humans.

Clinical signs (skin changes) of insufficient supply of ALA have been

reported at intakes of <0.05 E% during enteral nutrition and <0.1 E% during parenteral nutrition, but the specificity of these findings has been challenged. Humans are able to desaturate and elongate ALA to EPA and DPA, but further desaturation to DHA might be limited (Valsta et al. 1996). Conversion is higher in women (up to 21%) than in men (up to 8%) (12, 23, 24). The conversion rate is also affected by the intake of EPA and DHA as well as the intake of LA and of ALA itself (25–27). Two grams per day of DHA has been shown to be superior to the same amount of EPA in erythrocyte membrane incorporation of both EPA and DHA, but an ALA intake of 4 g/d did not increase the proportion of these longer chain n-3 fatty acids in a 6-wk intervention (28). There is also retroconversion of DHA to EPA and DPA. The estimated retroconversion rate varies between 1.4% and 12% depending on, for example, the DHA intake (29, 30).

DHA is found at high concentrations in the synapses of the central nervous system and in the rod outer segment of the photoreceptor cells of the retina where it is essential for the development of normal visual function (31). Studies in preterm infants strongly suggest that DHA is essential for normal development of visual function and perhaps for optimal psychomotor development (32, 33). These findings support the concept that it is necessary to consume n-3 fatty acids at least in amounts sufficient to replace physiological losses.

Several studies indicate that the enzymes that are responsible for the metabolism of EFA cannot synthesize enough long-chain PUFA from their parent fatty acids to meet the needs at birth, at least not in infants born before term, although the capacity for PUFA synthesis in preterm infants might be higher than in term infants (34). Therefore, AA and DHA, which are present in human milk, should be considered conditionally essential for a limited time after birth. It is recommended that a small proportion of AA and DHA, resembling the amounts in human milk, should be included in infant formula intended for preterm infants. There is as yet no consensus as to whether these fatty acids are also conditionally essential for infants born at term, although it has been recommended that formula intended for term infants should also be supplemented with AA and DHA (35). Supplementation of infant formula with long-chain PUFA has been associated with lower blood pressure during later childhood (36). Such supplementation is in accordance with the European directive on infant formula and follow-on formula intended for term infants, although the directive does not give a specific recommendation for supplementation with AA and DHA (37).

Intake of long chain n-3 fatty acids during pregnancy improves the n-3 status of the foetus and new-born child (38) and might be beneficial for the mental development of the child as assessed by their IQ (39). Plasma n-3 long chain fatty acid concentrations that are optimal for both mothers and infants have to be defined before general recommendations for intake are made (40). The n-3 content of breast milk is affected by the mother's intake (41), and this in turn can affect the development of visual acuity in the breastfed infant (42).

Cholesterol

Cholesterol is formed in various types of cells in the human body, and it is used for the production of bile acids and steroid hormones and for cell membrane structures. Cholesterol synthesis is highly regulated, and its uptake by cells reduces endogenous synthesis. About one gram of cholesterol is synthesised in human adults every day, and this is 3 to 4 times the amount absorbed from the average adult Nordic diet.

The most important dietary sources of cholesterol are meat and offal, eggs, and dairy products. The fractional absorption of cholesterol is reduced when the intake increases. On average, 40% to 50% of dietary cholesterol is absorbed, but absorption varies between individuals and can range from 20% to 80%. According to a meta-analysis of 17 randomized controlled trials (RCTs) published from 1974 to 1999 (24), 100 mg of dietary cholesterol increased serum total cholesterol by 0.056 mmol/L and HDL-cholesterol by 0.008mmol/L and slightly increased the total-cholesterol to HDL-cholesterol ratio by 0.020 units. In individuals with the apoprotein E4 allele, dietary cholesterol has a more pronounced effect on serum cholesterol concentration whereas in those without the apoprotein E4 allele dietary cholesterol has a weaker effect on serum cholesterol concentration (43).

Several expert groups, mainly in the US, have recommended that cholesterol intake in adults should be kept below 300 mg/d and those at high risk of cardiovascular diseases, e.g. those with T2DM, should not exceed 200 mg/d (44, 45). The average cholesterol intake in the Nordic countries is 250–350 mg/d. It is anticipated that the dietary guidelines promoting increased consumption of vegetable foods and limiting excessive intake of fatty dairy and meat products will lead to a reduction in cholesterol intake (46). Therefore, the current NNR does not set an upper intake level for cholesterol. Apparently, the endogenous capacity to synthesise cholesterol

is sufficient to meet the needs even of preterm infants. Therefore, there is no recommendation that infant formula should contain cholesterol even though cholesterol is a natural constituent of human milk.

Dietary fat, fatty acids, and health

Dietary fat and fatty acid composition has been linked to the risk of cardiovascular diseases (CVD), certain types of cancer, obesity, and gallstones. The relatively high amount of fat, especially SFA, in the diet in the Nordic countries during the 1960s and 1970s has contributed to the high prevalence of CVD in these countries (47). Serum/plasma LDL-cholesterol concentration has been identified as an important and causal risk factor for atherosclerosis, and a high serum/plasma HDL-cholesterol concentration and a low LDL-cholesterol to HDL-cholesterol ratio are associated with a reduced risk for atherosclerosis. A higher risk profile already seen in childhood is associated with an increased risk of atherosclerosis and CHD (48, 49).

For the update of NNR 2012, a systematic review (SR) was carried out with the aim of assessing the effect of, and to grade the evidence in regard to, the amount and type of dietary fat and biomarkers of the quality of dietary fat on risk factors and risk of non-communicable diseases, i.e. CVD, T2DM, and cancer, and body weight in healthy subjects or subjects at risk for these diseases (50). The SR included papers published from 2000 up to February 2012.

Serum lipid profile

Serum LDL-cholesterol concentration has been causally related to atherosclerosis based on modern genetic studies, and the ratio of LDL-cholesterol to HDL-cholesterol, as well as the non–HDL-cholesterol concentration, are good markers for CVD risk (51–53).

When SFA and TFA are replaced by cis-MUFA and PUFA, the LDL-cholesterol concentration in serum is reduced while the HDL-cholesterol concentration usually remains unchanged, i.e. the total-cholesterol to HDL-cholesterol ratio improves (54–62).

The NNR SR by Schwab and co-workers (50) included 45 RCTs investigating the effect of different fatty acids on serum lipids. The evidence that the serum/plasma concentrations of total cholesterol and LDL-cholesterol are reduced when SFA is replaced by cis-MUFA or PUFA was evaluated as *convincing* (50). There was no adverse effect on serum/plasma HDL-cholesterol concentration. Substituting cis-MUFA for SFA or carbohydrates

might even have a favourable effect on HDL-cholesterol concentration and the total-cholesterol to HDL-cholesterol ratio (57, 63). However, there is no direct evidence that increasing the HDL-cholesterol concentration itself lowers the risk of CHD (64). If total fat intake is markedly reduced in addition to replacing SFA or carbohydrates with cis-MUFA, the HDL-cholesterol concentration decreases and the concentration of triglycerides increases (57). Increased physical activity might counterbalance the effects of reduced fat intake on HDL-cholesterol (65, 66). In the SR by Schwab and co-workers (50), the evidence for replacing SFA by cis-MUFA or PUFA in regard to concentrations of serum/plasma HDL-cholesterol was evaluated as *limited – no conclusion*, and the effect on concentration of serum/plasma total triglycerides was *unlikely*. The evidence for replacing carbohydrates with cis-MUFA or PUFA was evaluated as *limited – no conclusion* for serum/plasma concentrations of total cholesterol, HDL-cholesterol, and total triglycerides. For LDL-cholesterol concentration, the evidence was evaluated as *unlikely*.

RCTs investigating dietary interventions aiming to improve serum or plasma lipid profiles in free-living individuals who have decreased the amount or improved the quality of dietary fat have shown a mean reduction in serum total cholesterol of 8.5% in 3 months and 5.5% in 12 months, but the dietary goals were seldom achieved (67). In metabolic ward studies, the compliance was better and the serum cholesterol concentrations were reduced by 10% to 15% (68).

The effects on LDL-cholesterol of specific SFA differ to some extent. Myristic acid (C14:0), palmitic acid (C16:0), and lauric acid (C12:0) increase both LDL- and HDL-cholesterol concentrations (C14:0>C16:0>C12:0), but stearic acid (C18:0) has a neutral effect comparable to that of oleic acid (n-9 C18:1). TFA from partially hydrogenated vegetable oils or fish oils increase LDL-cholesterol concentrations almost as much as the C12-C16 SFA but reduce HDL-cholesterol concentrations (34, 35, 36). Replacing 1 E% of TFA with 1 E% SFA, cis-MUFA, or PUFA decreases the total-cholesterol to HDL-cholesterol ratio by 0.31, 0.34, and 0.67 units, respectively (69). The source of partially hydrogenated fat might also have an effect because TFA from partially hydrogenated fish oils have been shown to affect LDL- and HDL-cholesterol concentrations more than partially hydrogenated soybean oil (70).

Long chain n-3 PUFA (EPA and DHA) can increase serum LDL-cholesterol concentrations (71, 72). In subjects with T2DM the increase of serum LDL-cholesterol concentration is 11% on average (73). The effects

of fish oil supplements and DHA might differ such that DHA has a stronger effect than fish oil when compared with cis-MUFA (50). The evidence for the effect on LDL-cholesterol concentration was evaluated to be *suggestive* for DHA and *inconclusive* for fish oil. In contrast to the effect on serum/plasma cholesterol concentrations, long chain n-3 PUFA decrease the concentration of serum triglycerides (73). In the SR by Schwab et al. (50), the evidence of the effect on the concentration of total triglycerides in serum/plasma was evaluated as *probable* for fish oil, i.e. EPA + DHA, but *inconclusive* for DHA alone. No adverse effects from EPA or DHA have been reported when consumed in the form of fish (74).

The SR by Schwab and co-workers (50) concluded that the evidence for the hypotriglyceridemic effect of fish oil supplementation compared with cis-MUFA was *probable*, whereas DHA supplementation did not seem to have a hypotriglyceridemic effect. In comparisons of fish oil with other types of PUFA, the evidence for the effect on serum/plasma total cholesterol concentration was evaluated as *unlikely*, and the evidence for its effect on concentrations of LDL- and HDL-cholesterol and total triglycerides was evaluated as *limited – no conclusion*.

Glucose tolerance and insulin sensitivity

The NNR SR by Schwab and co-workers (50) included 11 RCTs investigating the effect of dietary fat on insulin sensitivity and 20 studies on fasting serum/plasma insulin concentration.

In comparisons of the effects of cis-MUFA or PUFA and SFA on insulin sensitivity measured either by insulin sensitivity index (SI) or homeostasis model insulin resistance (HOMA-IR), insulin sensitivity was improved in both cis-MUFA-enriched and PUFA-enriched diets (56, 60). There are also studies showing no difference for cis-MUFA or SFA (58, 59, 75). However, obesity might alter the effect of the quality of fat on insulin sensitivity. When cis-MUFA has been compared with both carbohydrates and SFA (76–79), cis-MUFA resulted in improved HOMA-IR and SI. The amount of fat in the diet might also modify the effect of the quality of fat. In the KANWU study, it was shown that replacing SFA with MUFA improved insulin sensitivity in healthy subjects whose fat intake was below the median intake, i.e. 37 E% (56). There is also evidence that carbohydrates might result in better SI than SFA (80). The SR by Schwab and co-workers (50) concluded that the evidence for a favourable effect of cis-MUFA on insulin sensitivity or fasting serum/plasma insulin concentration in comparison with carbohydrates and SFA was *probable*.

In a meta-analysis of RCTs, n-3 fatty acids did not affect insulin sensitivity (81). The effects of fish oil as fish oil supplements and ALA do not differ in terms of SI (82). Fish oil supplements did not have an effect on SI, first phase insulin secretion, disposition index ($K_{G)}$ when added either to the diet high in cis-MUFA or SFA (56, 83). Regarding insulin sensitivity, 12 out of 15 studies included in a meta-analysis found no effect of the quality of dietary fat, but the quality of the studies was questionable (84).

When unsaturated fatty acids have been compared with SFA, no differences in fasting plasma or serum glucose concentrations have been found (56, 58, 60, 75). Regarding plasma or serum insulin concentrations, only one of these studies showed a favourable effect from MUFA (56). In a comparison between MUFA and carbohydrates, MUFA resulted in better fasting plasma/serum glucose concentration in one study (76) but in other studies no difference has been found (77, 78, 80). On the contrary, in all of these studies fasting plasma or serum insulin concentrations were improved while on a MUFA-rich diet compared to a SFA-rich diet. Most of these studies, however, were very short term, and in some of these studies the diets were high in fat (about 40 E%) (58, 78).

The SR by Schwab and co-workers (50) concluded that the evidence for an effect on blood glucose by replacing SFA with cis-MUFA or PUFA was *unlikely*. The evidence for replacing SFA with cis-MUFA or carbohydrates was evaluated as *limited – no conclusion*.

Blood pressure

Dietary fat composition might influence blood pressure, and it is possible that a very low intake of n-3 PUFA increases blood pressure (85). However, at intakes exceeding the minimum requirement blood pressure is not affected by PUFA intake.

In comparisons of cis-MUFA and SFA, diets rich in cis-MUFA have resulted in lower blood pressure in some studies (86–88). Recently, a prospective randomized intervention found lower blood pressure among those with lower intake of SFA from infancy (89). The amount of fat might play a role in the effect of changing the quality of dietary fat on blood pressure. In one study with a high intake of fat (about 40 E%), no difference between MUFA and SFA was found (58) and in another study the beneficial effect of MUFA was more pronounced in those subjects with a fat intake below 37 E% (87).

Fish oil supplement has been observed to give varying results. In randomized trials, it decreased blood pressure in young overweight adults (90),

in infants (91), and in adolescents (92). A recent observation found lower blood pressure among elderly people taking fish oil supplements (93), but such intake was found to increase blood pressure in pregnant women and decrease the size at birth of their babies (94, 95).

The SR of Schwab and co-workers (50) concluded that the evidence for an effect of any modification of the quality of dietary fat on blood pressure was *limited – no conclusion*.

Body weight

Intervention studies have shown that reduced-fat diets consumed *ad libitum* contribute to weight reduction (96), although the effect is limited and RCTs with durations from six months to over eight years have shown average weight losses of 1.4–1.6 kg. Results from prospective cohort studies do not indicate any association between fat intake and body weight (97) in contrast to the somewhat different results from the RCTs. The evidence from RCTs for a positive association between the amount of dietary fat and body weight was found to be *probable* in the SR by Schwab and co-workers (50). There is no evidence that the quality of fat has any effect on body weight (50).

CVD

The NNR SR included 29 publications on the association between dietary fat and fatty acids and cardiovascular outcomes (50). For *total fat intake*, the results from the included studies showed no difference with respect to the risk of any of the CVD outcomes (50). Mean intakes of total fat in the prospective studies varied from 35 E% to about 45 E%. In summary, a direct association between total fat intake and CVD outcomes is *unlikely*. For SFA, MUFA, and PUFA, a meta-analysis comprising 28 cohort studies and 16 RCTs found no association between the intake of SFA and the risk of CHD independent of the intake of unsaturated fat or a healthy dietary pattern (98).

In a meta-analysis of 48 RCTs, substituting unsaturated fatty acids for SFA reduced CVD events by 14% (99). Meta-analyses of intervention studies showed that reducing SFA intake by reducing and/or modifying dietary fat reduced the risk of cardiovascular events by 14%. The reduction in CVD events was seen in studies of fat modification of at least two years' duration in which the risk reduction was 22%. Significant risk reductions were seen in men, but not in women (99), and the effect might be more pronounced in younger subjects (100).

A meta-analysis of eight RCTs compared the effect on CHD of interventions with increased intake of PUFA as a replacement for SFA. PUFA intake in the intervention groups was 15 E% compared to 5 E% in the control groups. The results of those studies showed a significant overall risk reduction of 19%, which corresponds to a 10% reduced CHD risk for each 5 E% increase of PUFA intake. Studies of longer duration showed greater benefits (101). A pooled analysis of data from 11 US and European prospective cohort studies showed a 20% decreased risk of CHD in both men and women when 5% of the energy was changed from SFA to PUFA (102). Furthermore, pooled evidence from different types of studies showed a ≥2–3% reduced risk of CHD when 1 E% SFA was replaced with PUFA (103).

The SR by Schwab and co-workers (50) concluded that there is *convincing* evidence that partial replacement of SFA with PUFA decreases the risk of CVD, especially in men.

Substituting MUFA for SFA does not affect the CHD risk in epidemiological studies (102). In long-term prospective cohort studies, MUFA have been found to have a favourable effect on the risk of CHD, although unfavourable effects have also been reported (88).

The SR by Schwab and co-workers (50) concluded that the evidence for the favourable effect of cis-MUFA on CHD was *unlikely* for a direct association. It is of note, however, that the intake of MUFA correlates highly with the intake of SFA except in countries where olive oil is used in abundance (104).

When SFA is replaced with carbohydrates without regard to the quality of the carbohydrates, no beneficial effect on CHD risk has been found. In the pooled analysis of 11 US and European cohort studies, the effect of replacing SFA with carbohydrates on ischaemic heart disease was unfavourable (102). In populations with very low intake of both total fat and SFA (<15 E% and <5 E%, respectively), such as in rural China, CHD is rare (105). This discrepancy is most likely explained by the quality of carbohydrates in the diet and lower BMI as well as the level of physical activity (106). However, differences in life expectancy compared to the Nordic countries might also explain this discrepancy. In a Danish prospective cohort study, replacement of SFA with carbohydrates with high glycaemic index increased the risk of myocardial infarction whereas a replacement with carbohydrates with low glycaemic index did not affect the risk (107).

Dietary intake of n-3 fatty acids of animal origin such as fish and, in some studies, of ALA of plant origin has reduced mortality in patients with

CHD (108–111) as has the use of fish oil supplements (112). However, whole fish might be more beneficial than fish oil supplements (111, 113). The effect of n-3 fatty acids might be mediated by reduced risk of cardiac arrhythmias (113). An intake of 200–250 mg/d of EPA + DHA has been shown to be effective with no further benefit with an increasing dose (114, 115). A recent Scandinavian study reported an increased overall risk of CVD at a very low intake (<0.06 g/d) of n-3 long chain PUFA (85). In the SR by Schwab and co-workers (50), the evidence of long chain n-3 PUFA on CVD risk was evaluated as *suggestive*. However, it is important to pay attention to the source of long chain n-3 PUFA – either fish or fish oil supplement – when assessing the evidence.

In a Finnish study, the proportion of ALA in serum lipids showed a similar inverse association with the risk of CHD death as the proportions of EPA and DHA (46). ALA intake has also been shown to be associated with decreased risk of CHD (98, 116, 117). The evidence for ALA intake on CVD risk was evaluated as *suggestive* in the SR by Schwab and co-workers (50). However, the proportion of total PUFA, n-6 PUFA, and LA in plasma lipids also showed a favourable effect, and the evidence for the inverse association of these variables with CVD mortality was evaluated as *suggestive*.

A high intake of TFA has been associated with increased risk of CVD in some prospective studies (118–120) as well as in a meta-analysis of cohort studies (98). In a study using principal component analysis of the plasma phospholipid fatty acid composition, TFA were related to a greater risk of CVD risk and progression of atherosclerosis in women with ischaemic heart disease (121).

Stroke

Long chain n-3 PUFA in the form of fish intake reduces the risk of stroke mortality (122), and a very low long chain n-3 PUFA intake (<0.06 g/d) increases the risk of stroke (85). The meta-analysis by Hooper and co-workers (99) included stroke as a secondary outcome. Eleven trials reported on stroke events and showed no significant overall effect of reduced and/or modified fat intake, although this was largely driven by results from the WHI trial (123) that mainly focused on reduction in total fat intake.

T2DM

Total fat intake and SFA intake were associated with a higher risk of T2DM in a prospective cohort study, but these associations were not independent of BMI (124). An increase in PUFA intake from 3 E% to around 6 E% in

exchange for SFA or carbohydrates might be associated with a 20% reduction in the risk of T2DM (125–127). According to Schwab and co-workers (50), there is *probable* evidence that LA intake has a favourable effect on the risk of T2DM. The evidence for a favourable effect of the proportion of LA in plasma phospholipids and cholesteryl esters was *suggestive* (50). Non-significant associations have been reported as well (128).

An increase in the intake of long chain n-3 PUFA from <100 mg/d to >360 mg/d has been associated with a 20%–40% increased risk of T2DM (124, 126, 128, 129). However, in a recent meta-analysis, including studies examining the effect of both fish intake and fish oil supplementation, the effect of long chain n-3 PUFA on the risk of T2DM was not significant (130). As mentioned in the section on CVD, it is important to pay attention to the source of long chain n-3 PUFA – either fish or fish oil supplement – when assessing the evidence.

The proportion of SFA in plasma phospholipids and cholesteryl esters might be associated with increased risk of T2DM, and the evidence for this was evaluated as *suggestive* in the SR by Schwab and co-workers (50). Odd chain SFA (C15:0 and 17:0) might have an inverse association with the risk of T2DM, and the evidence for this was evaluated as *suggestive* (50). Odd chain fatty acids have been considered as a biomarker of dairy fat intake, but both C15:0 and C17:0 also exist in fish, even in higher amounts than in dairy fat (131–133). In the EPIC study, there was a strong positive correlation ($r = 0.8$) between total fish intake and C17:0 in plasma phospholipids (133).

Reduction of total fat and SFA intake in conjunction with modest weight reduction, increased intake of dietary fibre, and increased physical activity reduces the risk of diabetes in subjects with glucose intolerance (134–138). In the Finnish Diabetes Prevention Study (DPS), diabetes incidence was associated with a diet high in fat and low in carbohydrate. Thus, a diet high in fat might even be detrimental in people with impaired glucose metabolism, i.e. in 25–40% of the population (135).

Cancer

In experimental animal studies, fat intake promotes the development of breast cancer and colon cancer. Experimental studies also suggest that n-3 fatty acids counteract cancer cell proliferation, and n-6 fatty acids tend to have the opposite effect (139, 140). However, epidemiological studies examining the link between dietary fats and cancer risk have reached mixed results. Such discrepancies can partly be explained by the complex

composition of dietary fat and the presence of other bioactive compounds in the diet (141) or by diverse confounding factors such as drug use (142), unstable food habits over time (143), or genetic variations in key metabolising enzymes (140).

Breast cancer is the major cancer type in women, and the studies included in the SR by Schwab and co-workers (50) did not find any association between the risk of breast cancer and the intake of total fat in postmenopausal women. The evidence regarding both the intake and tissue markers of the quality of dietary fat was also evaluated as *inconclusive* in the SR by Schwab and co-workers (50). No association with the intake of total fat or quality of fat with other types of cancer, i.e. endometrial, colorectal, pancreatic, oesophageal, gastric, renal cell, bladder, lung, or skin cancer, was found in the SR by Schwab and co-workers (50). However, for ovarian cancer the evidence for a positive association with the intake of SFA is *suggestive*. There is also *suggestive* evidence for an inverse association with the intake of ALA and risk of prostate cancer.

Although the criteria for including studies were slightly different for the SR by Schwab and co-workers (50) and the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) report (139), the overall conclusions are generally similar. However, the WCRF/AICR report concluded that the evidence is *limited–suggestive* for a link between total fat and an increased risk of postmenopausal breast cancer and lung cancer. There was also *limited–suggestive* evidence for an increased risk of foods containing fat of animal origin and colorectal cancer. According to the WCRF/AICR report (139) there is an indirect link between energy-dense diets and cancer, and the evidence indicates a *probable* or *convincing* link between body fatness and most cancer types. Interestingly, an SR of food pattern studies (144) concluded that so called "prudent" dietary patterns are associated with reduced breast cancer risk while "Westernized" dietary patterns are associated with increased risk (See chapter on Foods and food patterns: Guidelines for a healthy diet). The quality of dietary fat is potentially closer to the recommendations in "prudent" dietary patterns compared to "Westernized" dietary patterns.

Pregnancy and lactation

DHA is necessary for growth of the brain and other membrane-rich tissues in foetal and early postnatal life. There is considerable inter-individual variation in the formation of DHA from ALA due to common polymorphisms in the Δ-5 and Δ-6 desaturase genes FADS1 and FADS2 (17).

Evidence from RCTs in which EPA + DHA was administered to pregnant women (from 150–200 mg DHA/d up to 1200 mg DHA/d) showed reduced risk of preterm birth (145, 146).

A consensus statement published in 2007 (147) advised that pregnant and lactating women's intake of DHA should be at least 200 mg/d. This is in line with the FAO (13), which set the average nutrient requirement (ANR) to 200 mg/d.

A Cochrane Review of six RCTs did not find convincing evidence for supplementation of n-3 LCPUFA with doses varying from 200 mg/d of DHA to between 1.5 and 2.7 g/d of EPA + DHA or 10 mL/d of cod liver oil to breastfeeding mothers for improving their children's neurodevelopment and visual acuity. However, supplementation had a positive effect on head circumference in two studies (10 mL/d of cod liver oil or 200 mg/d DHA) and decreased risk of allergic sensitisation in one study with a dose of 2.7 g/d of EPA + DHA (148). The results on allergic diseases and cognition differ somewhat between the effects of fish oil and other PUFA supplementation (149, 150). An intake of DHA slightly greater than 1 g/d or a total intake of 2.7 g/d of n-3 LCPUFA (both EPA and DHA) is considered safe (147).

Recommendations

Adults and children from 2 years of age

SFA: Intake of SFA should be limited to less than 10 E% calculated as triglycerides. Even lower levels might be desirable in persons with hypercholesterolaemia. Detailed recommendations on intakes of specific SFA are not given. The cholesterol-raising fatty acids are generally found in the same foods that are the main sources of total SFA.

TFA: The intake of TFA both from fat-containing dairy products and partially hydrogenated, industrially produced fats should be as low as possible. A reduction in SFA intake will generally also reduce the intake of TFA and dietary cholesterol.

Cis-MUFA should contribute 10–20 E%.

Intake of cis-PUFA (the sum of n-6 and n-3 fatty acids) should contribute 5–10 E%, including at least 1 E% from n-3 fatty acids. An intake of EPA + DHA up to 200–250 mg per day has been associated with decreased risk of CVD.

Intake of cis-MUFA and cis-PUFA should make up at least two thirds of the total fatty acids.

Because minimum requirements of cis-PUFA for adults are not known, the estimates are based on threshold intake data from children. The recommendation for EFA, i.e. LA and ALA, is 3 E%, of which at least 0.5 E% should be ALA.

For pregnant and lactating women, the contribution of cis-PUFA should be at least 5 E%, including 1 E% from n-3 fatty acids of which 200 mg/d should be DHA.

The upper intake range for total PUFA intake is 10 E%. Increased intakes are not recommended due to potential adverse effects.

The evidence for defining an optimal ratio between n-6 and n-3 PUFA is insufficient and in NNR 2012 no recommendation for the ratio of n-6 to n-3 has been set.

The total fat recommendation is 25–40 E%, which is mainly based on the recommended ranges for fatty acid categories. Very low-fat diets tend to reduce HDL-cholesterol concentration and increase triglyceride concentration in serum/plasma and might impair glucose tolerance in susceptible individuals (151). Furthermore, it is difficult to ensure sufficient intake of fat-soluble vitamins and EFA if total fat intake is below 20 E%.

A limitation of the total fat intake will facilitate achieving the recommended intakes of certain micronutrients and dietary fibre. The amount of dietary fat is also associated with body weight. Experiences from the STRIP and Young Finns studies show that a moderate fat intake (about 30 E%) with a reduction in SFA intake results in a better CVD risk profile and fewer atherosclerotic changes in early life (152–155).

For dietary planning purposes, a suitable target is the middle value of the range, i.e. about 32–33 E%, given that careful attention is paid to the quality of both fat and carbohydrates and the amount of dietary fibre.

Children 6–23 months

Due to the rapid growth rate during infancy, fat accounts for about 50% of the total energy intake in human milk and infant formula. Because exclusive breastfeeding is recommended during the first 6 months of life, and because the fat content of infant formula and follow-on formula is regulated (40–55 E% in infant formula and 35–55 E% in follow-on formula) (37), no further recommendations are given for the first 6 months of life. After 6 months of age, this high energy density is reduced with increasing amounts of complementary foods. Thus the fat intake can decline rapidly to around 30 E% at the end of infancy depending on the composition of the complementary food and the extent of partial breastfeeding. It is also common that after the first

year the proportion of fat increases gradually until 3 years of age to levels common among adults. If the proportion of fat and, therefore, the energy density of the diet becomes too low in the first year or in early childhood this might result in insufficient energy intake because children of this age have limited capability for ingesting more voluminous servings.

According to the EFSA, total fat intake below 25 E% has been associated with low vitamin intakes in some young children (10). The German-Austrian-Swiss recommendation (156) of total fat intake for infants 4 to 11 months of age is 35–45 E%. The US Institute of Medicine has set an adequate intake (AI) for 7–12 month olds to 40 E% (157). Similarly, the EFSA has set an AI at 40 E% for children aged 7–12 months based on AI and consensus reports (10, 158). In the NNR 2012, the intake of total fat for infants between 6 and 11 months of age is recommended to be kept between 30 E% and 45 E%, and this is the same as in the NNR 2004.

Some studies in children indicate that a fat content around or below 30 E% of the total energy is already applicable after the age of 1 year because fat intakes at these levels did not adversely influence children's growth and neurological development in the Finnish STRIP study (159). The German-Austrian-Swiss 2008 recommendation of total fat intake for children aged 1 to 3 years is 30 E% to 40 E% (156) and similarly the US Institute of Medicine set an acceptable macronutrient distribution range (AMDR) for the proportion of fat to 30–40 E% for children 1 to 3 years of age (157). The EFSA set the recommended intake for the same age group (1–3 years old) to 35–40 E% (10).

In NNR 2012, the intake of total fat for children from 12 to 23 months of age is recommended to be kept between 30 E% and 40 E%. From the age of 2 years, the recommendation of total fat intake is the same as for older children and adults in NNR 2012.

The quality of dietary fat is also important in infancy and childhood. From the age of 12 months, the intake of SFA should be less than 10 E%. The intake of TFA both from dairy fat and partially hydrogenated, industrially produced fats should be kept as low as possible. Partial breastfeeding is recommended from 6 months and throughout the child's first year, and can be continued for as long as it suits the mother and the child. Half or more of the energy from human milk is fat. Typical fatty acid composition (wt%) in mature breastmilk is 40–45% SFA, 40–45% MUFA and 13–16% PUFA (160–164) There is, however, no evidence for a higher recommendation of saturated fat intake for 6–11 month old children than the recommendation for older children, i.e. lower than 10 E%.

For the intake of cis-PUFA in childhood, no new convincing evidence has emerged for changing the recommendations from NNR 2004. The EFSA's AI for LA is 4 E% and AI for ALA is 0.5 E%, but the EFSA also adds an AI for DHA of 100 mg/d (10). This is primarily based on cohort studies and a few randomized trials with DHA supplementation to the foetus or young infants that indicate a positive effect on visual acuity, cognitive function and attention, maturity of sleep patterns, spontaneous motor activity, and immunity.

In the NNR 2012, it is recommended that the total intake of cis-PUFA for children 6–23 months of age should constitute 5–10 E% and that this should include at least 1 E% from n-3 fatty acids, including DHA, as in NNR 2004. However, the optimum ratio of n-6 to n-3 fatty acids is not known.

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11 Carbohydrates

	Dietary fibre	Added sugars, E%	Carbohydrates Total, E%
6–11 mo	–	< 10 E%	45–60*
1–17years	2–3 g/MJ	< 10 E%	45–60*
≥ 18 years	>3 g/MJ	< 10 E%	45–60*
- women	≥ 25 g/d		
- men	≥ 35 g/d		

* acceptable range.

Introduction

Carbohydrates provide energy in the diet mainly as starch and sugars and to a lesser extent as dietary fibre and sugar alcohols. Generally used energy conversion factors are 17 kJ per gram of available (glycaemic) carbohydrates, 8 kJ per gram of total fibre, and 10 kJ per gram of sugar alcohols (polyols). Conversion factors partly depend on the methods used to derive carbohydrate values, e.g. "by difference" or by analysis of individual constituents (see the chapter on energy).

Dietary sources and intake

Cereals and potatoes are the major sources of carbohydrates in the Nordic diet. Fruit, fruit juices, berries, and milk provide sugars (mono- and disaccharides). Sweets, soft drinks, fruit syrups, sweetened bakery products, and sweetened dairy products are main sources of refined, added sugars.

Wholegrain cereals, fruits, berries, and vegetables provide the main proportion of the dietary fibre intake. In the Nordic diets, total carbohydrates contribute on average 43–52 E%, including 10–16 E% added sugars, and provide 25–27 g of fibre per 10 MJ.

Chemical classification

The chemical classification of carbohydrates is usually based on molecular size and monomeric composition. The three principal carbohydrate groups are sugars (1 or 2 monomers), oligosaccharides (3–9 monomers), and polysaccharides (10 or more monomers) (1, 2). The most important food carbohydrates are glucose, fructose, and galactose (monosaccharides); sucrose, lactose, and trehalose (disaccharides); oligosaccharides; and polysaccharides. There are two main classes of polysaccharides, starch and non-starch polysaccharides (NSP). Starch is a homopolymer of glucose and comes in two main forms, amylose (basically unbranched) and amylopectin (highly branched). NSP include a host of different polymers and are highly variable in terms of molecular size and structure as well as in monomeric composition. The main classes of NSP are cellulose, hemicelluloses, pectins, and hydrocolloids. Due to their structural variability, different NSP can have very different physical-chemical properties and these are of key importance for their physiological effects. Cellulose is insoluble in water, and pectins and hydrocolloids, e.g. guar gum and mucilages, can form highly viscous solutions in water.

Nutritional classification

Nutritionally, carbohydrates can be divided into two broad categories. The first include those that are digested and absorbed in the human small intestine providing carbohydrates to body cells, and the second include those passing on to the large intestine forming substrates for the colonic microflora (3, 4). The concept of "glycaemic carbohydrate", meaning "providing carbohydrate for metabolism", was introduced by the FAO/WHO (1, 2). The non-digestible (unavailable) carbohydrates (NDC) are commonly referred to as "dietary fibre".

Glycaemic carbohydrates

The main glycaemic carbohydrates are:

- Glucose and fructose (monosaccharides)
- Sucrose and lactose (disaccharides)
- Malto-oligosaccharides
- Starch (polysaccharide)

The term "sugars" covers monosaccharides and disaccharides. In the literature, various terms are used to differentiate between sugars naturally occurring in foods, i.e. "intrinsic" sugars, and sugars and sugar preparations added to foods, i.e. "added" or "extrinsic" sugars (5, 6). In the NNR, the term "added sugars" refers to refined sugars such as sucrose, fructose, glucose, starch hydrolysates (glucose syrup, high-fructose syrup), and other isolated sugar preparations used as such or added during food preparation and manufacturing.

Fructose and glucose are mainly found in fruits, berries, juices, and some vegetables. Free galactose is rare in foods except in fermented and lactose-hydrolysed milk products. Fruits, berries, and juices also provide some intrinsic sucrose. Sucrose is found in varying amounts in manufactured foods, e.g. soft drinks and sweets, and is used as a sweetener and cooking ingredient in the household. More or less completely hydrolysed starches or high-fructose syrups, in which about half the glucose is isomerised to fructose, have been increasingly used to replace sucrose in confectionary and carbonated drinks. Lactose occurs exclusively in milk and milk products. Malto-oligosaccharides originate mainly from partially hydrolysed starch. Bread and other cereal products, potatoes, and tubers are major sources of starch (1, 2).

Sugar alcohols (polyols) such as sorbitol, xylitol, mannitol, and lactitol, are usually not included in the term "sugars". However, they are absorbed to some extent by the body and are included in "carbohydrates" according to the European legislation for nutritional labelling (7).

Organic acids such as lactic acid, citric acid, and malic acid, which occur in fermented foods, fruits, and berries, respectively, can contribute to carbohydrates if measured "by difference."[2]

2 (100–(sum of protein, total fat, ash, and water)).

Table 11.1. Classification of main food carbohydrates and related substances, all included in carbohydrate as assessed "by difference". Adapted from EFSA (8) and NNR 2004

				Analytical methods			
Class (DP *)	**Sub-group**	**Components**	**Monomers**	**Digestibility****	**Sugars**	**Starch**	**Dietary fibre AOAC[1]**
Sugars (1 or 2)	Mono-saccha-rides	Glucose		+	+		
		Galactose		+	+		
		Fructose		+	+		
	Disaccha-rides	Sucrose	Glu, Fru	+	+		
		Lactose	Glu, Gal	+(–)***	+		
		Trehalose	Glu	+	+		
		Maltose	Glu	+			
Oligo-saccha-rides (3–9)	Malto-oligo-saccha-rides	Malto-dextrins	Glu	+	+	+	
	Other oligo-saccha-rides	a-Galacto-sides (GOS)	Gal, Glu	–	+/–		
		Fructo-oligo-saccha-rides (FOS)	Fru, Glu	–	+/–		
		Poly-dextrose	Glu	–			
		Resistant dextrins	Glu	–			
Polyols	Maltitol, sorbitol, xylitol, lactitol			+ (–)****			
Poly-saccha-rides (>9)	Starch	Amylose, Amylo-pectin	Glu	+ (–)		+	+ (–)[3]
		Modified starch	Glu	–		+/–[2]	+

					Analytical methods		
Class (DP *)	Sub-group	Components	Monomers	Digestibility**	Sugars	Starch	Dietary fibre AOAC[1]
		Resistant starch	Glu	–		+/–[2]	+
		Inulin	Fru	–			+ (–)[3]
	Non-starch poly-saccha-rides	Cellulose	Glu	–			+
		Hemi-celluloses		–			
		Pectins	Uronic acids	–			
		Other hydro-colloids, e.g. gums, mucilages, β-glucans	Variable	–			
Related substances		Lignin		–			+
		Tannins/polyphenols		+ (–)[4]			+ (–)[3]
		Phytate		–			+ (–)[3]
		Organic acids		+			–

* DP = Degree of polymerisation.
** Denotes digestibility in the small intestine: + digestible, +(–) mainly digestible, +/– partly digestible, – non-digestible.
*** Lactose is poorly digested by individuals with low intestinal lactase activity.
**** Polyols are partly and variably absorbed.
1 AOAC: Association of Official Analytical Chemists.
2 +/– Determined in some but not all methods.
3 Partly determined.
4 Includes soluble, partly absorbable, and insoluble (non-absorbable) forms.
Fru = Fructose, Glu = Glucose, Gal = Galactose.

Dietary fibre

The main types of dietary fibre are:

- Non-starch polysaccharides – cellulose, hemicelluloses, pectins, hydrocolloids, etc.
- Resistant oligosaccharides – fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), and other resistant oligosaccharides

- Resistant starch
  - Physically enclosed starch
  - Some types of raw starch granules
  - Retrograded amylose
  - Chemically modified starches
- Lignin (and other usually minor components associated with the dietary fibre polysaccharides)

The term dietary fibre was originally defined as "that portion of food which is derived from cellular walls of plants which are digested very poorly by human beings" (9). The recognition that polysaccharides added to foods, notably hydrocolloids, could have effects similar to those originating from plant cell walls led to a redefinition of dietary fibre to include "polysaccharides and lignin that are not digested in the human small intestine" (10).

Internationally, definitions of dietary fibre vary somewhat. The EFSA (8) defined dietary fibre as "non-digestible carbohydrates plus lignin including non-starch polysaccharides (NSP) – cellulose, hemicelluloses, pectins, hydrocolloids (i.e. gums mucilages, β-glucans), resistant oligosaccharides – fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), other resistant oligosaccharides, resistant starch – consisting of physically enclosed starch, some types of raw starch granules, retrograded amylase, chemically and/or physically modified starches, and lignin associated with the dietary fibre polysaccharides". This definition is the basis for the EC legislation on labelling (Commission directive 2008/100/EC), which also requires that beneficial physiological effects have to be demonstrated before natural or synthetic fibre can be added to foods. This is in accordance with the definition by Codex Alimentarius (11), although whether non-digestible carbohydrates with 3–9 monomeric residues should be included or not is so far left to the national authorities. The US Institute of Medicine (IoM) (12) uses the term "total fiber", which is the sum of "dietary fiber" consisting of non-digestible carbohydrates and lignin that are intrinsic and intact in plants and "functional fiber" consisting of isolated, non-digestible carbohydrates that have beneficial physiological effects in humans.

With any definition of dietary fibre, NSP from plant cell walls, such as cellulose, hemicelluloses, and pectins, are the dominant components. Hydrocolloids can be either naturally occurring cell wall or storage components or added to foods as ingredients to obtain specific technological and/or nutritional benefits. Resistant oligosaccharides and resistant starch have partly similar physiological and nutritional effects as non-starch polysaccharides.

Cellulose is insoluble in water and occurs together with hemicelluloses in cereals. The lignified outer layers in wholegrain products are the predominant source of cellulose, and this type of fibre is most resistant to fermentation by the colonic microflora. Oats and barley contain high levels of β-glucan, a soluble viscous polysaccharide. Pectins – the main type of dietary fibre in fruits and vegetables – have similar properties.

The absorption of polyols in the small intestine depends on their structure and on the amount consumed, and when consumed in excess amount may cause gastrointestinal discomfort such as diarrhoea.

Considerable amounts of lactose can reach the colon in infants due to the high content of lactose in breast milk, and this can cause gastrointestinal discomfort and diarrhoea. This is also the case in children and adults with low intestinal lactase activity. A limited capacity to absorb fructose seems to be rather common, especially if this sugar is consumed alone without glucose, and this can be another cause of diarrhoea (13).

Analytical methods

Dietary fibre is usually analysed using enzymatic gravimetric or enzymatic chemical methods that include NSP, analytically resistant starch, and lignin. Methods measuring NSP alone give lower estimates in foods containing resistant starch and/or lignin, e.g. wholegrain flour and cereals processed in a way that generates resistant starch. Resistant oligosaccharides are not included in any of the current dietary fibre methods and, therefore, have to be measured separately and added to the total fibre estimate. Dietary fibre methods that include resistant starch measure the fraction resistant to the enzymes used in the assay. This "analytically resistant starch" includes mainly retrograded amylose, and the analytical methods need to be fine-tuned to correspond better to the physiologically resistant starch (3, 14).

In both epidemiological studies and mechanistic intervention studies, the term "dietary fibre" is usually used for non-digestible plant material as measured by official analytical methods approved by the Association of Official Analytical Chemists (AOAC). This means that dietary fibre includes NSP as the main component along with lignin and analytically resistant starch. Other NDC such as resistant oligosaccharides and inulin are not included and usually make up only a small part of the NDC in Nordic diets.

The dietary fibre recommendation in NNR 2012 refers to dietary fibre naturally occurring in plant foods as measured by AOAC methods for total dietary fibre.

With the methods currently used, some overlap might occur and some components might be missed (see Table 11.1.).

Physiology and metabolism

Glycaemic carbohydrates

The glycaemic carbohydrates provide carbohydrate to the cells of the body mainly in the form of glucose. In practice, only monosaccharides can be absorbed in the small intestine. The enzymatic degradation of starch begins by the action of salivary amylase and is continued in the small intestine by pancreatic amylase. The degradation products – mainly maltose and oligosaccharides – are further hydrolysed to glucose by a set of enzymes (disaccharidases) that are bound to the brush border membrane of the enterocytes. The same enzymes hydrolyse the dietary disaccharides. Glucose and galactose are absorbed efficiently by a secondary active carrier coupled with sodium (glucose transporter, GLUT 2), whereas fructose is absorbed by facilitated diffusion that does not involve sodium co-transport (GLUT 5). Absorption of monosaccharides is generally regarded as the rate-limiting step, but down-regulation of lactase (hypolactasia) occurs in most humans from 1 to 2 years of age to the teenage years resulting in a limited lactose absorption capacity. The same is true for sucrose in the rare case of sucrase deficiency (15–24) and for fructose in the hereditary congenital disorder fructose intolerance (25).

Absorbed sugars are transported to the liver and then to the systemic circulation, and cellular uptake is mediated by GLUT 1–4 that are variously expressed in different tissues. Insulin is a key hormone for the uptake and metabolism of carbohydrates, and the plasma insulin concentration increases immediately after ingestion of glycaemic carbohydrates. One important effect of increased insulin is an increase in the translocation of glucose transporters (GLUT 4) to cell membranes. This increases peripheral uptake and counteracts an excessive rise in blood glucose. Glucose is a preferred fuel for most body cells, and can be stored as glycogen in the liver and in the muscles. The storage capacity is limited to around 500 g, of which 300–400 g can be stored in the muscles. Liver glycogen is used to maintain normal blood glucose levels between meals, and muscle glycogen is used primarily as a source of energy within the muscles. Unlike glucose, fructose enters mainly liver cells without the need for insulin. The metabolism of fructose favours lipogenesis more than glucose. Galactose, arising from hydrolysis of lactose, is also transformed to glucose mainly in

the liver, and this transformation is inhibited by alcohol (ethanol).

The glycaemic carbohydrates reach the peripheral circulation mainly as glucose, and insulin is secreted in response to the elevated blood glucose concentration after a meal. Vagal signals, gastrointestinal hormones (incretins), and certain non-carbohydrate food components – especially amino acids – contribute to the stimulation of insulin secretion. The blood glucose level is determined by the following three main factors: 1) The rate of intestinal carbohydrate uptake, 2) the net liver uptake or elimination, and 3) the peripheral glucose uptake, which is dependent on both insulin production by the pancreas and the level of peripheral insulin sensitivity or resistance. Even with a constant dietary glycaemic carbohydrate load, there is a wide variety of blood glucose responses between individuals. These responses form a continuum from low responses to impaired glucose tolerance to type-2 diabetes.

Glycaemic index (GI)

The concept of glycaemic index (GI) was introduced by Jenkins and co-workers in 1981 (26) as a way to rank foods in a standardised way with regard to their effects on blood glucose levels after a meal. The FAO/WHO Expert Consultation on Carbohydrates in Human Nutrition (1, 2) defined GI as the incremental area under the blood glucose response curve after a 50 g carbohydrate portion of a test food expressed as a percentage of the response to the same amount of carbohydrate from a standard food taken by the same subject. Glucose and white bread have been used as standards. GI values obtained with the white bread standard are about 40% higher than those obtained with the glucose standard. An ISO standard that uses glucose as the standard for the determination of GI in foods was approved in 2010 (27). Application of this standard will contribute to more reliable and comparable GI values. It has been recommended that GI should only be used to rank food items with at least 10–20 g of glycaemic carbohydrates in the portion of the food analysed (28).

The factors that determine the GI of a carbohydrate are generally unrelated to the molecular size of the carbohydrate. For instance, both fructose and sucrose have a lower GI than white bread (29). Starchy foods, on the other hand, can have a low, intermediate, or high GI depending on the composition (amylose/amylopectin ratio), amount of resistant starch, and physical/chemical state. The swelling and dissolution of starch with wet heat treatment, known as gelatinisation, is particularly important in making starch more readily accessible to digestive enzymes (29).

Physical barriers such as intact cereal grains, the cellular structures in leguminous seeds, parboiled rice, and whole fruits, and the protein network in pasta products are food-related factors lowering the GI (29). Organic acids (acetic acid, propionic acid, and lactic acid) decrease the glycaemic response to foods or meals mainly due to inhibition of gastric emptying (30). Viscous, soluble types of dietary fibre can also delay gastric emptying in addition to their inhibitory effect on diffusion and transport in the small intestine (31). Other factors such as physical activity influence glucose metabolism and have the potential to influence insulin sensitivity and, therefore, the glycaemic response to any meal (See chapter on physical activity, (31) and (32)).

The concept of glycaemic load (GL) was introduced in 1997 by Harvard epidemiologists to quantify the glycaemic effect of a portion of food (33). GL is defined as the amount of glycaemic carbohydrate in a food multiplied by the GI of the food divided by 100. The glycaemic response to a meal can also be influenced by the protein and fat content as well as by the size of the meal and the amount of drink taken with the food. Several groups, however, have demonstrated that the glycaemic response to a meal can be predicted from properly determined GI of the constituent foods (34, 35). Lack of consistency in other studies (36) using published GI values might be due to these values not being applicable to the foods in question.

In conclusion, standardized analytical methods exist to measure GI. However, when studying the physiological effects of glycaemic carbohydrates many other factors have to be taken into consideration. This limits the use of GI in the prediction of the physiological effects of carbohydrates in meals and habitual diets.

Dietary fibre

Dietary fibre constituents pass through the upper gastro-intestinal tract and enter the colon substantially unmodified. In the colon, they are subject to anaerobic fermentation by the colonic microflora. The extent of fermentation is dependent on both substrate and host factors such as the molecular structure and physical form of the substrate, the bacterial flora, and the transit time. Less fermentable types of fibre, such as the lignified outer layers of cereal grains, generally have the most prominent faecal bulking effects due to their ability to bind water in the distal colon. Fermentable fibre also contributes to the faecal bulk through increased microbial mass. The main fermentation products are short-chain fatty acids (SCFA) such

as acetate, propionate, and butyrate and gases, the most notable of which are hydrogen and methane.

Dietary carbohydrates and health

Two reviews were conducted for the update of NNR 2012, one systematic review (SR) on dietary sugars (37) covering studies in adults and an overview on dietary fibre and glycaemic index (38). These reviews included original papers and expert reports published between 2000 and December 2011.

Total and glycaemic carbohydrates

Plasma lipids, glucose, and insulin

The influence of carbohydrates on plasma lipid, glucose, and insulin levels depends on several factors such as food source, physical form, and the amount and type of macronutrient replaced. Generally, a transient increase in fasting triglycerides and decreased HDL-cholesterol levels is seen when total dietary carbohydrate intakes are increased from 30–40 E% up to 60–70 E% (8). However, long-term effects depend on dietary carbohydrate sources. In an earlier controlled eight-month intervention study with healthy subjects following a fat-modified diet rich in fruits and vegetables, complex carbohydrates, and dietary fibre conforming to the NNR, an initial increase in triglyceride levels was seen that diminished with time (39).

A specific triglyceride-elevating effect of fructose has been demonstrated in animal experiments. In earlier, mainly short-term human studies, a high intake of refined sugars (> 20 E% sucrose or > 5 E% fructose) resulted in elevated triglyceride levels (8, 37). Results from more recent randomised controlled trials (RCTs) with high intakes (up to 17 E%) of refined sugars are partly conflicting, and evidence from epidemiological studies is also limited (8, 37). Results from two prospective studies reviewed by Sonestedt et al. (37) showed a positive association between intake of sugar-sweetened beverages and dyslipidaemia, i.e. elevated triglycerides and low HDL-cholesterol, and one study also showed a positive association with elevated LDL-cholesterol. Results from two prospective cohort studies and two RCTs on blood glucose and insulin levels/response did not show any consistent associations with intake of sugars or sugar-sweetened beverages (37). The EFSA evaluated five RCTs, three of which were published before 2000 (8). Two of those three studies showed increased insulin concentrations at high

intakes of sucrose (18–30 E%) compared to low intakes (3–10 E%), but no difference was seen in the third study. An effect on glucose concentration was observed in one study with no difference seen in another.

In summary, there is *insufficient* evidence to draw conclusions on effects on plasma lipids with respect to fructose or sucrose (of which half is fructose) in the general population. The evidence for effects on glucose and insulin response is *limited*. There is *limited-suggestive* evidence that high intake of sugar-sweetened beverages might be associated with dyslipidaemia indicating that the specific food source of sugar might influence metabolic response.

Blood pressure

The NNR SR on sugars included three prospective cohort studies and one RCT on the association between intake of sugars and blood pressure (37). A significant positive association with sugar-sweetened beverages was found in one of the prospective studies (40), but no significant association was found in the other two. The authors concluded that no consistent evidence for an association between dietary sugar intake and blood pressure was found. However, intake of sugar-sweetened beverages ≥ 1 serving per day (1 bottle, glass, or can) was significantly associated with incident hypertension after 16 to 38 years follow-up in three US cohorts (41).

It can be concluded that there is *suggestive* evidence that frequent consumption of sugar-sweetened beverages has an unfavourable effect on blood pressure. This is in line with studies examining whole diets low in sugar and fat and high in natural fibre-rich foods (e.g. the DASH studies) (42).

Type-2 diabetes

Results from trials aiming at preventing type-2 diabetes have shown that fat-modified, high-fibre diets together with 20–30 min daily physical activity reduced type-2 diabetes onset in high-risk, glucose-intolerant individuals (43–45).

The NNR SR included nine prospective cohort studies (8 of good quality and 1 of low quality) that examined the association between intake of sugars and incidence of type-2 diabetes (37). The results showed no consistent association between intake of total sugars, sucrose, or fructose and type-2 diabetes. Four of the six studies that investigated the association with sugar-sweetened beverages reported a significantly increased relative risk of type-2 diabetes with increasing intake. In one study, a significant positive association was found in the model that did not adjust for BMI.

The NNR SR concluded that there is *probable* evidence that high consumption of sugar-sweetened beverages increases the risk of type-2 diabetes (37), and this supports a limitation on the intake of added sugars. The apparent inconsistency in the studies examining total or individual sugars might be due to confounding because sugars in the form of whole fruits and vegetables have different effects compared to refined, added sugars, especially as sugar-sweetened beverages.

Body weight

The role of carbohydrate intake as a primary determinant for body weight maintenance has been less studied. Most studies using iso-energetic or ad-libitum designs have focused on changes in fat and protein content with changes in carbohydrate intake as a consequence of dietary modifications. Results from an SR and meta-analysis of 38 prospective studies and 30 RCTs showed that reduced intake of sugars was associated with a modest decrease in weight among adults (0.80 kg, 95% CI: 0.39–1.21; $P < 0.001$), and an increased sugar intake was associated with a weight increase of similar magnitude (0.75 kg; 95% CI: 0.30–1.19; $P = 0.001$) (46). Results for children showed generally no association, although high intakes of sugar-sweetened beverages were associated with an increased risk of obesity. The authors conclude that the observed effect on body weight "seems to be mediated via changes in energy intakes, since isoenergetic exchange of sugars with other carbohydrates was not associated with weight change" (46). Previous reviews and meta-analyses have found a positive association (47, 48) or no association (49) between intake of sugar-sweetened beverages and body weight.

Regarding the association between total carbohydrates and body weight, most studies have focused more on the effects of variations in total fat and less on the details of the type and dietary sources of carbohydrates replacing fat. An SR and meta-analysis of 33 RCTs on adults, without intentional weight loss as endpoint, found that a reduced total fat intake was associated with less weight gain of 1.4–1.6 kg, and nine of these studies showed a lower BMI of −0.51 kg/m^2 (50). Total fat intake was 28–43 E% at baseline and was typically 5–15 E% lower in the intervention arms. The reduction in fat intake was generally achieved through a proportional increase in total carbohydrates. Results from the NNR SR covering prospective cohort studies published from 2000 to 2011 suggest that the proportion of macronutrients in the diet has a limited role in prevention of obesity, and that plenty of fibre-rich foods and dairy products – and fewer

refined grains, meats, and sugar-rich foods and beverages – were associated with less weight gain (51). The results indicate that gross macronutrient composition per se might have only a limited impact on long-term weight change or maintenance. The observed effects on body weight changes might, therefore, be partly mediated by food-related factors that affect long-term energy intake.

Meta-analyses of intervention trials aiming at weight-reduction among overweight and obese individuals have shown that low-carbohydrate, high-protein diets resulted in similar or lower body weight compared to fat-reduced diets up to 6 months (52, 53). Long-term effects of such dietary changes, however, were less clear.

Fructose has been suggested to play a specific role in weight gain and insulin resistance syndrome (54). Unlike glucose, fructose is preferentially metabolised to lipids in the liver. On the other hand, fructose has a low glycaemic index. Fructose induces metabolic alterations typical for insulin resistance syndrome (metabolic syndrome) in animal models, but data in humans are less clear. A meta-analysis of human intervention trials did not find any evidence that fructose causes weight gain when substituted for other carbohydrates in diets with similar energy content. High intakes of free fructose providing excess energy intake were associated with modestly increased body weight (55). There is no basis for specific recommendations regarding fructose beyond the general limitation of added refined sugars.

Pregnancy outcomes

Results from a Norwegian pregnancy cohort have shown that consumption of sugar- sweetened beverages were associated with adverse pregnancy outcomes including preeclampsia and preterm delivery (56, 57). It should be noted that consumption of artificially sweetened beverages was also associated with preterm delivery both in the Norwegian study and a parallel study in a Danish pregnancy cohort (57, 58).

Dental caries

Caries develop as tooth tissues demineralise upon pH decrease due to fermentation of carbohydrates by tooth-colonising bacteria. Thus, dental caries is an infectious disease but sucrose and other easily fermentable mono- and disaccharides play a key role (59, 60). Foods rich in starch can also contribute to dental caries, especially when the starch molecule is easily available for degradation by amylase. The presence of sucrose intensifies the cariogenic potential of starch, but acid production from lactose

is normally low (61). Bacterial fermentation of sugar, mainly to lactic acid, causes pH decreases well below 5.5, which is considered critical for the development of caries in the enamel (the tooth crown). In tooth roots, the critical pH for demineralisation is approximately 6.5, a pH reached already when bread without added sugar is consumed. In addition to lactic acid, sucrose induces production of insoluble extracellular glucose polymers, i.e. glucans and mutans, leading to voluminous biofilms that favour colonisation of cariogenic streptococci on the surfaces of the teeth surfaces.

The prevalence of dental caries has declined in the Nordic countries in recent decades up to around the year 2000, but no corresponding reduction in total sugar intake was observed in this time period. Prophylactic use of fluoride and improved oral hygiene are important factors that modify the effect of sugar intake (62). However, in Norway and Sweden an increase in the prevalence of dental caries has been observed in some age groups in recent years (63, 64). Substantial socioeconomic and geographical differences still persist in caries prevalence, especially among children (65, 66).

Previous SRs have found a weak correlation, or no correlation, between sugar intake and caries development (67, 68). Intake data, however, were not provided in these reviews, which limits the interpretation of the results. The review by Burt and Pai (67) included all main forms of sugars, including added mono- and disaccharides and starch hydrolysates, while the review by Anderson et al. (68) mainly focused on sucrose. Generally, sugars other than sucrose contribute significantly to both the intake of total sugars and total refined sugars.

Results from a Finnish longitudinal study indicate that intake of sucrose and sucrose-containing foods is associated with caries development during childhood, including those children with fluoride prophylaxis (69–71). The main sources of sucrose were sweetened milk products, sugared drinks and juices, sweets, and chocolate (69, 71). Results from a Swedish study showed that frequent intake of sugar-containing foods among children aged 2–3 years was associated with caries prevalence (72) and that intake at 2 years of age predicted caries at 3 years of age (73).

As stated above, factors such as fluoride prophylaxis, oral hygiene, meal pattern, and meal composition interact (62). Frequency of sugar intake was found to be moderately related to caries development in the review by Anderson et al. (68), and there was generally a close correlation between intake frequency and intake amounts. Limiting the frequency of intake of refined sugars, and especially limiting sugar-rich foods as snacks, might contribute to reduced caries risk. A general level of safe refined sugar intake

cannot be provided because net caries development upon sugar challenge is modified by various other life-style factors (exposure to fluoride, meal frequency, and diet composition), heredity, illness, medication, malnutrition, and the flow and composition of the saliva.

Nutrient density

Nutrient density is the amount of essential nutrients found in foods per unit of energy content. An adequate nutrient density is essential for providing recommended intakes of nutrients, especially in individuals with a low energy intake. Added refined sugars mainly provide energy and no or only a few nutrients and thus tend to decrease the nutrient density. A review of 15 cross-sectional studies mainly from Europe and North America comprising children and adults concluded that there are insufficient and conflicting data with respect to the relation between intake of sugars and the density of selected micronutrients (74). This can be partly attributed to different definitions of the terms "sugars" or "added sugars" and on contributions of micronutrients from food fortification. Dietary fibre was not included in the analysis. However, studies among both children and elderly nursing home residents in the Nordic countries (75–78) have shown that a high intake of refined sugars (>10–15 E%) might adversely affect the intake of essential nutrients and dietary fibre. High intakes of sugar-rich foods might also be associated with poor dietary habits, e.g. low fruit and vegetable intake (78). A limitation of the intake of refined sugars is of special importance for children and adults with low energy intake. In the Finnish STRIP project, increasing sucrose intake was associated with a generally poorer quality of the diet in childhood (79). Thus higher sucrose intake (>10 E%) is associated with lower intake of many micronutrients and dietary fibre and a higher intake of saturated fatty acids.

GI, GL

Type-2 diabetes

Based on an evaluation of international expert reports (2, 28, 80, 81) and Nordic studies published from 2000 to December 2011, Øverby et al. (38) concluded that there is *suggestive*, but inconsistent, evidence that GI is associated with an increased risk for type-2 diabetes, especially in overweight and obese subjects. A meta-analysis of 13 prospective studies conducted in the US (8 studies), Europe (2 studies), Australia (2 studies), and China (1 study) published between 1997 and 2010 found a significantly increased

risk of type-2 diabetes when comparing the highest to lowest GI categories (Dong et al. 2011). Relative risk (RR) was 1.16 (95% CI: 1.06–1.26) with evidence of heterogeneity ($p = 0.02$). In a Finnish study on male smokers included in the review by Øverby et al. (38), but not in the meta-analysis by Dong et al. (82), no significant association with GI was found (83).

Cancer

SRs and meta-analyses of prospective cohort studies do not support an independent association between diets with high GI or GL and colorectal cancer (84) or breast cancer (85). A meta-analysis of four prospective cohort studies and one hospital-based case-control study on endometrial cancer published between 2003 and 2007 showed an increased risk when comparing the highest to lowest GL categories (86). RR was 1.20 (95% CI: 1.06–1.37), with a higher RR among obese women (RR = 1.54; 95% CI: 1.18–2.03). No significant associations were observed for GI.

In summary, an association between GI or GL and colorectal or breast cancer is unlikely. There is *limited-suggestive* evidence for an association between GL and endometrial cancer.

Blood lipids, glucose, insulin

Results from controlled, mainly short-term, intervention studies in humans have led to conflicting results with respect to effects on metabolic risk factors (38). Evidence from epidemiological studies is also conflicting. There are a number of methodological problems involved, including reliability of GI measurement, diet composition, and other food characteristics and constituents.

Pregnancy outcomes

Pregnancy is a physiological condition in which the GI might be of particular relevance because glucose is the primary fuel for foetal growth (87). High glycaemic load has been shown to be associated with the risk of gestational diabetes mellitus (88) as well as excessive gestational weight gain and post-partum weight retention (89).

Conclusions

The review by Øverby et al. (38) concluded "that there is not enough evidence that choosing foods with low GI will decrease the risk of chronic diseases in the population overall. However, there is suggestive evidence that ranking food based on their GI might be of use for overweight and

obese individuals. Issues regarding methodology, validity and practicality of the GI remain to be clarified. It is still unclear how much of the possible health effects are due to the GI per se, and how much additional benefit a low GI diet may offer after compliance with recommendations to increase intake of dietary fibre, whole grains, legumes and fruits and vegetables. Issues regarding methodology, validity and practicality of the GI remain to be clarified".

Dietary fibre

Dietary fibre has several physiological effects including faecal bulking and colonic fermentation and it affects blood glucose response, blood lipid levels, and blood pressure. These effects differ between various fibre constituents and food sources.

Laxation

Insoluble fibre, especially lignified types of fibre such as those in wheat bran, has the most prominent effects on faecal bulk. The increase in faecal weight ranges from 1.3 g for each gram of ingested pectin to 5.7 g for each gram of ingested wheat bran fibre (90). Oligosaccharides and resistant starch can also provide some faecal bulk (91).

Plasma lipids

Viscous types of soluble fibre lower plasma levels of total cholesterol and LDL-cholesterol. Although fasting triglyceride levels are generally not affected, different kinds of fibre – especially soluble and viscous types – can reduce post-prandial hyperlipidaemia (92). These effects are related to diminished cholesterol and/or bile acid absorption (93) and hypothetically also to products of colonic fermentation. The effects on lipid metabolism that have been demonstrated by resistant starch and resistant oligosaccharides in experimental animals have so far not been reproduced in man.

Blood pressure

Dietary fibre, mainly in the form of viscous fibre, can modulate blood pressure. In a meta-analysis by Streppel et al. (94) including 24 RCTs, fibre supplementation with an average dose of 11.5 g/d for a mean duration of 9 weeks was associated with a 1.13 mm Hg decrease in systolic blood pressure (95% CI: −2.49 to 0.23) and a 1.26 mm Hg decrease in diastolic blood pressure (95% CI: −2.04 to −0.48). Reductions in blood pressure

tended to be larger in individuals older than 40 years of age and in hypertensives. Similar results were found in a meta-analysis by Whelton et al. (95) that included 25 RCTs. These findings are in line with those of whole-diet trials such as the DASH studies (42). The potential mechanisms for the blood pressure-lowering effect are less documented, but they might involve effects on insulin response, vascular endothelial function, and mineral absorption (94). Foods rich in fibre such as fruit and vegetables also contain potassium and magnesium, which might contribute to reductions in blood pressure.

Blood glucose attenuation

Intake of viscous, soluble fibre has been shown to contribute to lower postprandial blood glucose and insulin response (8, 96, 97). The mechanism of action might in part be reduced absorption of food carbohydrates (98, 99). Of the expert reports included in the review by Øverby et al. (38), the EFSA (8) concluded that fibre intakes > 2.6 g/MJ were associated with reduced risk of impaired glucose control.

Colonic fermentation

Dietary fibre components are subject to anaerobic fermentation by the colonic microflora. The main fermentation products are SCFA such as acetate, propionate, and butyrate and gases, most notably hydrogen and methane. The decrease in pH of the colonic content has been shown to be protective against colon cancer through the reduced formation of bile salt metabolites that have been implicated in carcinogenesis. Furthermore, butyrate is recognised as a main source of energy for colonocytes and this has effects on cell differentiation and apoptosis that might be protective (100, 101). Acetate and propionate are absorbed and have possible systemic effects on carbohydrate and lipid metabolism. Propionate has been shown to inhibit liver cholesterol synthesis in experimental animals, but the importance of such a mechanism in humans remains to be established (92). The proportions of different SCFA differ with the fermentation substrate. Resistant starch and oat fibre have been shown to produce large amounts of butyrate (for a review, see (91)).

Certain oligosaccharides, such as FOS (i.e. inulin and shorter molecules) have been shown to increase the numbers of bifidobacteria in the colon, and this seems to be a general effect of increased amounts of non-digestible carbohydrates such as other oligosaccharides (GOS and resistant maltooligosaccharides) and resistant starch (91, 102).

Cancer

The reduced transit time and increased faecal weight with dilution of the intestinal contents and improved laxation were factors behind the early hypothesis that an appropriate intake of dietary fibre would reduce the risk of both colorectal cancer and diverticular disease. There is an inverse relationship between faecal weight (influenced by non-starch polysaccharide intake) and risk of colon cancer (103).

Results from epidemiological studies show clear evidence of a protective effect of dietary fibre on colorectal cancer (38). Aune et al. (84) assessed the association between fibre intake and colorectal cancer using data from 25 prospective cohort studies. The summary RR risk of developing colorectal cancer expressed per 10 g/d of total dietary fibre (16 studies) was 0.90 (95% CI: 0.86–0.94). Corresponding analyses for different food sources showed significantly reduced risk for cereal fibre (RR = 0.90; 95% CI 0.83–0.97, 8 studies). No significant associations were seen in separate analyses of fibre from fruits, vegetables, or legumes. Based on these results, the WCRF upgraded the evidence that foods containing dietary fibre protect against colorectal cancer from *probable* to *convincing* (104). Similar estimates were observed in the large European prospective cohort study EPIC (105) where an increase of 10 g/d of total dietary fibre was inversely associated with colorectal cancer (hazard ratio = 0.87, 95% CI: 0.79–0.96). Fibre from cereals and fibre from fruits and vegetables were inversely associated with colon cancer, but for rectal cancer such an inverse association was only seen for fibre from cereals.

An SR and meta-analysis of 16 prospective cohort studies covering breast cancer showed a significant moderate risk reduction (106). The summary RR for a 10 g increase in fibre intake was 0.95 (95% CI: 0.91–0.98). Effects were mainly seen in studies with a large range of fibre intakes.

In summary, there is *convincing* evidence for a protective effect of dietary fibre against colorectal cancer and *limited-suggestive* evidence for a protective effect against breast cancer.

Cardiovascular disease (CVD)

Based on the review of recent international expert reports, SRs, and Nordic studies, there is clear evidence that a high intake of dietary fibre is protective against CVD (38). This is supported by results from the large European cohort study EPIC on the association between fibre intake and ischaemic heart disease mortality in which 306,331 subjects free from CVD were followed for a mean of 11.5 years (107). The RR for an increase in fibre intake

of 10 g/d was 0.85 (95% CI: 0.73–0.99, P = 0.031). The associations for various food sources of dietary fibre were in the same direction, but not statistically significant.

An SR including eight cohort studies found an inverse association between total intake of dietary fibre and risk of both haemorrhagic and ischaemic stroke as well as some evidence of heterogeneity between studies (RR per 7 g/d = 0.93; 95% CI: 0.88–0.98; I^2 = 59%). Viscous, soluble fibre intake of 4 g/d was not significantly associated with reduction in stroke risk and there was evidence of low heterogeneity between studies (108).

In conclusion, there is *probable* evidence for a protective effect of dietary fibre from various foods against CVD.

Body weight

Adults

Several physiological effects of foods rich in dietary fibre, including diminished energy density, slower gastric emptying, short-term increase in satiety, and decreased rate of nutrient absorption, might be important for body weight regulation. Of the expert reports included in the review by Øverby et al. (38), the EFSA (8) concluded that dietary fibre is associated with lower body weight, and the SR included in Dietary Guidelines for Americans 2010 (80) showed "moderate evidence that intake of wholegrain and grain fibre is associated with lower body weight".

Results from mainly short-term intervention studies on adults have shown that increased intake of various fibre types resulted in moderate weight loss (109, 110). The SR by Wanders et al. (110) studied 59 RCTs in which the effects of different fibre types on body weight were assessed. Effect sizes were calculated as an average that was weighted by the number of subjects who completed the study. Study durations varied from 3 weeks to 13 weeks with large variations in fibre intakes in the intervention arm from 3.0 g/d to 48 g/d. The average change in body weight was a reduction of 0.72 kg (1.3%), corresponding to a reduction of 0.4% every 4 weeks.

Results from prospective cohort studies on adults published since 2000 generally show that increased dietary fibre intake is associated with lower body weight (51) and waist circumference (111). The SR by Fogelholm et al. (51) included five prospective cohort studies, and the evidence linking high fibre intake to prevention of weight gain was judged to be *probable*. Reported effect sizes, however, were variable. In a European cohort study including 89,432 subjects free from cancer, CVD, and diabetes at baseline, an increased intake of total fibre of 10 g/d was associated with a −39 g/y

(95% CI: −71, −7 g/y) weight change and a −0.08 cm/y (95% CI: −0.11, −0.05 cm/y) waist circumference change over an average of 6.5 years (111).

In summary, there is *probable* evidence that dietary fibre intake is associated with lower weight gain in adults.

Children

Of the expert reports included in the review by Øverby et al. (38), the EFSA (8) used normal laxation as a criterion to set an adequate intake of dietary fibre of 2 g/MJ for children > 1 year of age. The SR included in Dietary Guidelines for Americans 2010 (80) concluded that the evidence for an association between dietary fibre and adiposity in children is insufficient.

A few studies, mainly on British vegan children, indicated slower growth in some of the children (112, 113), but it is not clear if this can be attributed to the fibre content of their diet (114). Studies among children consuming a mixed diet do not indicate that a high fibre intake would compromise growth (114). A high fibre intake is often linked to higher intake of fruits, vegetables, and cereals and might be an indicator of more favourable dietary habits (115, 116). Results from the Finnish intervention study STRIP (Special Turku Coronary Risk Factor Intervention Project) show that children who were allocated a diet in line with the NNR from 7–8 months of age grew and developed normally (116–118). Intake of fibre was positively related to nutrient intake (116). Mean intake of fibre was 9.2 g/d at 13 months of age and 11.8 g/d at 5 years of age corresponding to 2.3 g/MJ and 2.0 g/MJ, respectively (119). There were no differences in weight or growth in relation to fibre or fat intake. At age 7, fibre intake varied from 12.3 g/d to 15.5 g/d corresponding to 1.9–2.4 g/MJ (120). Results from studies among German children who had been followed from 6 months to 18 years of age showed that the fibre intakes, expressed as g/MJ, were highest at 1 year (3 g/MJ) and then decreased somewhat to 2.5 g/MJ in pre-school and school-age children (77). In a subsequent study, no clear association between increased fibre intake from 2 to 7 years of age and per cent body fat or BMI was found. Mean fibre intake was 2.5 g/MJ. Increased fibre intake was associated with lower percentage of body fat among children who at 2 years of age consumed fewer than six meals per day (121).

Pregnancy outcomes

Intake of dietary fibre and dietary patterns characterised by vegetable foods with high content of dietary fibre (>22 g/d) have been shown to be asso-

ciated with decreased risk of gestational diabetes (88) and preeclampsia (122, 123).

Type-2 diabetes

The NNR review by Øverby et al. (38) concluded that there is moderate evidence that high intake of dietary fibre is associated with a lower risk of type-2 diabetes. This was mainly based on the EFSA opinion (8) and results from a Finnish prospective cohort study (124). Intake of wholegrain and cereal fibre has been associated with reduced risk of type-2 diabetes (125). A meta-analysis by Schulze et al. (126) comprising nine prospective cohort studies and 393,385 subjects, which was evaluated in the EFSA report, showed a reduced risk for type-2 diabetes with higher cereal fibre intake (RR for extreme categories = 0.67, 95% CI: 0.62–0.72).

In summary there is *probable* evidence that dietary fibre intake is inversely associated with type-2 diabetes. This might partly be mediated by wholegrain intake.

Requirement and recommended intake

Glycaemic carbohydrates

Only cells in the central nervous system, red blood cells, and some other cells dependent on anaerobic glycolysis have an absolute requirement for glucose. In the body, glucose can be synthesised from proteins and glycerol, and it has been assumed that there is no need for dietary carbohydrates as long as adequate amounts of fat and of protein for de novo synthesis of glucose are consumed. With prolonged glucose deficit, brain cells can partially adapt by utilising fat-derived metabolites such as β -hydroxybutyric acid and acetoacetic acid. A very low carbohydrate diet (below 50 g/d), however, results in chronically increased production and increased plasma levels of these acids resulting in a condition known as ketosis. An intake of 50–100 g/d of glycaemic carbohydrates generally prevents ketosis.

An intake of 50–100 g/d of glycaemic carbohydrates per day is sufficient to avoid ketosis among children and adults, and an intake of 130 g/d for both children older than 1 year and adults has been estimated to cover the glucose needs of the brain (5). This intake corresponds to about 20 E% and 25 E% in adult males and females using a reference intake of 11 MJ and 9 MJ/d, respectively. For children up to 11–13 years of age, this intake corresponds to 25–45 E%. These levels are used in NNR 2012 as average requirements (AR) for glycaemic carbohydrates.

Added sugars

A restriction in the intake of added, refined sugars is important to ensure adequate intakes of micronutrients and dietary fibre (nutrient density) as well as supporting a healthy dietary pattern. This is especially important for children and persons with a low energy intake. Consumption of sugar-sweetened drinks has been associated with an increased risk of type-2 diabetes and excess weight-gain and should, therefore, be limited. Frequent consumption of sugar-containing foods should be avoided to reduce the risk of dental caries. The recommendation from NNR 2004 is maintained.

Added sugars (sucrose, fructose, and starch hydrolysates) should be kept below 10 E%.

Dietary fibre

In NNR 2004, the recommendation of dietary fibre intake was mainly based on the amounts required for bowel regularity and for maintaining a faecal bulk that was associated with a diminished risk of colon cancer (90, 103). Since then, a number of studies have been published supporting the beneficial effects of dietary fibre and/or dietary fibre-rich foods such as wholegrain cereals, fruit, and vegetables on a number of diseases. An adequate intake of dietary fibre reduces the risk of constipation. There is *convincing* evidence for a protective effect of dietary fibre against colorectal cancer, *probable* evidence for a protective effect against CVD, and *limited-suggestive* evidence for a protective effect against breast cancer and type-2 diabetes. Moreover, fibre-rich foods help in maintaining a healthy body weight. The evidence supporting the recommendation from NNR 2004 has been strengthened by these recent studies. There is also evidence that intake of appropriate amounts of dietary fibre from a variety of foods is important for children.

Adults: Intake of dietary fibre should be at least 25–35 g/d, i.e. approximately 3 g/MJ. Wholegrain cereals, whole fruit, vegetables, pulses, and nuts should be the major sources.

Children: An intake corresponding to 2–3 g/MJ is appropriate for children from 2 years of age. From school age the intake should gradually increase to reach the recommended adult level during adolescence.

Note: These recommendations are based on AOAC methods for total dietary fibre.

Total carbohydrate

The health effects of dietary carbohydrates are related to the type of carbohydrate and the food source. Dietary patterns associated with reduced risk of chronic diseases are characterised by abundant intake of fibre-rich foods consisting mainly of slowly digestible carbohydrates such as wholegrain cereals, whole fruit, berries, vegetables, and pulses (127). These foods should be the major sources of dietary carbohydrates. Typical ranges of total carbohydrate intakes in studies on dietary patterns associated with reduced risk of chronic diseases among adults are 45–60 E%. This is considered a reasonable range of total carbohydrate intake in NNR 2012, and this range is also applicable for children from about 6 months of age.

For planning purposes, the focus should be on achieving the recommended amounts of dietary fibre and added sugars. The ranges for total carbohydrates can be used as complementary goals using the middle value (52–53 E%) as an appropriate target.

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12 Protein

	Adults 18–64 y	≥65 y	Children 2–17 y	12–23 mo.	6–11 mo.
E%	10–20	15–20	10–20	10–15	7–15

The range of 10–20 E% for adults corresponds to about 0.8–1.5 g protein/kg body weight/d, provided a physical activity level (PAL) of 1.6 for an intake of about 10 E%, and a PAL of 1.4 for an intake of about 20 E%, respectively.

The range of 15–20 E% for the elderly corresponds to about 1.1–1.3 protein/kg body weight/d, provided a PAL of 1.6 for an intake of about 15 E%, and a PAL of 1.4 for an intake of about 20 E%, respectively.

Introduction

Proteins are a constituent of all organic material in the cells of animals and plants and are built from 20 unique amino acids. Within the body, proteins provide enzymatic activity, antibody activity, and muscle work; are involved in repair processes and the transport of various substances; and are the building blocks for several cellular structural elements. Dietary protein has two roles in nutrition; it has a specific role as source of nitrogen and amino acids and a non-specific role as an energy source. In individuals in energy balance and with a moderate physical activity level, the protein requirement is defined as the lowest intake of protein to maintain nitrogen balance (N-balance). In the NNR, the energy content from protein in a mixed diet is calculated as 17 kJ/g.

Dietary sources and intake

Dietary proteins are found in almost all foods of animal and plant origin. Meat, fish, milk, and eggs have large quantities of high-quality protein. Pulses, nuts, and seeds also have high protein content. This makes them important sources of proteins in vegetarian diets, especially for vegans who also exclude milk and eggs from their diet.

The average protein intake among adults is high in the Nordic countries, ranging from 15 E% in Denmark to 18 E% in Norway and Iceland according to national dietary surveys.

Physiology and metabolism

During digestion and absorption, dietary proteins are broken down into their constituent amino acids. Within the body, amino acids absorbed into the blood are incorporated into tissue protein and other nitrogen-containing compounds such as neurotransmitters, creatinine, and drug elimination ligands. Thus, the protein requirement is actually a requirement for amino acids and nitrogen.

Body proteins are continually being broken down and synthesised. The protein turnover (which is about 300 g/d in adults) is many times higher than the amount of proteins consumed from the diet. This indicates an extensive reutilisation of amino acids in protein metabolism. Nitrogen from the amino acids leaves the body via the urine in the form of urea, uric acid, creatinine, etc. Small quantities of nitrogen are also lost from faeces, sweat, and other secretions and from the skin, hair, and nails. The body needs amino acids to compensate for these losses, and amino acids are also needed for protein synthesis during anabolism, e.g. during growth, pregnancy, and lactation.

It is usually assumed that almost all of the dietary nitrogen is incorporated as protein. Dietary nitrogen × 6.25 is accepted as a reasonable approximation of the amount of protein in the diet because the average protein contains 16% nitrogen. However, because the nitrogen content of various amino acids ranges from 7.7% to 32.2%, the nitrogen content of protein in individual foods depends on the amino acid composition. Thus the conversion factor can vary from 5.83 in wheat to 6.38 in milk (1). N-balance is the difference between nitrogen intake and nitrogen output. A negative N-balance (i.e. losses greater than intake) is seen during fasting and starvation. A positive N-balance is seen during active growth. On a

long-term basis, healthy adult subjects should be in nitrogen equilibrium, i.e. intake and losses should be equal.

Amino acids from dietary protein are classified as either essential (indispensable) amino acids that cannot be synthesised in the human body and thus must be provided in the diet, or nonessential (dispensable) amino acids that are synthesised within the body from other amino acids (transamination) provided that there is an adequate nitrogen supply. The essential amino acids in humans are isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, and histidine. Histidine is considered essential although it does not fulfil the criterion of reducing protein deposition and inducing negative nitrogen balance when removed from the diet (2, 3).

In humans, the nonessential amino acids are alanine, arginine, asparagine, aspartic acid, cysteine, glutamine, glutamic acid, glycine, proline, serine, and tyrosine (4). Conditionally essential amino acids, including arginine, cysteine, glutamine, glycine, proline and tyrosine, are amino acids whose synthesis requires the availability of another amino acid either as the carbon donor or as the donor of an accessory group, e.g. the sulphur group of cysteine (5). Under normal conditions, conditionally essential amino acids are synthesised in sufficient amounts but during certain conditions, such as prematurity (6) and illness (7), synthesis might not support all of the body's metabolic needs.

Protein constitutes 15–20% of the human body, which corresponds to approximately 12 kg in a person with a body weight of 70 kg.

Dietary proteins differ in their nutritional quality due to differences in amino acid composition, the total amount of each amino acid, and the digestibility of the protein. In 1991, the FAO/WHO (8) introduced the Protein Digestibility-Corrected Amino Acid Score (PDCAAS) based on an age-related amino acid reference pattern that is representative of human requirements combined with estimates of the digestibility of the protein. For mixed diets or whole foods, PDCAAS values >1 are not used, but extrapolated to 1. The WHO (9) defined good- quality protein as proteins with a PDCAAS value of 1.0.

Most recently, the FAO (10) has introduced the Digestible Indispensable Amino Acid Score (DIAAS). The main difference between DIAAS and PDCAAS is that in DIAAS the true ileal amino acid digestibility for the indispensable amino acids is used rather than a single faecal crude protein digestibility value.

Dietary proteins of animal origin (meat, fish, milk, and eggs) or a com-

bination of plant protein from, for example, legumes and grains, will give a good distribution of essential amino acids. Most proteins are also reasonably well digested although those found in grains have slightly lower digestibilities.

The quality of dietary proteins is usually high in the typical Nordic mixed diet. In practice, the differences in quality between proteins might be less important in diets containing a variety of protein sources (11).

Requirement

The WHO/FAO/UNU (9) define the protein requirement of an individual as "*the lowest level of dietary protein intake that will balance the losses of nitrogen from the body, and thus maintain the body protein mass, in persons at energy balance with modest levels of physical activity, plus, in children or in pregnant or lactating women, the needs associated with the deposition of tissues or the secretion of milk at rates consistent with good health.*"

Despite limitations in the method that are mainly related to accuracy of the measurements and interpretation of the results, N-balance remains the method of choice for determining the protein requirement in adults in the absence of validated or accepted alternatives and in the absence of a reliable biological marker of protein status.

For the NNR 2012 update, two systematic reviews (SRs) were conducted to assess the scientific evidence behind the dietary requirement for protein. One SR included healthy adults (12), and the other included healthy elderly populations with a mean age of ≥65 years (13).

The two SRs included one meta-analysis (14) and four additional balance studies (15–18). The meta-analysis by Rand et al (14) included 19 N-balance studies, and they found no statistically significant differences in estimated requirements between the locations of the study sites, the adult age of the participants, gender, or source of dietary protein, although there was an indication that women might have a lower requirement. The authors emphasized that the data did not provide sufficient power to detect possible differences. The median estimated average requirement (EAR) of good-quality protein was 105 mg nitrogen, which corresponds to 0.66 g protein/kg body weight (BW)/d. The estimated recommended dietary allowance (RDA) was set to 0.83 g good-quality protein/kg BW/d, corresponding to the 97.5th percentile. Only one study in elderly persons was included (19). The median nitrogen requirement was 130.5 mg/kg BW/d in the elderly group versus 103.9 mg/kg BW/d in the younger group. This

corresponded to a difference of 0.17 g protein/kg BW/d or a 26% higher requirement in the elderly group. Rand et al (14) concluded that healthy elderly persons might have higher requirements, but there was not enough evidence to make different recommendations for this group.

The objective of the high-quality N-balance study by Campbell et al (16) was to study the effect of age on the EAR for protein. They found no difference in the EAR between the young and old participants, and the calculated adequate protein allowance of 0.85 g good-quality protein/kg BW/d for all participants combined was not statistically different from the RDA estimated in the meta-analysis by Rand et al (14). An earlier study by Campbell et al (15) also found 0.8 g protein/kg BW to be sufficient to obtain N-balance in 10 elderly participants. Steady state was reached at week 2 indicating that the protein intake was adequate for the participants. However, after two weeks the urinary nitrogen excretion decreased and was associated with a loss in mid-thigh muscle area. The authors suggested that the protein intake might have been marginally inadequate and resulted in long-term accommodation in skeletal muscle (15).

In a controlled metabolic study by Morse et al (17), 11 healthy elderly women were provided eucaloric diets with three different protein intake levels. These included a low-protein diet of 0.5 g/kg BW; a medium-protein diet of 0.75 g/kg BW; and a high-protein diet of 1.0 g/kg BW during three periods of 18 days with a minimum of one week habitual diet between the periods. N-balance was determined on week 2 and 3 of each diet. The mean dietary allowance was estimated to be 0.90 g protein/kg BW at week 2 and 0.76 g/kg BW at week 3, but the urinary nitrogen excretion decreased between week 2 and 3 indicating that a steady state was not yet reached.

A short-term study was also included in the SR because it compared a high protein (HP) intake in the test meal versus usual protein (UP) intake (18). Young men and women (UP 1.04 g/kg BW and HP 2.08 g/kg BW, respectively) versus old men and women (UP 0.89 g/kg BW and HP 1.79 g/kg BW, respectively) were tested for 10 days on each diet in a crossover design. There was no age-related difference in N-balance. However, in the elderly participants with a habitual low glomerular filtration rate (GFR) the HP diet corresponding to about 24 E% did not result in the expected increase in GFR after intake of the HP diet.

From these studies, the evidence was assessed as *probable* regarding a median daily EAR of nitrogen of 105 mg/kg BW. This corresponds to 0.66 g good-quality protein/kg BW/d regardless of sex or age.

It should be noted that two of the studies among the elderly (15, 17) found a decrease in the urinary nitrogen excretion. In the study by Campbell et al (15), this was associated with loss of muscle mass, but this was not the case in the study by Morse et al (17).

The use of N-balance as a basis for establishing dietary protein recommendations is a matter of debate. This methodology provides an indirect determination of protein turnover, and no information about whole-body nitrogen or protein turnover, or various protein metabolic pathways, can be obtained. Furthermore, obtaining complete urine collections and strict measurements of energy intake/balance are challenging in field studies. If the energy balance changes during the study, this will influence the results, thus eucaloric diets are needed. Also, low protein intake might induce protein sparing and thus lead to underestimation of needs.

Over the last several years more direct methods of measuring turnover of various body proteins have been developed, including stable isotope tracer methods. This has enabled a mechanistic approach to the effects of various dietary proteins. In 1992, Tarnopolsky et al (20) used stable isotopes. They also studied sedentary individuals at three different protein intakes for 13 days at each intake and found the average requirement (AR) to be slightly less than 0.7 g protein/kg BW. This led to a recommendation of 0.89 g protein/kg BW. The main limitation is the lack of prolonged studies using this methodology as evidenced by the fact that most articles using stable isotope methods from 2000 onward only describe acute effects of protein or amino acid intake (12) and these are mainly focused only on muscle protein metabolism. However, the WHO (9) used stable isotope studies to increase the estimated requirements for essential amino acids based on the biologically sound criterion that the point of intake where oxidation of the essential amino acids investigated begins to increase reflects the point at which intake is above requirements. Similar logical reasoning cannot be applied to whole-body protein turnover beyond what can already be deduced from N-balance studies. Rates of whole-body protein synthesis and degradation are usually reported to increase in parallel with protein intakes above the amount required for N-balance, but the relation between whole-body protein turnover rate and health or body functions needs to be established. Similarly, studies of muscle protein turnover have not yet added to an understanding of muscle function because no studies are available demonstrating a correlation between, for example, muscle strength or endurance and the dynamics of muscle protein turnover. Thus, in the future it will be important to use more advanced methodologies in strictly

controlled long-term studies to establish mechanistic links between health outcomes and protein intake from various sources.

Severe protein deficiency results in oedema, muscle weakness, and changes to the hair and skin. Protein deficiency is often linked to energy deficiency and protein-energy malnutrition, as well as deficiency of other nutrients based on a general nutrition deficiency. Sarcopenia has recently been defined as the loss of muscle mass and function leading to adverse clinical outcomes. The diagnosis is based on the combined finding of reduced muscle mass/lean tissue and reduced power or strength (21). At present, there are no specific blood tests for protein deficiency. Plasma albumin and other plasma proteins decrease in very severe malnutrition, but this is difficult to distinguish from dilution due to hunger oedema.

Protein intake and health

For the NNR 2012 update, three SRs were conducted on the health effects of protein intake. One study was in infants and children ≤18 months of age (22), one was in healthy adults (12), and one was in healthy elderly populations with a mean age of ≥65 years (13). The literature searches covered the years 2000 to 2011, and the SRs assessed the health effects of varying protein intakes to evaluate the evidence for an optimal protein intake.

Mortality

The two SRs carried out in adults and elderly (12, 13) only included two studies that addressed protein intake *per se* in relation to all-cause mortality. In the PREVEND study (23), the protein intake was calculated from two 24-hour urinary urea excretions and was expressed as protein intake in grams per kilogram of "ideal" BW, i.e., after correcting BW to a BMI corresponding to 22. Thus, the level of protein intake could not be assessed because the correction probably overestimated intakes and because no correction was made for possible loss of urine in the collections. After 7 years, they found that quintiles of protein intake were inversely associated to all-cause mortality and non-cardiovascular mortality. Among British elderly, Bates et al (24) found a decreased risk of all-cause mortality associated with total protein intake after 14 years, but their study was flawed by underreported energy intake. Thus, the evidence for a relation between total protein intake and all-cause mortality was assessed as *inconclusive* (12, 13).

The SR (12) also assessed three longitudinal cohort studies that included about 200,000 men and women. The studies used a low-carbohydrate/

high-protein (LC/HP) diet score based on the protein E%, and one of the studies also used a LC/HP- high fat score (25). All three studies found an increased risk of all-cause mortality, thus the evidence was assessed as *suggestive* regarding an increased risk of all-cause mortality in relation to an LC/HP diet with total protein intakes of at least 20–23 E% (12). In addition to the SR, a Swedish population-based cohort study from 2012 included 77,319 men and women aged 30–60 years at baseline who were followed for a mean of 10 years (26). The study used a LC/HP score and found no statistically significant association to all-cause, cancer, or cardiovascular disease mortality after accounting for saturated fat intake. It should be noted that 97.2% of the participants had a reported protein intake in line with the recommended range of 10–20 E%.

For cardiovascular mortality, the evidence was assessed as *suggestive* for an inverse relation to vegetable protein intake based on three studies in which the protein intake was expressed in E% and on one study with an LC/HP diet score based on vegetable protein (12). Additionally, in a Swedish cohort study in elderly men comparing dietary patterns, an LC/HP diet was associated with increased risk, but a Mediterranean-like diet was associated with decreased risk of cardiovascular mortality (27). However, very few participants were in the highest protein score corresponding to 18 E% (n = 7) compared to the lowest protein score of 12 E% (n = 12).

In the study by Fung et al (25) that included 44,548 women and 85,168 men in the Nurses' Health Study and Health Professionals' Follow-up Study, respectively, they found that an animal-based LC/HP score was associated with a higher risk of cancer mortality.

Generally, the use of an LC/HP score makes it uncertain whether the effects result from reduced carbohydrate or increased protein and/or fat, and thus the effect of protein *per se* cannot be assessed from LC/HP diets.

Cancer

The overall association between cancer and protein intake was assessed as *inconclusive* (12). Most studies on the relation between protein intake and cancer are food based (28) and, therefore, cannot isolate the effect of the protein intake *per se* from other nutrients or ingredients in the foods For instance, The World Cancer Research Fund (28) found that the consumption of red and processed meat was associated with several cancers, especially colorectal cancer.

Cardiovascular diseases and serum lipids

For cardiovascular diseases, the association between protein intake and coronary heart disease and stroke was statistically non-significant in six cohort studies, and the evidence was regarded as *inconclusive* (12). However, apart from the SR in a cohort study from 2012 of 43,396 Swedish women, Lagiou et al (29) found that an LC/HP diet was associated with an increased risk of cardiovascular disease after 15.7 years.

The evidence for an association between protein intake and blood pressure was assessed as *inconclusive* for total and animal protein, but an inverse association with vegetable protein intake was assessed as *suggestive* (12) and this is in agreement with the WHO/FAO/UNU report (9). The SR included one feeding study among African-Americans and non-Hispanic white participants, the OmniHeart study (30), that was based on a carbohydrate diet similar to the Dietary Approaches to Stop Hypertension (DASH) diet but with 15 E% protein versus 25 E% protein and with the 10 E% protein replaced with carbohydrates. The subgroup analysis in the Caucasian group found no significant relation between protein intake and blood pressure (30). Both the SUN cohort study (31) and the Chicago Western Electric Study (32) found an inverse relation with vegetable protein (expressed as E%) and the risk of hypertension, and blood pressure change, respectively, and the most recent meta-analysis with soya intake in controlled trials (33) supported the conclusion that the evidence is *suggestive* for an inverse association between hypertension and intake of vegetable protein (12).

In the elderly, the Rotterdam prospective cohort study looked at the association between risk of hypertension and intake of energy-adjusted tertiles of total, animal, and vegetable protein among persons ≥55 years of age without hypertension at baseline. The lowest tertile of total protein intake was 70 ± 15 g/d (14 E%) and the highest was 97 ± 19 g/d (19 E%). They found no statistically significant associations except in persons ≥70 years of age where animal protein intake was related to an increased risk of hypertension after 6 years of follow-up (13). A recent comprehensive SR regarding protein and blood pressure included the above mentioned studies and studies before 2000, but also cross-sectional studies and studies among risk groups (overweight/obese, hypertensive, and diabetic patients) and in non-Nordic settings, and they found a small beneficial effect of dietary protein, especially for vegetable protein (34).

Two high-quality meta-analyses of randomized controlled studies (35, 36) found a statistically significant inverse effect for a mean daily intake

of 25–30 g soya protein, corresponding to 1 or 2 servings per day, on LDL-cholesterol concentration. Studies with participants with the highest baseline LDL-cholesterol concentration had greater reductions than studies with the lowest values, thus the effect might be smaller in normo-cholesterolemic persons. The evidence was assessed as *probable* to *convincing* in regard to the effect of soya protein on LDL-cholesterol concentration (12), but the intake level in those studies was much higher than in the present Nordic diet so the relevance of these results for the average Nordic diet is questionable.

Bone health

The role of dietary protein on bone health has been controversial. Urinary calcium loss increases in high-protein intakes, but at the same time protein increases calcium absorption and bioavailability and these seemingly contradictory effects make it uncertain as to what the net effect of high protein diets is on calcium metabolism and bone health (37). Any negative effect of protein might be opposed by an increase in the protein-sensitive anabolic mediator insulin-like growth factor, IGF-1.

In the SR by Pedersen et al (12), the evidence for beneficial or adverse effects of higher protein intake in relation to bone health was assessed as *inconclusive*. Also, the EFSA (38) found the available evidence regarding protein and bone health to be insufficient. The assessment of protein intake and risk of bone loss was based on three small and low-quality cohort studies carried out mainly in women (12), and a single good-quality meta-analysis (39) that found a "small benefit of protein on bone health". Based on Darling et al (39) and three cohort studies that included risk of fractures, the association between bone health and protein intake was assessed as *inconclusive* (12). However, there seems to be an interaction with the intake level of calcium. Under conditions of low calcium intake an increased risk of fractures was found to be related to high animal-protein intake, but under conditions of high calcium intake (>800 mg) a decreased risk of fractures was related to high animal-protein intake. This finding is supported by an older Norwegian study of 39,787 middle-aged men and women that showed an elevated risk of hip fracture in women with a high intake of animal (non-dairy) protein under conditions of low calcium intake (40). The evidence for an association between vegetable protein intake and fracture risk was *inconclusive* (12), and this finding was supported by an older study of 32,050 postmenopausal women that showed a decreased risk of hip fracture related to a high animal protein intake but not to vegetable

protein intake (41). Fenton et al (42) published an SR and meta-analysis on the association between dietary acid load (including protein intake) and bone health and did not find support for the hypothesis that an "acidic" diet causes osteoporosis or that an "alkaline" diet prevents osteoporosis.

In the elderly, Pedersen & Cederholm (13) assessed the evidence as *suggestive* in regard to a positive association between protein intake and bone mineral density based on one intervention study and three prospective cohort studies. The evidence was assessed as *inconclusive* regarding the relation of protein intake to bone loss and risk of fractures. Interestingly, in the included randomized controlled study with calcium and vitamin D supplementation by Dawson-Hughes & Harris (43) the highest tertile of protein intake (20 E%, or 1.2 g/kg BW) was associated with less bone loss compared to the lowest tertile (14 E%, or 1.1 g/kg BW) but only in the intervention group. The habitual mean intake in the placebo group was 871 mg calcium and about 7 µg vitamin D per day, which is close to the recommended values in the NNR 2004 (44). Thus, the possible effect of protein intake on bone health might depend on an intake of calcium and vitamin D above this level.

Energy intake and body weight control

Higher satiety after protein intake than after carbohydrate and fat intake has been reported in test-meal and short-term studies (45). An SR covering the period of 1966–2003 on the effect on weight loss of LC/HP diets in the treatment of obesity showed that weight loss was associated with decreased energy intake and not with the macronutrient composition of the diet (46) but a recent SR including studies from 2002 to 2007 found LC/HP diets to be effective in reducing body weight at 6 months and up to one year (47). However, long-term results have so far been disappointing (48), and perhaps this is a reflection of difficulties with adherence to the diets. It should be emphasized that LC/HP diets cannot be used to assess the effect from protein *per se*.

An SR of dietary macronutrients and food consumption as determinants of long-term weight change in adults was conducted for the update of NNR 2012 (49). The authors found that the evidence for an association between the dietary macronutrient composition in prevention of weight gain after prior weight loss was *inconclusive*. The results suggested that the proportion of macronutrients in the diet was not important in predicting changes in weight or waist circumference.

The majority of studies addressing protein and energy intake, appetite

regulation, and body weight have been performed in overweight/obese persons, and very few studies have assessed the prevention of overweight/obesity in normal-weight populations. The NNR intend to prevent an undesired increase in body weight and overweight, thus the SR addressing protein intake in relation to energy intake and body weight control in healthy adults (12) excluded studies on overweight/obese participants or participants on weight-loss diets. Based on one prospective cohort study and two intervention studies, Pedersen et al (12) assessed the evidence for an association between protein intake and energy intake as *inconclusive*. The evidence for an association between protein intake and body weight change was also assessed as *inconclusive* (12). This assessment was based on a cohort study of 89,432 men and women that found weight gain to be significantly positively associated with total and animal protein intake, on two small cohort studies that found no significant associations, and on two small controlled trials, one low-quality and one good-quality study (50), that found high protein intake to be related to weight loss.

Based mainly on intervention studies with overweight/obese participants, the EFSA (38) assessed the protein intake data as insufficient to establish reference values in relation to body weight control.

Muscle mass, strength, and function

Adequate muscle mass and function is crucial for body function and survival and for the prevention of sarcopenia, i.e. the age-related loss of muscle mass and function, is highly relevant. Advanced sarcopenia is associated with increased risk of physical frailty and, therefore, is associated with increased likelihood of falls and impairment in the ability to perform activities of daily living (51).

The SR by Pedersen et al (12) included only one randomized controlled trial with body composition as outcome (52). This study included 15 physically active men who were prescribed either a high-protein diet (1.9 g/kg BW per day (22 E%)) or a normal diet (1.3 g/kg BW per day (15 E%)) for 6 months. No association between protein intake and change in fat mass or fat-free mass was found.

Based on one intervention study and two prospective cohort studies in the SR of the elderly (13), the evidence was assessed as *suggestive* with regard to a positive relation between muscle mass and a total protein intake in the range of 13 E% to 20 E%. In the included Health ABC Study (53), which was the first longitudinal study to examine the role of dietary protein on changes in body composition using state-of-the-art body-composition

measurements, the mean protein intake was 0.9 g/kg BW and the mean 3-year loss of lean body mass was 0.68 ± 1.9 kg. Participants in the highest quintile of protein intake (≈19 E%) lost less lean mass compared to those in the lowest quintile (≈11 E%). It is notable that there was no statistically significant association between total protein intake and 3-year loss of muscle mass adjusted for physical activity in the 49.5% of the participants who were weight stable, and this raises the awareness of a sufficient energy intake among the elderly. In a strictly controlled metabolic study with a focus on N-balance (15) and on resistance training (54), a protein intake of 0.8 g/kg BW (≈10 E%) for 14 weeks resulted in a loss of mid-thigh muscle area in the sedentary control group during a period of body weight stability.

Frailty is a geriatric term (characterized by slowness, weakness, fatigue, low physical activity, and unintentional weight loss) indicating that older persons are at increased risk of developing adverse health outcomes such as the onset of disability, morbidity, institutionalization, or mortality (55). An important and fundamental component of frailty is sarcopenia (56). The SR by Pedersen & Cederholm (13) included only one study that addressed protein intake and the relation to frailty, and this study found that reduced protein intake was associated with an increased risk of frailty after three years (57).

Muscle function, expressed as activities of daily living (ADL) or physical performance, is the clinically relevant outcome of muscle mass and muscle strength. Very few studies have addressed the association of protein intake to physical performance, and most of the ones that have been performed have been among disabled or frail elderly (58) and in combination with exercise (59–61). Tieland et al (58, 59) found improvements in physical performance after protein intervention, but the older studies (60, 61) found no effect from protein supplements on physical performance in the frail elderly.

Type-2 Diabetes

Based on four prospective cohort studies with long-term LC/HP diets, including one study with an LC/HP and high fat diet, the SR by Pedersen et al (12) assessed the evidence as *suggestive* regarding the relation of total and animal protein intake to increased risk of type-2 diabetes. In two of the included studies, this association was most clearly associated with intake of animal protein, but this could be a reflection of the fact that animal protein was the main protein source. Again it should be emphasized that LC/HP diets cannot be used to assess the effect from protein *per se*.

Renal function and kidney stones

The evidence for associations between protein intake and kidney function and kidney stones was regarded as *inconclusive* in the SR by Pedersen et al (12). Also, the EFSA (38) assessed the available evidence as insufficient to derive an upper level of protein intake based on kidney function.

Protein and physical exercise

Whether there is an increased protein requirement as a result of heavy physical exercise is still a matter of debate. Aerobic exercise leads to increased protein oxidation in the muscles in absolute terms. However, the relative contribution of protein to energy turnover is remarkably reduced in relation to that of fat and carbohydrate. Because the body gives priority to covering its energy needs – even when protein turnover is increased – it is important when analysing data to ensure that energy needs are being met before concluding that there are increased protein requirements during physical exercise. A critical analysis of the background data in many studies that give support for increased protein needs indicates that energy needs were not being met.

An increased demand for protein during physical exercise might be due to increased muscle mass as a result of training, increased breakdown of muscle tissue and protein turnover during strenuous physical activity, and increased gluconeogenesis from muscle protein if energy needs are not met leading to muscle protein catabolism and negative N-balance (62, 63). Studies using both the N-balance technique and stable isotope technique have suggested that the daily protein requirement might be as high as 1.4–1.8 g/kg BW in athletes with heavy training (20, 64–67). Long-term studies using stable isotope techniques (68–70) indicate, however, that there seems to exist a compensatory reduction in leucine oxidation during the recovery phase after aerobic exercise indicating a homeostatic response to conserve body protein. For strengthening exercise, the acute anabolic response to exercise and amino acid nutrition, measured by stable isotope technology, was found to reflect the 24 hour response in regularly active young persons (71). Resistance training, however, attenuated the response to an acute bout of strength training but elevated the resting muscle protein turnover (72, 73). Thus, protein utilisation might improve and become more efficient as a result of prolonged training (74, 75).

The SR by Pedersen et al (12) assessed the evidence regarding the effect

of physical training on protein requirements as inconclusive based on three intervention studies with protein intakes at or above the RDA for healthy adults. The evidence was assessed as *suggestive* for the effect of training on whole-body protein retention. The literature search on the interaction between physical activity and protein intake resulted for the most part in studies of short duration, studies in athletes, or studies of specific protein or amino acid supplements, and these studies were not eligible for the review. The conclusion from the SR (12) is in agreement with the most recent position statement on 'Nutrition and Athletic Performance' from the American Dietetic Association, Dieticians of Canada, and the American College of Sports Medicine (76) that states that protein requirement for N-balance, even in athletes, generally can be met through diet alone without use of protein or amino acid supplements. Thus, the same should be valid for healthy adults who are physically active. The position statement does, however, recommend a slightly higher daily protein intake of 1.2 to 1.7 g/kg BW in endurance and strength-trained athletes.

Even though strenuous physical training could potentially double the daily protein requirements (as suggested by earlier studies), the daily energy need in such populations would also be very high. Therefore, there are no data to support the use of protein supplements in athletes consuming a variable, mixed diet (62, 63), and thus there are no data to support such use in healthy adults performing regular physical activity.

Exercise among the elderly, especially resistance training, is a strong anabolic muscle stimulus with proven effects (77), but only a few studies have addressed the issue of dietary protein intake for the optimal effect of physical exercise in older adults. The SR by Pedersen & Cederholm (13) included only two intervention studies (54, 78). Due to the small number of included studies, the evidence was assessed to be *inconclusive*. Studies of short duration or studies of specific protein or amino acid supplements were not eligible for the review. However, it has been suggested from short-term human studies in the elderly that provision of essential amino acids (79, 80), especially the branch-chained essential amino acid leucine (81, 82), might have specific protein anabolic effects, but more long-term studies on leucine supplementation are needed.

Although supplementation does not seem to be needed to ensure adequate protein intake, the timing of protein supplementation in relation to exercise might be important for the anabolic effect of the supplementation in both young (67) and older (83) subjects. These findings might be explained by interacting effects between acute exercise and nutrition

on net muscle-protein balance in the post-exercise period (84). However, long-term dietary protein-based studies are still lacking.

There has also been discussion as to whether there is a threshold for post-exercise protein intake to initiate an augmented protein synthesis response. A minimum amount of approximately 25–30 g of high-quality protein is necessary to maximally stimulate muscle protein synthesis (67). Accordingly, a short-term study by Symons et al (85) demonstrated that the protein synthesis effect was the same irrespective of an intake of 30 grams or 90 grams of protein during one meal.

Despite the above findings, it is still premature to make recommendations regarding timing and distribution of protein intake in the elderly based on the present scientific evidence.

Recommended intake

Adults

Based on Rand et al's meta-analysis (14), the WHO/FAO/UNU (9) recommends 0.83 g good-quality protein/kg BW/d based on an estimated average requirement (EAR) of 0.66/kg BW per day. The values are based on the 97.5th percentile to allow for individual variability, and these values are about 10% higher than the previous values proposed by the FAO/WHO/UNU report from 1985 (86).

The 2002 US recommendations from Institute of Medicine, IoM, (87) for protein were also based on the meta-analysis of N-balance studies by Rand et al (14) and cite an EAR of 0.66 g/kg BW per day and an RDA of 0.8 g good-quality protein/kg BW per day. These recommendations are for healthy adults based on a coefficient of variation of 12% and with no significant differences according to adult age or sex. In addition, IoM 2002 (87) recommends an Acceptable Macronutrient Distribution Range of 10–35 E% from protein. The EFSA (38) also based their Population Reference Intake of 0.83 g good-quality protein/kg BW per day on the meta-analysis by Rand et al (14).

For the update in NNR 2012, two SRs were conducted to assess the evidence behind the dietary requirement of protein. One SR included healthy adults (12) and one included healthy elderly populations (13), and they both assessed the evidence as *probable* for a median EAR of nitrogen of 105 mg/kg BW per day. This corresponds to a daily intake of 0.66 g good-quality protein/kg BW and a subsequent RDA of 0.83 g good-quality protein/kg BW per day regardless of sex or age.

The SRs also assessed the possible health effects of varying protein intake in order to evaluate the evidence for an optimal protein intake. For most outcomes, the evidence of a relation to protein intake was assessed as *inconclusive* (e.g. all-cause mortality, cancer mortality and cancer diseases, cardiovascular disease, bone health, body weight control, body composition, and renal function). However, an inverse relation of intake of vegetable protein to cardiovascular mortality and blood pressure was assessed as *suggestive* (12). Thus, despite some studies finding a decreased risk of outcome associated with vegetable protein intake, there is at present insufficient evidence for a recommendation of an increased intake of protein from vegetable food sources.

Many of the protein intake data from the observational studies were flawed by misreporting, and poor adherence to the diets was an issue in some of the intervention studies. Thus, the SR by Pedersen et al (12) failed to identify high-quality studies that could alter the classical criterion for protein recommendations, i.e. studies based on N-balance. Also the EFSA Panel (38), WHO (9), and IoM (87) considered several health outcomes associated with protein intake and concluded that currently available data were insufficient to establish reference values or recommendations.

At reference energy intakes (see the chapter on Energy), a protein intake of 0.8 g/kg BW/d corresponds to approximately 10 E% from protein provided a moderate physical activity level (PAL) of 1.6. Thus, 10 E% protein might represent the *lower intake range* for healthy adults with a PAL of 1.6.

Based on the available evidence, and according to the Nordic dietary habits, a protein intake corresponding to 10–20 E% is recommended. Thus, the recommended range is the same as in NNR 2004.

The range of 10–20 E% corresponds to about 0.8–1.5 g protein/kg BW/d provided a PAL of 1.6 for an intake of about 10 E% and a PAL of 1.4, for an intake of about 20 E%, respectively.

For food planning purposes with energy intake in the range of 8–12 MJ, an appropriate target is 15 E% and this corresponds to about 1.1 g protein/kg BW/d. This intake of protein should also adequately meet the requirements for essential amino acids. With decreasing energy intake below 8 MJ (e.g., decreased physical activity or during intentional weight loss), the protein E% should increase accordingly and still correspond about 1.1 g protein/kg BW/d.

In relation to physical activity, the protein requirement can generally be met through a diet that meets the energy need. Thus, a protein intake

corresponding to 10–20 E% is recommended for adults, and an intake corresponding to 15–20 E% is recommended for the elderly.

Elderly

Chronic diseases are more frequent in the elderly, and such conditions might lead to periodic temporary losses of body protein through catabolic exacerbations of the disease, temporary periods of bed rest, or loss of appetite. The losses must be replaced from the diet and thus represent an added need for dietary protein (88). In addition, older individuals exhibit a gradual loss of muscle mass and strength with age (sarcopenia). This is estimated to be a daily loss of 0.5 mg nitrogen per kg BW (89) that occurs naturally and is not simply due to decreased physical activity (90).

Based on N-balance studies, Pedersen & Cederholm (13) assessed the evidence as *probable* regarding a median EAR of nitrogen of 105 mg/kg BW per day which corresponds to 0.66 g high-quality protein/kg BW per day and the subsequent RDA of 0.83 g high-quality protein/kg BW per day to represent the *minimum dietary protein intake* for virtually all healthy elderly persons. Despite being in N-balance, two studies (15, 17) also found a decreased urinary N-excretion, which in the study by Campbell et al (15) also was related to a loss of muscle mass, indicating that a higher protein intake might be necessary to maintain muscle mass among the elderly. Thus, N-balance *per se* might not reflect a preservation of muscle mass.

The SR (13) also assessed the health effects of varying protein intakes in order to evaluate the evidence for an optimal protein intake. For maintenance of bone mass, muscle mass, and strength, as well as for a relationship with morbidity and mortality, the assessment of the evidence ranged from *suggestive* to *inconclusive*. Results from prospective cohort studies in particular suggested that a safe intake of up to at least 1.2–1.5 g protein/kg BW/d or approximately 15–20 E%, represents an *optimal intake level*.

Short-term studies, including studies with protein hydrolysates or amino acids and studies that have looked at the effect of timing or meal distribution, point to specific anabolic effects but larger long-term studies are still needed as background for future recommendations.

Based on data from N-balance studies in relation to maintenance of muscle mass (supported by prospective cohort studies and by suggestive health effects) it is recommended to increase the protein intake for those ≥65 years of age. In relation to the age-related decrease in energy intake, a diet with a protein content in the range of 10–14 E% might not sufficiently cover the need for protein in absolute amounts.

A protein intake corresponding to 15–20 E% is recommended, and with decreasing energy intake the protein E% should be increased accordingly because the protein needs do not change in a corresponding manner.

The range of 15–20 E% corresponds to about 1.1–1.3 g protein/kg BW/d provided a PAL of 1.6 for 15 E%, and a PAL of 1.4 for 20 E%, respectively, as estimated from body weights and energy expenditure by Gaillard et al. (91).

For food planning purposes, the recommendation is 18 E%, which corresponds to about 1.2 g protein/kg BW/d. This is an increase of 20% compared to the NNR 2004 recommendation.

Infants and children

Recommended protein intakes for infants and children are based on the factorial method. The calculation is based on estimates of the need for maintenance and growth, the efficiency of conversion from dietary protein to body protein, and intra individual variation in growth. There is, however, considerable discussion about the appropriate values to use for these calculations during the first year of life, and this has led to large differences in the recommendations for protein intake during the first year of life, especially the first 6 months.

A highprotein intake results in a high renal solute load. However, it is only during the first months of life that the kidneys cannot handle a high solute load (92). For NNR 2012 (as well as for the previous NNR 2004), no adequate intake for protein is given for the first 6 months. During this period, infants are either breastfed or receive infant formula. The protein content of breast milk is considered adequate for term infants and the protein content of infant formula is regulated by EC legislation. The protein content of infant formula and especially follow-on formula has decreased over the years. According to the current regulation/directive (REGULATION (EC) No 1243/2008 and Directive 2006/141/EC), the protein content of infant formula should be between 0.45 and 0.7 g/100 kJ and the protein content of follow-on formula should be between 0.45 and 0.8 g/100 kJ.

Based on N-balance studies, the WHO/FAO/UNU (9) calculated a maintenance requirement of 0.66 g protein/kg BW between 6 months and 18 years of age. Adding a requirement for growth results in an estimated average requirement that falls very rapidly during the first two years of life (1.12 g/kg BW at 6 months and 0.79 g/kg BW at two years) and then falls more slowly reaching 0.75 g/kg BW at 10 years and 0.69 and 0.66 g/kg BW for boys and girls, respectively, at 18 years. The “safe level of intake”

is calculated by adding 1.96 standard deviations (SD) to the average requirement. Compared to previous calculations (86), the recommended safe level has decreased for all ages but especially for the first two years. The EFSA (38) has accepted the WHO/FAO /UNU 2007 (9) figures, and these form the basis of the recommended levels for children aged 6 months to 18 years in NNR 2012 (Table 12.1.).

In relation to body weight, the WHO/FAO/UNU (9) gives the reference values of 0.9 g/kg BW per day from 3 to 18 years of age for boys and from 3 to 15 years of age for girls. This value decreases slightly for girls to 0.8 g/kg BW per day between 15 and 18 years of age. The protein energy percentage necessary to cover the adequate protein intake can be calculated by combining these reference values with the reference values for energy intake for age and sex. The average requirement calculated as E% is about 5.3 E% at 6 months, followed by a decline to 4.3 E% at 2 years. Thereafter there is a gradual increase to about 7 E% and 9 E% at 17 years of age for boys and girls, respectively.

Table 12.1. Safe level of protein intake (average requirement + 1.96 SD) in weaned infants and children

Age	Protein g/kg BW	E%	g/100 kJ
6–11 months	1.1	7–15	0.4–0.9
12–23 months	1.0	10–15	0.6–0.9
2–17 years	0.9	10–20	

Expressed as E%, the protein intake increases considerably during the first 1 to 2 years of life when the infant gradually changes from breast milk with a protein content of about 5 E% to the family diet that typically provides around 15 E% from protein. The average protein intake among children varies between 13 E% and 16 E% from about 1 year of age in most European countries, including the Nordic countries (38).

With regard to later risk of non-communicable diseases such as cardiovascular disease, both the quantity and quality of protein intake in infancy and childhood is of interest. In the Nordic setting, the quantity is more important because the protein sources are usually of animal origin and quality is not a concern. The upper level of a healthy protein intake in infancy and childhood, however, has yet to be firmly established.

One of the SRs carried out for the update of NNR 2012 (22) aimed

to review the scientific data published between 2000 and 2011 on the short- and long-term health effects of different levels of protein intake in infancy and childhood. Special focus was on growth, serum lipids, glucose and insulin, blood pressure, body weight, body composition, and bone mineral density. The authors concluded that the evidence was *convincing* that higher protein intake in infancy and early childhood contributes to increased risk for obesity later in life. Which age period is most sensitive to high protein intake was not clear, but with regard to the available data the authors state that the first two years of life seems probable and that a protein intake between 15 E% and 20 E% in early childhood increases the risk of being overweight later in life. A high-quality European multi-centre, double-blind, randomized controlled trial included in the SR tested the effect on growth of a low *vs.* a high protein intake during the first two years of life (93). The protein content in the formulas and follow-on formulas used in the trial represented approximately the lowest and highest acceptable levels in the range given in the European Union (EU) directives from 1991 (when the directives for follow-on formula, at 0.5–1.0 g/100 kJ, were slightly higher than the present) and corresponded at 12 months to 14.0 E% in the low-protein formula group and 16.7 E% in the high-protein formula group. The higher intake in the latter group was associated with increased risk for overweight at 24 months. In several Nordic countries, mean protein intake is close to 15 E% during the first years of life indicating that a large proportion of young children have a higher protein intake that might contribute to increased risk of later obesity (22).

With regard to other outcomes, the evidence was not as strong (22). The protein source appears to be important and there was *suggestive* evidence that intake of animal protein, especially from dairy products, has a stronger association with growth, and particularly with weight gain, than vegetable protein. The evidence was also *suggestive* that higher intake of animal protein was associated with earlier onset of puberty and that total protein intake was positively associated with bone mineral content. Other associations with early protein intake and different health outcomes were assessed to be *inconclusive*. Part of the lack of evidence could be due to different effects depending on BMI, phenotypes, or gender, and the effects of these factors warrant further studies.

The recommendations for protein intake in children in the NNR 2012 are the same as in the NNR 2004, i.e. 7–15 E% from 6 to 11 months of age, 10–15 E% for 12 to 23 months of age, and 10–20 E% for 2 to 17 years of age.

Pregnant and lactating women

During pregnancy, the average protein requirement is increased to provide additional protein for deposition in maternal (blood, uterus, and breasts), foetal, and placental tissues. Additional protein is also needed to maintain the increased mass of the pregnant body. According to the WHO/FAO/UNU report (9), the additional safe intake of protein for a healthy woman gaining 13.8 kg body weight during her complete pregnancy is 0.7, 9.6, and 31.2 g/d during the first, second, and third trimester, respectively. This represents less than 12 E% protein for a reference woman of reproductive age assuming a PAL of 1.6. The dietary protein content in the Nordic countries is generally higher than 12 E%, and the protein quality is generally high. Consequently, most pregnant women are able to cover their protein needs by consuming their normal diet in a quantity that allows a weight gain within the recommended limits. However, it is recommended that the increased intake of protein during pregnancy – due to increased energy intake – should consist of normal food rather than of high-protein supplements. The basis for this is that studies (94, 95) have indicated that supplements with a high protein content during pregnancy might result in adverse pregnancy outcomes.

The average protein requirement is also increased during lactation when the breast milk produced by a woman provides all of the protein needed by her infant. The WHO/FAO/UNU (9) recommends that the safe level of additional protein for a lactating woman in full lactation is 18–20 g per day. This figure is applicable during the first six months of lactation. During partial lactation, i.e. 6–12 months post partum, the recommended amount is 12.5 g/d. This represents less than 12 E% protein and, therefore, a lactating as well as a pregnant woman can, in most cases, cover her protein requirements with her normal diet if her energy requirements are covered.

Based on this, the recommended E% protein during pregnancy and lactation is the same as for non-pregnant women.

Reasoning behind the upper intake range

Based on the risk of mortality and morbidity, the SR by Pedersen et al (12) also assessed the evidence for potential adverse effect of a high protein intake.

There was no indication of adverse effects of protein intake in relation to bone health provided a sufficient calcium intake, and an included meta-

analysis did not find support for the hypothesis that "acid" from the diet causes osteoporosis (42).

The evidence was assessed as *suggestive* regarding an increased risk of all-cause mortality and type 2 diabetes in relation to long-term LC/HP diets with a total protein intake of at least 20–23 E% (12). However, the use of an LC/HP score makes it uncertain whether the effects result from reduced carbohydrate or increased protein intake. A biologically plausible explanation might be that diets rich in plant foods like vegetables, fruits, nuts, and whole-grain cereals are associated with a lower risk of chronic diseases (96) while protein intake in the form of red and processed meat increases the risk of cancers, especially colorectal cancer (28). Notably, the data evaluated the health consequences of long-term habitual dietary intakes and should not be interpreted as indicating that short-term use of LC/HP diets is detrimental to health.

One study with elderly subjects (34) found that animal protein intake was related to increased risk of hypertension among persons ≥70 years of age. The lowest tertile of total protein intake was 14 E% and the highest was 19 E%.

With regard to renal function, the SR by Pedersen et al (12) called for reflection. An increase in GFR is a physiological adaption to increased protein intake (97). Walrand et al (18) found that a high protein intake did not increase GFR in the elderly participants in their study from a baseline GFR that was lower than that of the young participants. This was probably due to the reduced kidney function in the elderly because patients individuals with mild to moderate chronic kidney disease also do not show the usual protein-induced increase in GFR (98). Caution is also required due to the observation of a decline in GFR among women with mild kidney insufficiency (99), and because older adults might have severely reduced GFR without knowing it.

With regard to microalbuminuria, one experimental study found an increase in urinary albumin after seven days on a high protein intake of 2.4 g/kg BW per day, but a similar increase in protein intake in another short-term experimental study of healthy young men did not find an increase in 24 hour urinary albumin excretion (12). Further studies are needed to settle whether this discrepancy is due to the different durations of the studies or due to different methods of analysis of albumin in the urine. A review by Friedman (100) cites an earlier 3-week study showing a reduction in proteinuria with reduced protein intake (from 75 g per day to 43 g per day). Caution is required until this matter is settled.

The upper range for protein intake in adults of 20 E% is unchanged from the NNR 2004. This recommendation takes into account the potential harmful effects of a long-term dietary protein intake above 20–23 E% seen in studies with protein *per se* and with LC/HP and/or high-fat diets, the caveat from renal function studies, and a consideration of the recommendations for fat and carbohydrates.

Although possible negative consequences of a high-protein intake have not been clearly demonstrated in infants and children, a decrease in the upper levels for the ages of 6 to 23 months is deemed prudent. The following upper ranges for protein intake are suggested, assuming sufficient intake of other nutrients: 0–6 months, 10 E%; 6–11 months, 15 E%; 12–23 months, 17 E%; and 2 years and older, 20 E%.

Upper intake levels

No upper intake level could be established based on the present evidence.

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13 Alcohol

	Adults	Children and adolescents
Women Men	< 10 g/d (< 5 E%) < 20 g/d (< 5 E%)	Abstain

Introduction

Alcohol (ethanol) is generally consumed as beer (about 2.5–6 vol% alcohol), wine (about 12 vol%), or spirits (about 40 vol%). The energy liberated upon oxidation of alcohol in the body corresponds to 29 kJ per gram. At high alcohol consumption, however, the energy efficiency appears to be lower with relatively higher heat dissipation than with the other energy-yielding nutrients (1). Alcohol is efficiently absorbed through passive diffusion, mainly in the small intestine and is distributed throughout the total water compartment of the body. Most of the absorbed alcohol is oxidized in the body but a small amount (5%–10%) is lost through expired air and in the urine.

In the Nordic countries, mean alcohol consumption accounts for about 2% to 6% of the total energy intake in adults, but the intake is very unevenly distributed.

Nutritional aspects

Replacing part of the food intake with alcoholic beverages can impair the quality of the diet. In particular, the consumption of dairy products, fruits, and vegetables appears to decrease when the intake of alcohol is increased. Some exceptions to this pattern, however, are noted. For example, a Danish study showed a strong positive association between fruit and vegetable consumption and wine intake (2). A high level of alcohol consumption can also result in impaired absorption of nutrients and increased nutrient loss

in the urine. From a nutritional point of view, therefore, it is reasonable to recommend moderation in alcohol intake. Nutritional status among high alcohol consumers is always affected (3), and deficiencies in ascorbic acid, thiamine, magnesium, phosphorus, vitamin D, and protein are frequent (4, 5).

Alcohol and health

Alcohol is a toxic substance that affects all organs of the body. Both acute and chronic alcohol-induced damage contributes significantly to morbidity and mortality. From a public health perspective, it is important to bear in mind that overall consumption is a main determinant of the alcohol-related harm rates in the population (6). The negative health effects of alcohol are primarily determined by the total amount of alcohol to which the body is exposed. This means that alcohol damage might develop in individuals who have not been visibly drunk. It is likely that daily consumption of 70 g alcohol will result in alcohol-related damage (7).

A review of the health aspects of alcohol consumption was carried out for the revision of the Nordic Nutrition Recommendations (NNR) with a focus on those areas in which new scientific knowledge has emerged since the 4th edition and that has special relevance for the Nordic setting (8). The literature search covered articles published between January 2000 and November 2010, with a complementary search up to February 2012. The majority of the research covered the following topics: Cardiovascular disease and related metabolic risk factors, total mortality, cancer, weight change/outcome, and pregnancy or birth outcomes.

Cardiovascular disease

Alcohol has been associated with coronary heart disease (CHD), atrial fibrillation (AF), ischemic stroke, haemorrhagic stroke and congestive heart failure (CHF).

Coronary heart disease

A meta-analysis and review comprising data from 84 prospective cohort studies with and a total of 3,159,720 study participants assessed the relative risk (RR) of various cardiovascular outcomes. CHD among drinkers and non-drinkers (9). The pooled, adjusted RRs for alcohol drinkers relative to non-drinkers were 0.71 (95% CI: 0.66–0.77) for incident CHD (29 studies) and 0.75 (95% CI: 0.68–0.81) for CHD mortality (31 studies). These results

persisted after excluding former drinkers from the category of abstainers. In analyses exploring dose-response, alcohol consumptions of 2.5–14.9 g/d, 15–29.9 g/d, or 30–60 g/d were all associated with similar and statistically significant reductions in the RR of CHD relative to non-drinkers. The highest consumption category (> 60 g/d) was associated with an RR of 0.76 (95% CI: 0.52–1.09). There is evidence, therefore, of a maximal upper range of intake for the cardioprotective effect of alcohol but no indication of a higher risk among the heaviest drinkers. In contrast, an earlier meta-analysis found that the association between alcohol and CHD risk was J-shaped implying a minimum RR of 0.80 at 20 g/d, a significant protective effect up to 72 g/d, and a significantly increased risk at intakes above 89 g/d (10).

The impact of drinking pattern has been addressed in fewer studies, but the majority of these find a non-beneficial or even harmful effect of a drinking pattern that involves drinking large amounts of alcohol per occasion (binge drinking).

The finding that CHD risk is lower in light to moderate drinkers compared with non-drinkers is very consistent across study populations with different distributions of confounders and potential effect modifiers (9). Due to the heterogeneity of the exposure in studies investigating the independent effects of drinking patterns, it is premature to make a firm conclusion of the exact measure of drinking pattern that most accurately captures the non-beneficial effect. However, most evidence suggests that a drinking pattern in line with the NNR 2004 recommendations (< 10 g/d for women and < 20 g/d for men) is not detrimental. In conclusion, the current evidence is in accordance with NNR 2004.

Atrial fibrillation

In a meta-analysis and review comprising data from five case control and nine prospective cohort studies, of which six were hospital based, and included a total of 138,020 participants, high alcohol intake was associated with increased risk of AF (11). In pooled analyses, the RR for the highest versus the lowest alcohol category was 1.51 (95% CI: 1.31–1.74), but the definition of 'high' intake differed from study to study (11). In dose-response analyses, each 10 g/d increment was associated with an increased risk of AF (RR = 1.08, 95% CI: 1.05–1.10). Results of the meta-analysis indicate that the risk of AF is probably increased by heavy drinking, while the effect of light to moderate intake is more uncertain due to a lack of high-quality studies. In conclusion, the current evidence is in accordance with the recommendations in NNR 2004.

Stroke

Two meta-analyses and reviews assessed the association between alcohol intake and stroke (9, 12). These papers analysed the results of 16 studies on haemorrhagic stroke and 20 studies on ischemic stroke that included a total of 737,038 study participants. The results of the analyses show that high alcohol intake is consistently associated with an increased risk of both haemorrhagic and ischemic stroke. With moderate intakes of up to 3 drinks per day, the results are inconsistent; moderate consumption seems to be protective against ischemic stroke, but neutral or slightly detrimental for haemorrhagic stroke. In conclusion, the current evidence is in accordance with the recommendations in NNR 2004.

Congestive heart failure

A meta-analysis and review (13) included six prospective cohort studies with a total of 164,479 study participants. Compared with never drinkers, the pooled RRs for CHF were 1.16 (95% CI: 0.90–1.51) for former drinkers and 0.90 (95% CI: 0.83–0.98), 0.80 (95% CI: 0.73–0.88), 0.78 (95% CI: 0.65–0.95), and 0.77 (95% CI: 0.63–0.95) for current drinkers of 0.1–0.9, 1–7, 8–14, and >14 drinks/week, respectively (13). There was no heterogeneity in the findings between the six individual studies. Light to moderate drinking was not associated with increased CHF risk, and at best was associated with a lower risk of CHF. In conclusion, the current evidence on this subject is in accordance with the recommendations in NNR 2004.

All-cause mortality

A meta-analysis and review was carried out on 34 prospective cohort studies published up to 2005 reporting on mortality from Australia, China, Japan, Europe, and the US that included 1,015,835 study participants (14). A J-shaped relationship between alcohol and all-cause mortality was found in adjusted analyses of both men and women. Consumption of alcohol of up to 2–4 drinks per day in men and 1–2 drinks per day in women was inversely associated with total mortality, with a reduction of 18% in women (99% CI: 13%–22%) and 17% in men (99% CI: 15%–19%). Higher intakes of alcohol were associated with increased mortality. Risk reductions were somewhat lower in analyses adjusting for age, socioeconomic status, and dietary markers and were apparent at up to 3 drinks per day for men and up to 2 drinks per day for women. The calculated reversion point (the dose of alcohol at which the protection against mortality was

not statistically significant at the 99% confidence level) was 30 g per day in the adjusted model. Because the relative incidences of alcohol-related diseases and outcomes differ by age, the J-shaped association between alcohol and all-cause mortality also differs by age. The nadir (representing the alcohol intake at the lowest risk of mortality) is achieved at a lower intake at younger ages. In a British study, the lowest mortality risk among women 16 to 34 years old and men 16 to 24 years old was observed among the non-drinkers (15). Hence, a beneficial effect of alcohol is not observed among the young, and instead alcohol is directly associated with mortality in this age group.

Results from studies regarding the role of drinking pattern consistently imply an increased mortality risk associated with drinking large amounts of alcohol per session, or binge drinking (16). Furthermore, there is good evidence that the protective effect of alcohol on cardiovascular disease only occurs if the pattern of drinking is not a binging pattern (16). Hence, the J-shaped association between alcohol intake and all-cause mortality depends upon the drinking pattern.

The association between alcohol and all-cause mortality is J-shaped; the nadir of the 'J' reflects a relatively lower risk of CHD among light to moderate drinkers compared with abstainers and the ascending leg of the J is reflective of an increased risk of alcohol-related diseases such as liver cirrhosis, pancreatitis, upper gastrointestinal cancers, cardiomyopathy, polyneuropathy, and deaths from accidents and violence among excessive alcohol users. Because the association between alcohol and all-cause mortality represents the sum of the numerous diseases and outcomes that are related to alcohol, the shape and nadir of the risk curve depends upon the distribution of other variables such as age, relative incidences of diseases, the prevalence of drunk-driving, etc. Thus, the association between alcohol and all-cause mortality does not have the same causal interpretation as associations between alcohol and singular endpoints.

In conclusion, light to moderate drinking is not associated with increased mortality risk and is at best associated with a lower risk among middle-aged and older adults who do not engage in episodes of heavy drinking. Total abstinence is associated with the lowest risk of mortality in young adults, and binge drinking should be avoided in all age groups.

Cardio-metabolic risk markers

Serum lipids

A comprehensive high-quality meta-analysis of intervention studies was published in 2011 (17) and found that alcohol significantly increased levels of high-density lipoprotein and adiponectin and significantly decreased levels of fibrinogen. These favourable changes in cardiovascular biomarkers provide indirect physiological support for a protective effect of moderate alcohol use against CHD.

Hypertension

There is convincing evidence that high alcohol intake is associated with increased blood pressure (18) and risk of hypertension (19). During recent years, there has been some discussion as to whether light to moderate alcohol intake is associated with lower blood pressure and lower risk of hypertension, especially among women (19).

Insulin and glucose concentrations

Reviews and meta-analyses are sparse in this area, but individual studies have found that an alcohol intake of 1–2 drinks per day is associated with reduced fasting insulin concentration and improved insulin sensitivity (20–24). Furthermore, fasting glucose levels were similar in non-drinkers and moderate alcohol drinkers in a prospective cohort study (25).

Cancer

The evidence that intake of alcohol is related to several types of human cancers has been strengthened since the mid-1990s. Alcohol (ethanol) is classified as a human carcinogen by the International Agency for Cancer Research (26). The 2007 World Cancer Research Fund report included an extensive systematic review of the available evidence on the association between alcohol intake and the development of cancer (27). Evidence was graded as "convincing" for an increased risk of cancer of the mouth, pharynx, larynx, and oesophagus and for colorectal cancer among men and breast cancer among women. There was "probable" evidence for an association between alcohol intake and the risk of liver cancer and colorectal cancer among women. Several subsequent meta-analyses and reviews have been published. For the cancers with sufficient evidence in the WCRF report (27), new studies have supported the evidence of a relation between alcohol intake and cancer risk (28–38). This is especially the case for can-

cers of the upper aerodigestive tract and colorectal cancer and for breast cancer among women.

The WCRF review concluded that a substantial effect on risk was unlikely with regard to renal cell cancer (27). A subsequent meta-analysis by Song et al. (39) included 20 case-control studies, 3 cohort studies. A pooled analysis of the cohort studies found an inverse association with the greatest reduction at the moderate level of intake, while an alcohol intake >15 g per day does not confer additional benefits for prevention of renal cell cancer.

A meta-analysis indicated an association between heavy alcohol intake (≥ 3 drinks/d) and increased risk of pancreatic cancer (33). There was no association between moderate drinking and pancreatic cancer risk. However, because smoking is a strong risk factor for pancreatic cancer, residual confounding is a potential problem in these studies. This could also be the case in the studies between alcohol intake and lung cancer, where a suggestive increased risk has been shown (40). No strong association was shown for alcohol intake and the risk of ovarian, endometrial, or non-Hodgkin lymphoma (41–43). A suggested possible protective effect of alcohol intake on lymphoma risk might differ by lymphoma type.

There is some evidence suggesting that alcohol increases the risk of liver cancer through alcohol-associated fibrosis and hepatitis (27, 44). Liver cirrhosis was found to be present among 80% of patients with liver cancer (45).

A review on alcohol consumption and prostate cancer (46) concluded that a daily consumption up to about 3 drinks per day does not appear to influence prostate cancer risk, but heavy consumption of 7 or more drinks per day might be associated with an increased risk. However, the data on high exposure in this review were limited to only one prospective study and four case-control studies.

In a meta-analysis on alcohol intake and bladder cancer, the overall estimate showed no association (47). Sub-analysis did show a relation between beer and wine intake and a reduced risk of bladder cancer in a dose-dependent manner, and this should be explored further in future studies.

The overall conclusion is that the evidence for associations between alcohol intake and cancer does not show any "safe limit" of intake. This is especially true for breast cancer where even very moderate intake has been shown to increase the risk (48). The effect is from ethanol irrespective the type of drink (27). The current evidence on the relationship between alcohol and cancer risk is in accordance with the recommendations in NNR 2004.

Weight maintenance

Results from a review including 31 publications with 13 prospective cohort studies and 4 clinical trials did not show any consistent associations between alcohol intake and weight gain (49). Some studies, however, found that higher levels of consumption (> 2–3 drinks/d) were associated with weight gain. The type of beverage seems to be of importance with a lower weight gain observed for wine compared to beer and spirits. Only four prospective studies reported on the relation between alcohol intake and waist circumference or waist to hip ratio. The findings were inconsistent with studies finding positive, negative, or no associations. The effect of alcohol on weight gain and waist circumference is not clear from the current evidence, and no final conclusion could be drawn.

Prenatal alcohol exposure

Alcohol can affect the developing foetus in a dose-dependent manner. Alcohol is teratogenic and can lead to Foetal Alcohol Syndrome (FAS), which is characterized by craniocephal abnormalities, physical and mental retardation, and cardiac and joint abnormalities (50). These effects are mainly seen with an alcohol intake above 24–48 g/d.

A systematic review of prenatal alcohol exposure (51) found that low to moderate levels of alcohol consumption had no consistently significant effects on miscarriage, stillbirth, intrauterine growth restriction, prematurity, birth weight, small for gestational age at birth, or birth defects. However, weaknesses in the evidence preclude the conclusion that drinking at moderate levels during pregnancy is safe.

Alcohol intake during lactation

Although no effects of alcohol consumption on the infant during breastfeeding have been established, some studies (52) – but not all (53) – have suggested that there is impaired development in infants whose mothers consume alcohol when lactating. Reduced milk production (54), reduced milk intake (55), and sleep disturbances in the child (56) have been described. These effects are transient and compensated for by the child within 24 hours if the mother does not continue to drink during that time. No medical consequences have been seen in the child if a lactating mother occasionally drinks small amounts of alcohol (57). Mothers in Sweden are advised that there are no positive effects of alcohol intake while breastfeeding, but also that occasional intake of small amounts (not exceeding 1–2 small glasses of wine 1–2 times per week) is not harmful to the child.

Recommendation

Alcohol consumption is associated with both negative and positive health effects and tends to have a negative effect on diet quality. The evidence shows that regular, moderate alcohol consumption might confer cardio-protective effects among middle-aged and older individuals, but alcohol consumption among young adults is detrimental. For most cancers, there is convincing evidence that alcohol consumption increases the risk and it not possible to set any "safe limit" of intake. This is especially true for breast cancer, where even very moderate intake has been shown to increase the risk. Light to moderate regular alcohol consumption is not associated with increased mortality risk among middle-aged and older adults. Among young adults, however, alcohol consumption is associated with increased mortality.

Based on the overall evidence, it is recommended to limit alcohol intake. Based on estimates of the maximal mortality risk reduction associated with moderate alcohol consumption (15, 16), the intake should not exceed 10 g (approximately 1 unit*) per day for women and 20 g (approximately 2 units*) per day for men. The consumption of alcohol should not exceed 5% of the energy intake in adults.

Pregnant women, children, and adolescents are recommended to abstain from alcohol. Lactating women are recommended to limit alcohol intake.

* 1 unit is defined as 12 g alcohol (41) corresponding to the alcohol content in one bottle of beer (330 mL), one glass of wine (120 mL), or one glass of spirits (40 mL). The definition of a unit varies in different countries from approximately 8 g to 12 g (17).

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14 Dietary antioxidants

Introduction

Free radicals and other reactive oxygen and nitrogen species (ROS and RNS) are formed continuously in the body, partially through the normal cellular oxidative metabolic reactions, that are required to maintain homeostasis. Such reactive species also develop as the result of diseases (e.g., during inflammation) as well as exposure to tobacco smoke, environmental pollutants, drugs, radiation, excessive alcohol consumption, and other unknown factors. Antioxidants are substances that delay or prevent (quench) the oxidation of oxidisable substrates such as lipids, carbohydrates, proteins, and DNA. If not adequately quenched by endogenous or exogenous antioxidants, the free radicals can react with and potentially alter the structure and function of cellular components such as lipid-containing cell membranes, lipoproteins, proteins, carbohydrates, RNA, and DNA. Many substances show antioxidative properties in vitro but do not necessarily show such activity in vivo.

Oxidative stress results when the critical balance between the endogenous generation of ROS or RNS and antioxidant defences is severely disrupted, rather than when the balance is only mildly affected for a short time period (1–5). Studies from the past three decades have shown that such oxidative damage or oxidative stress is involved in the pathophysiology of many otherwise unrelated types of disease. Oxidative stress has been associated with inflammatory diseases, ischemic diseases (heart disease, stroke, and intestinal ischemia), cancer, obesity-related diseases (dyslipidaemia, vascular inflammation, hypertension, and diabetes), hypertension and preeclampsia, and neurological diseases (multiple sclerosis, Alzheimer's disease, and Parkinson's disease) (1, 2, 5–8).

A complex endogenous antioxidant defence system has evolved in all living organisms to counteract oxidative stress and is essential for all aerobic cells. Both enzymatic and non-enzymatic processes prevent radical forma-

tion, remove radicals before damage can occur, repair oxidative damage, eliminate damaged molecules, and prevent mutations (1, 8, 9).

In addition to the endogenous antioxidants, diet might also contribute to the antioxidant defence system of the body. The roles of vitamin C, vitamin E, and selenium as antioxidants are discussed in their respective chapters. Recent research has shown, however, that whole plants and plant extracts contain numerous known and unidentified compounds with antioxidant properties (10). The role of these dietary antioxidants is not well understood because evaluation of their impact on health and disease is difficult, but they are potentially important modulators of several diseases related to oxidative stress.

Types and food sources of compounds with antioxidative properties

Foods containing high levels of total antioxidants include several berries (blueberries, blackberries, strawberries, and raspberries), fruits (pomegranates, grapes, and oranges), nuts and seeds (walnuts and sunflower seeds), vegetables (kale, red cabbage, and pepper), and drinks (green tea and red wine) (11, 12). The dietary antioxidants in fruits and vegetables might contribute to two important components of the antioxidant defence system: 1) the ability to scavenge or neutralize free radicals directly and 2) the ability to induce endogenous antioxidants. In this context, the redox process, where both oxidation and reduction occur simultaneously, is system dependent. The redox-active compound might be an antioxidant in one system (such as a plant subcellular system or an in vitro system) but inactive or a pro-oxidant in another biological system (13).

Compounds with ability to scavenge or neutralize free radicals

Carotenoids are ubiquitous in the plant kingdom, and more than 1000 naturally occurring variants have been identified. Carotenoids are good examples of compounds that both inhibit and enhance oxidation depending on the biological system (14). About 600 different carotenoids have been characterised in plants, and our diet contains at least 60 of these (9). The main carotenoids present in the diet are the provitamin A carotenoids α- and β-carotene and β-cryptoxanthin; lycopene; and the hydroxy-carotenoids (xanthophylls) lutein and zeaxanthin. In plants, carotenoids are auxiliary light harvesting components, and they quench excited molecules formed during photosynthesis (1, 8, 9).

Phenolic compounds are also ubiquitous in many edible plants (9). They are synthesised as various types of molecular families such as benzoic acid derivatives, flavonoids, proanthocyanidins, stilbenes, coumarins, lignans, and lignins. Over 8,000 plant phenols have been isolated. Plant phenols are antioxidants by virtue of the hydrogen-donating properties of the phenolic hydroxyl groups (9).

Glutathione, the major cellular antioxidant, is present in abundant amounts in the diet, although it is not absorbed as such from the diet but is broken down into its constituent amino acids during digestion. However, the dietary availability of sulfur amino acids can modulate cellular glutathione production (1, 8, 9, 15, 16).

Antioxidants from the different molecular families with different chemical and biochemical properties likely activate each other through complex and integrated processes. Packer and colleagues (16) have shown such in vitro interactions for α-tocopherol, α-tocotrienol, ascorbic acid, lipoic acid, and thiols, but Buettner (15) has suggested that the concept could have much broader applicability. This implies that a variety of antioxidants is necessary to maintain the proper endogenous antioxidant defence system. Thus, incorporating the appropriate amount and balance of antioxidants (i.e., electron- or hydrogen-donating reductants) in the diet might be a better concept than focusing on individual dietary antioxidants.

The antioxidant defence system in humans consists of both antioxidants obtained from the diet and endogenous antioxidants generated in the body. However, the antioxidant defence capacity in a plant is not necessarily relevant to human health (17). The methods used to assess the total antioxidant capacity of dietary plants could produce different results when applied to plasma or bodily fluids in humans (17–22). These methods are based on the different chemical properties of the antioxidants, and the ability to detect both water- and fat-soluble antioxidants varies with the substrate.

Compounds with ability to induce antioxidant enzymes

An additional antioxidant defence mechanism involves the induction of several classes of detoxification enzymes.

Phase 2 enzymes. One family of enzymes includes γ-glutamylcysteine synthetase, which is required for the synthesis of the endogenous antioxidant glutathione, glutathione reductase for glutathione reformation, and NAD(P)H:quinone reductase for inhibition of redox cycling (23, 24). These enzymes

are generally referred to as phase 2 enzymes because they are regulated along with enzymes that catalyse the conversion of xenobiotics, which are mutagenic metabolites, or their precursors into compounds that are more readily excreted. It is thought that if benign or non-damaging plant compounds induce the phase 2 enzymes, cells are better able to 'neutralize' toxic agents such as free radicals and other toxic electrophiles when they appear.

Glucosinolates and several other sulfur-containing plant compounds are the major plant compounds believed to support antioxidant defence through this mechanism. Glucosinolates are common components of plants, and glucosinolate breakdown products (such as the isothiocyanate sulforaphane) are thought to induce phase 2 enzymes and are, therefore, responsible for the protective effects shown by Brassica vegetables (9, 23, 24). Dietary plants rich in compounds that induce phase 2 detoxification enzymes include broccoli, Brussels sprouts, cabbage, kale, cauliflower, carrots, onions, tomatoes, spinach, and garlic. However, the evidence for phase 2 enzyme induction at ordinary intake levels of plant foods in humans is limited, and the importance of this defence mechanism in the overall protection against oxidative damage is still uncertain.

Catalase, glutathione peroxidases, superoxide dismutases, paraoxonase, and several other enzymes are included in another important but heterogeneous class of antioxidant enzymes that are directly involved in the removal of reactive oxygen species. Several of the enzymes in this class are inducible by factors in food. For example, glutathione peroxidase 1 is induced by increased intakes of fruit, berries, vegetables, and many other polyphenol-rich foods (25).

Both of the above enzyme classes include selenoenzymes, and the control of their regulation is related to selenium homeostasis. Selenium (see Selenium chapter) is sometimes referred to as an antioxidant because it is present in these enzymes. Several genetic variants of these enzymes have been shown to alter the risk of disease (26, 27) suggesting that enzymes from both groups are important for the defence against oxidative stress.

Effects of antioxidant-rich diets in experimental animal and human studies

The suggested role of dietary antioxidants in protection against oxidative damage is often based on extensive studies in cell culture systems. However, it is uncertain whether the effects of antioxidants observed in cell cultures, often with high doses of single compounds, can be extrapolated to humans. For example, cell culture studies do not usually show how the phytochemicals are processed in vivo, how they are absorbed and metabolised in the body, or whether they are available to the tissues of interest. Antioxidant-rich diets also contain many compounds that are not redox active, so other mechanisms might also provide benefits. These mechanisms might be involved in interventions with plant compounds, but direct proof is still lacking. Direct proof would be obtained only from studies in which different and well-defined preparations of antioxidants are shown to protect a specific molecular target from oxidation and that this target is shown to be beneficial to health. In these complex circumstances, long-term adequate clinical studies on intake of antioxidant-rich diets are necessary. Further, suitable gold-standard biomarkers of oxidative stress in vivo are needed to clarify the health benefits of antioxidants.

Initial experimental dietary studies have confirmed the beneficial effects of dietary plants rich in either phytochemicals that scavenge free radicals or phytochemicals that induce phase 2 enzymes. A diet of strawberries, spinach, and blueberries retarded and reversed age-related neurodegeneration in rats (28, 29). Antioxidant-rich raspberries and strawberries (30, 31) also efficiently inhibited carcinogenesis in experimental animals. Walnuts (32, 33) and pomegranates (34, 35), which are exceptionally rich in scavenging antioxidants, reduced LDL oxidation and atherosclerosis-related processes in animals and humans. Brussels sprouts, onions, and tomatoes have been shown to reduce the excretion of 8-oxo-deoxyguanosine (8-oxo-dG), a biomarker for oxidative free radical DNA damage, into urine and to reduce the level of DNA damage in lymphocytes in animals and humans (36–40). However, in some rigidly controlled studies, little effect was observed after intervention with plant food items rich in antioxidants (41, 42). Low bioavailability and extensive metabolism of some plant-derived antioxidants might explain some of these discrepancies.

Many of the reviewed studies were performed with animals, and relating these beneficial findings to human studies is complicated because of the differences in absorption, distribution, metabolism, excretion, gut

microbiota, endogenous antioxidant systems, and inappropriate doses. In addition, interpreting studies of complex foods such as berries, fruits, and vegetables is difficult due to the lack of comparable controls. With these considerations in mind, detailed clinical studies of longer duration and inclusion of new biochemical technologies (including metabolomics, proteomics, genomics, etc.) are needed to confirm the beneficial effects of antioxidants and polyphenols (43).

Intervention trials with antioxidant supplements

A protective effect of antioxidant supplements such as vitamin E, vitamin C, or β-carotene has not been conclusively shown in intervention trials. Indeed, supplementation with antioxidants has often resulted in no effect or even adverse disease outcomes in clinical trials. A review concluded that no studies so far have convincingly shown that giving vitamin C, vitamin E, or β-carotene supplements to non-depleted humans affects biomarkers of oxidative stress (44).

The majority of such clinical trials have examined effects of treatment with high doses of supplements containing antioxidant vitamins, and study participants have often been at high risk for, or have been recovering from, acute chronic disease events. Therefore, less is known about the health protection of low dose antioxidant supplements (similar to doses found in everyday diets) in essentially healthy individuals. However, a recent study in which different antioxidant supplements extracted mainly from fruit, berries, and vegetables were given to overweight men for six weeks and to type 2 diabetes patients for twelve weeks did not show any effect on F_2-isoprostanes or 8-OHdG, the two currently reliable biomarkers of in vivo oxidative stress (45, 46).

Results from the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study of smoking men who received a daily supplement of α-tocopherol (50 mg), β-carotene (20 mg), both α-tocopherol and β-carotene, or a placebo for 5–8 years (median 6.1 years) showed that β-carotene supplementation was associated with about a 20% increase in lung cancer risk (47). Rapola et al. (48) found significantly higher coronary heart disease mortality among the men in the β-carotene groups who had a previous myocardial infarction. Similar findings were observed in the Beta-Carotene and Retinol Efficacy Trial (CARET) by Omenn et al. (49) who tested a combination of 30 mg β-carotene and 25,000 IU retinyl palmitate taken daily against a placebo in 18,314 men and women at high risk of developing

lung cancer. The CARET intervention was stopped 21 months early because of clear evidence of no benefit and substantial evidence of possible harm; there were 28% more lung cancers and 17% more deaths in the active intervention group that was administered the combination of β-carotene and retinyl palmitate. The CARET study also found that the active treatment group had a 26% increase in relative risk of death from cardiovascular disease (49). In a study that included 160 patients with coronary disease, Brown et al. (50) observed that antioxidants (100 mg selenium, 1 g vitamin C, 800 IU vitamin E, and 25 mg β-carotene) had no effect alone, but they decreased the protective effects of simvastatin on both lipid markers and clinical endpoints. Waters et al. (51) also observed potential adverse effects of antioxidants (800 IU vitamin E and 1 g vitamin C per day) in a study of coronary atherosclerosis in 423 postmenopausal women with coronary stenosis. Finally, Graat et al. (52) studied the effect of antioxidant supplement on immune response in 652 non-institutionalised individuals aged 60 years or older. They observed that the individuals treated with 200 mg vitamin E per day had an increased severity of infections compared to the controls.

Several studies have shown no clinical effects of antioxidant treatment. For example, the MRC/BHF Heart Protection Study (53), which included 20,536 adults with coronary disease, observed that an antioxidant mixture (600 mg vitamin E, 250 mg vitamin C, and 20 mg β-carotene) improved plasma biomarkers but had no effects on clinical endpoints. Furthermore, the Heart Outcomes Prevention Evaluation (HOPE) Study (54), in which 9,541 men and women 55 years of age and older who were at high risk for cardiovascular events were enrolled, observed no significant effects of a daily 400 IU vitamin E supplement given for a mean of 4.5 years.

There have, however, been studies that have shown positive effects of antioxidants on clinical endpoints. The Cambridge Heart Antioxidant Study (CHAOS) (55), which consisted of 1,035 patients with coronary atherosclerosis who received either 800 IU vitamin E or a placebo, observed that vitamin E reduced the rate of non-fatal myocardial infarction after one year of treatment. A non-significant increase in all-cause mortality was also seen. Increased mortality was suggested by a study of subjects who received vitamin E in doses of 400 IU per day or higher (135,967 participants in 19 clinical trials; (18). In addition, in the Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study (n = 520), retarded progression of carotid atherosclerosis was observed in men, but not in women, after treatment with 182 mg α-tocopherol and 500 mg vitamin C per day for three years (56).

Several meta-analyses of RCTs with supplements with high doses of nutrients with antioxidant properties have shown no protective effects on CVD, gastrointestinal cancer or mortality (18, 57–59). Analysis of 47 high-quality studies included in the meta-analysis by Bjelakovic et al. (58) showed a significant increased risk of total mortality for β-carotene (7%), retinol (16%) and tocopherol (4%). Results from subsequent studies have failed to show any protection against cancer or CVD (60–62).

Dietary antioxidants and health

There is a large body of evidence that a diet rich in fruits, berries, vegetables, pulses, nuts, and seeds reduces the risk of cardiovascular disease, cancer, and other chronic diseases associated with major oxidative stress (11, 12, 63, 64). However, the NNR systematic review on foods graded the evidence for a protective effect of berries per se as limited-inconclusive due to too few studies (65). There is insufficient scientific evidence to show that the antioxidative mechanisms are specifically involved in the protective effects of fruits, berries, and vegetables. Severe difficulties to reliably determine oxidative stress in vivo still remain because of the complexities associated with measuring free radical reactions and defining them correctly for different biological conditions. For instance, the variable effects of fruit, berry, and vegetable intake on oxidative stress markers seen in many observational studies possibly depend on the different assays used (25, 66, 67). Therefore, recommendations for specific antioxidant-rich fruits and vegetables beyond the ordinary dietary recommendations cannot be given at this time. Several governmental and non-governmental organizations (68–72) do not recommend the intake of supplemental antioxidants either individually or in combination.

Conclusion

There is a large body of evidence suggesting that elevated intakes of certain supplements, mainly vitamins with antioxidative properties, might increase the risk of certain adverse health effects, including mortality. Thus, there is no scientific justification for using supplements as a tool for adjusting an unbalanced diet.

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15 Vitamin A

Vitamin A RE/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	700	900	350	400	600
Average requirement	AR	500	600			
Lower intake level	LI	400	500			
Upper intake level	UL	3,000*				
		1,500*#				

* as preformed retinol.
\# Post-menopausal women.

Introduction

Vitamin A refers to any compound possessing the biological activity of retinol (1). The term 'retinoids' includes both the naturally occurring forms of vitamin A as well as the many synthetic analogues of retinol with or without biological activity (2).

All-trans retinol, the parent retinoid compound, is a primary alcohol. In most animal tissues, the predominant retinoid is retinyl palmitate but other fatty acid esters, such as retinyl oleate and retinyl stearate, are also found. Most of these compounds also occur in the all-trans configuration. Furthermore, the 11-cis aldehyde form, 11-cis retinal, is present in the retina of the eye, and several acid forms such as all-trans retinoic acid, 13-cis retinoic acid, and 9-cis retinoic acid can be present in many tissues (3, 4).

Vitamin A exists in the plant world only in the form of precursor compounds such as β-carotene. β-carotene is one of 50 to 60 members of a large class of naturally occurring compounds called carotenoids that have vitamin A activity. In all cases, a requirement for vitamin A activity is that at least one intact molecule of retinol or retinoic acid can be obtained from the carotenoid.

Recommendations on vitamin A include both vitamin A activity as retinol and some provitamin A carotenoids. The term 'retinol equivalents'

(RE) is used to convert all sources of preformed retinol and provitamin A carotenoids in the diet into a single unit. The conversion factors for the relevant carotenoids are based on human studies that showed that the absorption of a single dose of 45 mg to 39 mg β-carotene ranges from 9% to 22% (5). In addition, a number of factors such as protein-energy malnutrition, zinc deficiency, dietary fat, alcohol consumption, infections, and the degree of food processing and food matrix can affect the bioavailability and bioconversion of retinol and carotenoids (3–5). Based on these and similar studies, the US Institute of Medicine, IoM (5) introduced the concept 'retinol activity equivalents' (RAE). 1 RAE is equal to:

- 1 µg of dietary or supplemental preformed vitamin A (i.e. retinol)
- 2 µg of supplemental β-carotene
- 12 µg of dietary β-carotene
- 24 µg of other dietary provitamin A carotenoids (e.g. α-carotene and β-cryptoxanthin)

The same factors are used in the NNR, but the term 'retinol equivalents' (RE) is maintained.

Dietary sources and intake

Vitamin A is present in the diet either as preformed vitamin A (i.e. retinol and its fatty acyl esters) in animal sources such as milk, eggs, butter, and fish liver oils or as provitamin A carotenoids in dark-green leafy vegetables and in red or orange-coloured fruits and vegetables such as carrots. In addition, preformed vitamin A is also contained in a number of mono- and multivitamin supplements (6).

The mean intake of vitamin A in the Nordic countries varies from 960 to 1,240 RE/10 MJ. The corresponding range for preformed retinol is 740 to 1,100 µg/10 MJ. Icelanders used to have the highest intake followed by Norwegians. However, retinol intake in Iceland has decreased 31% between 2002 and 2010/2011 mainly as a result of changes in the vitamin A content of cod liver oil. Still, 4.6% of Icelanders exceed the upper limit of 3,000 mg/d of vitamin A when using the MSM method of estimating the distribution of intake (7). The main sources of retinol are liver and liver products, edible fat, milk, and dairy products including retinol-fortified margarine, spreads, and milk. The main sources of vitamin A-active carotenoids are vegetables and some fruits.

Physiology and metabolism

Vitamin A is essential for the life of all vertebrates. The vitamin has numerous important functions including a role in vision, maintenance of epithelial surfaces, immune competence, growth, development, and reproduction (3, 4, 8). When intake of vitamin A is inadequate to meet the body's needs, clinical vitamin A deficiency develops and is characterised by several ocular features (xerophthalmia) and a generalised impaired resistance to infection. A series of epidemiological and intervention studies in children living under poor socioeconomic conditions have documented a relationship between poor vitamin A supply and increased rates and severity of infections as well as mortality related to infectious diseases such as measles (9). Vitamin A deficiency is a public health problem in over 120 countries (10). The problem is probably uncommon in developed countries but might be under-diagnosed because there is a lack of simple screening tests to measure sub-clinical deficiency. Vitamin A might, however, be a double-edged sword because it has been suggested that intake even marginally above the recommended dietary intake is associated with embryonic malformations (8, 11), reduced bone mineral density, and increased risk for hip fracture (12).

The major dietary sources of vitamin A are provitamin A carotenoids from vegetables and preformed retinyl esters from animal tissues (3, 4, 13, 14). Carotenoids such as α- and β-carotene and β-cryptoxanthin are absorbed by passive diffusion, and the absorption of carotenoids can vary considerably depending on factors such as food matrix, preparation method, and processing (15). After entry into the enterocytes, provitamin A carotenoids are cleaved to yield either one or two molecules of retinol. Absorption of retinyl esters includes enzymatic conversion to retinol in the intestinal lumen prior to entry into enterocytes. Retinol is then esterified to long-chain fatty acids before incorporation into chylomicrons. In general, 70% to 90% of ingested preformed vitamin A (e.g. retinol) is absorbed.

Most of the chylomicron retinyl esters are transported to the liver. In vitamin A sufficient states, most of the retinyl esters taken up by hepatocytes are transferred to perisinusoidal stellate cells in the liver for storage. Normally, 50% to 80% of the body's total retinol is stored in the hepatic stellate cells as retinyl esters, and the normal reserve of stellate cell retinyl esters is adequate to last for several months (16).

Retinol bound to retinol-binding protein is released from the liver and circulates in the plasma to ensure an ample supply of retinol to target cells.

Inside target cells, retinol is oxidized to retinal and retinoic acid, which are the active retinol metabolites. These metabolites are usually synthesised in target cells by a complex metabolic system involving numerous enzymes and binding proteins (3, 4, 13, 14). Retinal functions as a chromophore in the visual process and retinoic acid activates specific nuclear retinoic acid receptors and thereby modulates gene transcription (4).

Requirement and recommended intake

Earlier recommendations have mainly been based on studies aimed at eliminating symptoms of vitamin A deficiency. In the Sheffield study (17), symptoms of vitamin A deficiency (reduced plasma retinol, reduced dark adaptation, dryness of the skin, and eye discomfort) developed in several of 16 healthy men following intake of a diet essentially free of vitamin A for 8 months. Of the 16 subjects studied, only 3 had changes in dark adaptation of sufficient magnitude to serve as a criterion to investigate the curative ability of varying amounts of retinol and β-carotene. Addition of 390 µg retinol per day to one of the individuals with vitamin A deficiency eventually improved dark adaptation and also somewhat improved the plasma retinol levels. Supplementation with 780 µg retinol per day for 45 days had little further effect on the subject's plasma retinol level. However, supplementation with 7,200 µg retinol per day increased his plasma retinol above his initial level of 1.2 mmol/L. Furthermore, it was demonstrated in the other vitamin A-deficient individuals that daily intake of 1,500 µg β-carotene in oil, but not 768 µg β-carotene in oil, improved dark adaptation and plasma retinol levels. Hume and Krebs (17) concluded that a daily retinol intake of 390 µg represents the minimum protective dose, but this figure should be raised to 470 µg to correct for an error in the conversion factor used in the analytical measurements (18).

Similar observations were obtained in the Iowa study (19) in which vitamin A deficiency developed in 8 healthy men after several months on a vitamin A-deficient diet. Abnormal electroretinograms occurred at plasma retinol levels of 0.1–0.4 mmol/L, impaired dark adaptation was observed at plasma retinol levels of 0.1–0.9 mmol/L, and follicular hyperkeratosis was found at plasma levels of 0.3–1.3 mmol/L. Plasma levels below 1.1 mmol/L were associated with a mild degree of anaemia that responded to retinol supplementation. The Iowa study also found that daily intake of 300 µg retinol partially corrected the abnormal electroretinograms, but supplements of 600 µg/d were needed to prevent eye changes in adult men.

Based on isotope-labelled retinol experiments it was calculated that the average rate of utilization of retinol during the state of vitamin A depletion was about 910 µg retinol per day. The study concluded that a daily retinol intake of 900 µg per day would maintain a plasma level of 1.1 mM in most adult men. For women, the requirement would be reduced in proportion to body weight.

The US Dietary Reference Intakes (5) for vitamin A were based on estimated requirements that assured adequate body stores of retinol and where no clinical signs of deficiency were observed, adequate plasma retinol levels were maintained, and there was protection against vitamin A deficiency for approximately 4 months on a vitamin A-deficient diet. The underlying evaluation assumed that the body turnover of retinol is 0.5%, the minimal liver reserve is 20 mg/g, the liver weight to body weight ratio is 1:33, the total body to liver vitamin A reserve ratio is 10:9, and that the efficiency of storage (i.e. retention of absorbed vitamin A in the liver) is 40%. Based on these assumptions (5), and using reference weights for US adults, the estimated average requirement (EAR) of preformed vitamin A required to assure an adequate body reserve in an adult male was 627 µg/d. The corresponding value for women was estimated to be 503 µg/d. Using a factor of 1.4 to account for variation in the population, the recommended daily allowance (RDA) was set to 900 µg/d for men and 700 µg/d for women above 19 years of age (5). These estimations are in general agreement with a large number of studies using functional criteria for vitamin A status, such as dark adaptation, papillary response test, conjunctival impression cytology, and markers of immune function (see (5) for a review of these studies).

In a more recent study (20), the estimated AR for vitamin A in adult males was studied using the deuterated retinol dilution technique in 16 men in Bangladesh. The results indicated that 254–400 µg/d was sufficient to assure an adequate body reserve (equivalent to 362–571 µg/d for a 70 kg man in the US), which is lower than the AR in the NNR 2004. Using the factor of 1.4 to cover the variation, this would result in a recommended intake of 500–800 µg/d. However, more studies of the variation in the AR are needed before a change in the current recommendations can be discussed.

Using the above factorial method for the Nordic reference subjects, the estimated AR for vitamin A would be very similar as for the US reference subjects, i.e. close to 600 µg/d and 500 µg/d for men and women, respectively. In NNR 2004, the recommended intakes (RI) for adults were based

on these considerations and thereby set to 900 RE/d for men and 700 RE/d for women. There are limited scientific data to change the reference values from NNR 2004. Therefore, the RI of 900 RE/d for men and 700 RE/d for women are maintained. Also, the ARs of 600 RE/d for men and 500 RE/d for women and the lower intake levels (LI) of 500 RE/d for men and 400 RE/d for women are kept unchanged.

In infants, no functional criteria of vitamin A status have been published that reflect the response to dietary intake. Breast milk from well-nourished mothers in the Nordic countries usually contains sufficient amounts of vitamin A. For non-breastfed infants, the vitamin A content of formula is sufficient. Therefore, no specific recommended intake of vitamin A for infants aged 0–6 months is given. Any contribution by carotenoids was not considered because the bioconversion of carotenoids in infants is not known.

Direct studies on the requirement for vitamin A are not available to estimate an AR for infants, children, and adolescents aged 1–17 years. Thus, the RIs for children and adolescents are extrapolated from those for adults by using metabolic body weight and growth factors ($BW^{0.75}$, see (5)).

Experimental data to estimate an AR during pregnancy are lacking. Using the retinol accumulation in foetal liver as a criterion, about 50 µg vitamin A per day would be needed in addition to the AR for non-pregnant women (5). The RI for pregnancy is set to 800 RE/d to cover individual variation.

The vitamin A content of breast milk varies with the dietary vitamin A intake. Reported values for Western countries are 450–600 RE/L. With an average milk production of 750 mL/d, this corresponds to 350–450 RE/d. An additional intake of 400 RE/d is, therefore, recommended during lactation.

In elderly subjects, intakes of 800–900 RE/d vitamin A seem more than adequate (21). Some early studies (22) found an age-related trend toward higher serum retinol values with advancing age, but recent studies have found trends toward a slight decrease (23). None of these elderly subjects had retinol values below a cut-off value of 0.35 mmol/L. Using a cut-off value of 0.7 mmol/L as proposed by NHANES data from subjects ranging in age from 18 years to 74 years resulted in only very few subjects being at risk (23). In a Danish cross-sectional study of 80-year-old men and women, 10% had a dietary intake of vitamin A below the lower limit but only one subject had a retinol value below 0.7 mmol/L (24). Use of the same vitamin A-containing supplements has been linked to higher circu-

lating retinyl ester levels in elderly subjects compared to younger subjects (25), and this is due, perhaps, to delayed plasma clearance in the elderly (26). An intervention study found an altered postprandial plasma retinol concentration in older subjects compared to younger, but the intestinal absorption and esterification were the same in the elderly compared to the younger subjects (27).

Serum retinol levels are generally considered to be a relatively poor reflection of vitamin A status – unless liver stores are either very depleted or highly saturated – but plasma β-carotene seems to be a possible biomarker of β-carotene status (28). Several studies (23, 29, 30) have found a positive relationship between plasma levels and the intake of β-carotene in elderly subjects. Consumption of fruits and vegetables rich in β-carotene is inversely related to overall mortality and cardiovascular mortality, even in the elderly (31, 32). However, the role of β-carotene in the prevention of age-related diseases is still too weak to use as a basis for vitamin A recommendations. The RI for elderly subjects > 60 years of age is the same as for younger adults.

Reasoning behind the recommendation

There are limited scientific data to change the reference values from NNR 2004. Therefore, the RIs of 900 RE/d for men and 700 RE/d for women are maintained. In addition, the ARs of 600 RE/d for men and 500 RE/d for women and the LIs of 500 RE/d for men and 400 RE/d for women are kept unchanged.

Upper intake levels and toxicity

Several studies have shown that doses up to 180 mg β-carotene per day as supplements can be used for many years with no evidence of vitamin A toxicity and without the development of abnormally elevated blood retinol concentrations. Serious adverse effects of β-carotene in the form of supplements have, however, been reported but these are not related to its conversion to retinol (see discussion in the chapter on antioxidants).

Adverse effects of dietary retinol need to be considered in Nordic populations where the dietary intake of preformed retinol has been relatively high, especially in Iceland.

Vitamin D antagonism

Several studies have provided evidence of an antagonism between retinol and vitamin D both in animals (33–37) and humans (38). Animal studies have shown that retinol serves as an antagonist to vitamin D action, not only in toxic amounts but also at the physiological level (39). In a meta-analysis, which included all cases of retinol intoxication published in the scientific literature up to the year 2000 (40), it was found that the mean dose of retinol causing hypervitaminosis A was higher when the dose originated from a formula containing vitamin D. This observation implies that there is increased sensitivity for retinol toxicity among subjects with vitamin D insufficiency.

Risk of acute and chronic hypervitaminosis A

Retinol toxicity related to osteoporosis and teratogenicity is discussed in separate sections below. There have been no reports in the Nordic countries describing either classical chronic or acute hypervitaminosis A due to intake of foods such as liver except a few cases of early Arctic explorers eating polar bear liver (41). Although adults in the Nordic countries have a generous intake of retinol, very few if any healthy individuals are likely to ingest amounts that might lead to classical hypervitaminosis A. Thus, the risk of hypervitaminosis A due to retinol-rich foods is very low.

A major issue when evaluating the potential toxicity of retinol is the observation that intake of retinol in various physical forms appears to have different thresholds for toxicity (6, 40). Retinol in water-soluble, emulsified, or solid preparations generally seems to have more acute toxic effects than retinol in foods or oils (40). This might be relevant for potential hypervitaminosis A from supplements and from foods fortified with retinol. Several foods commonly used in the Nordic countries are fortified with retinol. If the diet consists of large amounts of retinol-fortified foods, the daily intake might approach the upper safe levels. Therefore, oil-based retinol preparations should preferably be used in supplements and fortification of foods, and supplements and fortification with water-miscible and emulsified preparations should be kept to a minimum.

A total of 17 suspected cases of supplement-induced chronic hypervitaminosis A, but no acute cases, have been reported in the scientific literature in the Nordic countries up to 2003 (6). Chronic hypervitaminosis A is induced after daily doses of 2 mg/kg of retinol in oil-based preparations for many months or years (40). In contrast, only a few weeks of daily intake of doses as low as 0.2 mg/kg of retinol in emulsified/water-miscible

and solid preparations caused hypervitaminosis A (6). Thus, emulsified/water-miscible and solid preparations of retinol are about 10 times more toxic than oil-based preparations of retinol. The safe upper single dose of retinol in oil or liver seems to be about 4–6 mg/kg bodyweight (40). These thresholds do not vary considerably with age.

Hepatotoxicity is a manifestation of hypervitaminosis A, and toxic symptoms seem to depend on both the amount and duration of exposure. Mechanisms of hepatic effects are linked to overload of the storage capacity of the liver for vitamin A that can cause cellular toxicity, production of collagen, and eventually fibrosis and cirrhosis in the liver. The lowest dose reported to cause cirrhosis was a consumption of 7,500 RE/d for 6 years, and it can be hypothesized that this value might be the upper threshold of the storage capability of the liver (42).

Risk of retinol-induced teratogenicity

Animal studies demonstrate that both retinol deficiency and retinol excess can give rise to embryonic malformations and that a single high dose of retinol or retinoic acid can be teratogenic if given at a susceptible stage of early embryonic development (see discussion in (6) and references therein). In humans, several cases of teratogenicity have been reported due to retinoic acid medication, but no cases due to preformed retinol in foodstuffs. Epidemiological data suggest that intakes of retinol supplements up to 3 mg vitamin A per day during pregnancy are not associated with an increased risk of giving birth to a malformed child. Because epidemiological data indicate that the threshold for teratogenicity is higher than 3 mg retinol/d, it is assumed that this level offers adequate protection against teratogenic effects (42). Thus, it is recommended that the intake of retinol supplements during pregnancy should be limited to no more than 3 mg per day unless other medical aspects argue for a higher intake. Because the possible adverse effects of excess retinol intake appear very early during pregnancy, this advice applies to all women of childbearing age. Furthermore, due to high retinol content in liver, it is recommended that pregnant women should avoid eating whole liver as the main course of a meal.

Risk of retinol-induced osteoporosis

Results from animal experiments, in-vitro studies, pharmacological studies, and clinical observations have shown that retinol intoxication is associated with severe detrimental effects in the skeleton (see (6). Most human

studies published during the last decade, however, have not shown any association between retinol intake and bone density (43–52), which is in line with animal data (53). In studies on rats, bone density was unaffected while bone diameter and strength were diminished. This seems to be related to increased periosteal bone resorption and reduced bone formation (54, 55). Observations on a human foetus have identified that a mutation in the enzyme CYP26B1 that specifically inactivates the bioactive vitamin A metabolite retinoic acid has effects resembling those seen when high retinol doses are administered to experimental animals, including a pronounced reduction in the diameter of the long hollow bones (56). In summary, most human studies have not found an association between retinol intake and bone density.

Retinol and fractures

A few prospective and case-control studies have found an increased risk for fractures in groups with retinol intakes from foods and supplements > 1.5 mg/d (e.g. (12, 57, 58). Caire-Juvera and coworkers (59) found no overall association between total retinol intake and the risk of hip or total fractures among 75,747 postmenopausal women from the Women's Health Initiative Observational Study. However, an increased risk for fracture was seen in the group with the highest quintile of total retinol intake (≥ 1.426 µg/d) among women with a vitamin D intake below the mean (≤ 11 µg/d), but the overall trend was not significant. In other studies, no associations between fractures and retinol intake from foods (47) or from foods and total intake (60) have been found. There are a few studies indicating associations between use of dietary supplements containing vitamin A and fractures (60, 61). Mean retinol intakes varied between studies, however, and some only measured retinol from foods (12, 47) while others report associations for both total and food retinol intake (57–60). There are also some studies showing an association between serum retinol levels and fractures (49, 58, 62). However, no retinol intake data were available in the studies by Barker et al (49) and Opotowsky et al (62).

In summary, results from some prospective cohort studies indicate that high intakes of retinol (> 1.5 mg/d) from foods and supplements might be associated with fracture risk, but others have shown no associations.

Upper intake level for retinol or retinyl esters

Toxic effects have primarily been linked to preformed vitamin A, i.e. retinol or retinyl esters. It is clear that the hazards and their associated doses

are different for different groups of the population, and the severity of the adverse effect varies from minor to irreversible.

Because of the low margin between the RI value and doses that might pose a risk to different groups of the population, setting an upper level (UL) of intake is not easy. In NNR 2004 the recommended maximum intake of 3 mg/ d of retinol supplements for women of childbearing age was chosen as the UL for the entire population. This level is 2.5 times below the level that might cause hepatotoxicity. This UL is kept unchanged in NNR 2012.

In NNR 2004, the UL of 1,500 µg/d was set for postmenopausal women in order to reduce the possible risk of osteoporosis. The results from the studies published after NNR 2004 are conflicting and do not give any clear indication as to what levels of intake increase the risk for fractures. Still, it cannot be ruled out that long-term intakes above 1,500 µg/d might increase the risk for fractures. Therefore, the previous recommendation that postmenopausal women who are at greater risk for osteoporosis and bone fractures should restrict their intake to 1,500 µg/d is maintained.

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16 Vitamin D

Vitamin D µg/d		Women	Men
Recommended intake	RI		
2–60 years		10	10
61–74 years		10	10
≥ 75 years		20	20
Average requirement	AR	7.5	7.5
Lower intake level	LI	2.5	2.5
Upper intake level	UL	100*	100*

* IoM 2010; EFSA 2012.

Introduction

Vitamin D_3 (cholecalciferol) is a steroid-like molecule that can be synthesised from 7-dehydrocholesterol in the skin under the influence of ultraviolet B light (wavelength between 290 nm and 315 nm) (1). Vitamin D_3 is also present in some animal foods, and vitamin D_2 (ergocalciferol) can be found in some mushrooms. The basic requirement for vitamin D_3 can be satisfied by exposing the skin to the sun. Experience demonstrates, however, that under the living conditions and at the latitude of the Nordic countries (55° N–72° N), vitamin D deficiency can occur if the diet is devoid of the vitamin. Infants can develop rickets and elderly people can develop osteomalacia, and for this reason vitamin D is considered a micronutrient. Vitamin D is also a pro-hormone because it is converted to a hormone, 1,25-dihydroxyvitamin D (calcitriol), in the body.

One IU (international unit) corresponds to 0.025 µg vitamin D.

Dietary sources and intake

Oily fish, edible fats, and milk products enriched with vitamin D are the major dietary sources. Certain lean freshwater fish might also contain high concentrations of vitamin D_3 (2, 3). Meat and eggs contribute some vitamin D_3, but they also contain $25OHD_3$ (4) that has a higher biopotency (4, 5). Vitamin D_2 is formed by UV irradiation of ergosterol present in some mushrooms and in yeast, and vitamin D_2 has a somewhat lower biopotency compared to vitamin D_3 (4, 5). Some plant-based milk substitutes contain added vitamin D.

Dietary survey data from the last decade show average intakes in both adults and children ranging from 3.5 µg/10 MJ in Denmark to12.8 µg/10 MJ in Finland (6–10).

Assessment of vitamin D status

The circulating serum 25OHD concentration is regarded as a good marker of vitamin D status (11). The reliability of the assays for serum 25OHD measurement has been questioned, however, and several studies have shown that different assays give different results (e.g. (12–15). In 1989, the Vitamin D External Quality Assessment Scheme was initiated (www.deqas.org) to provide laboratories with external control of accuracy. Later, standard reference material (SRM) of serum became available from the National Institute of Standards and Technology with an indicative value for 25OHD. Since 2009, a certified standard reference serum (SRM972) with assigned values for the content of $25OHD_2$, $25OHD_3$, and 3-epi-$25OHD_3$ has been available (www.nist.gov/mml/csd/organic/vitamindinserum.cfm). This material has been used in NHANES studies to standardize the values for vitamin D status obtained by various radioimmunoassay and LC-MS/MS methods (16). Currently, no standard method for measuring serum 25OHD concentrations has been selected but candidate methods based on LC-MS/MS techniques have been published (17, 18). An international standardization project (Vitamin D Standardization Program, VDSP) has the aim of standardizing serum 25OHD concentration measurements (19). Despite some methodological uncertainties, serum 25OHD concentration is so far the best available marker for assessing vitamin D status and sufficiency.

Vitamin D status in Nordic populations

Infants

As a consequence of a good public health service and because most infants receive vitamin D supplements, rickets has become very rare in the Nordic countries over the past 3–4 decades. In a review of studies on population groups in dietary transition in the Nordic countries published from 1990 to 2011, a high risk of vitamin D deficiency (serum 25OHD concentrations below 25 nmol/L) was evident among some ethnic groups (20). Among young children of immigrant parents, the risk of rickets was 50 times higher compared to children of indigenous parents (20).

Children and adults

Studies from Denmark show that serum 25OHD concentrations are generally low during wintertime with between 50% and 90% of the study population having insufficient status (< 50 nmol/L) (21, 22). Dietary vitamin D intake was low (median intakes were 2.4 µg/d to 3.4 µg/d). In a study on Icelandic adults aged 30 to 85 years, mean serum 25OHD concentrations were 43 nmol/L in the youngest age group (33–45 years) and 52 nmol/L in the oldest (70–85 years). Mean vitamin D intakes in the two respective age groups were 9.7 µg/d and 16.6 µg/d. Among those not taking vitamin D supplements, including cod liver oil, mean dietary intake was 5.2 µg/d and mean serum 25OHD levels were below 50 nmol/L throughout the year and reached a mean high of 45 nmol/L during the summer (23).

A systematic review (SR) by Holvik et al. (24) concluded that the vitamin D status in Norway was sufficient (serum 25OHD concentrations ≥ 50 nmol/L) for the majority of the general population and that available data suggested that the vitamin D status in Norway is better than more southerly locations in Europe. In Sweden, two small studies on children indicate adequate status during the summer season (25, 26). In a study of preschool children in northern Sweden (latitude 63–64 °N), 40% had insufficient vitamin D status during wintertime and the deficiency was greater in children with dark compared to fair skin pigmentation (26). In the other study conducted in southern Sweden (latitude 57–58° N), less than 10% of preschool children (4 years of age) had insufficient status during the winter. At 8 years of age, however, about 20% to 30% of the same children had insufficient status, and this difference was related to more frequent use of vitamin D supplementation at age 4. In a study of 116 Swedish women aged 61 to 86 years (mean age 69 years) and living

at latitude 60° N, the mean serum 25OHD concentration during winter (January–March) was 69 nmol/L and about 20% had concentrations below 50 nmol/L. Estimated mean dietary intake of vitamin D, including vitamin D-fortified foods, was 6.0 µg/d (27). Previous studies in Sweden showed mean serum 25OHD concentrations of 50 nmol/L to 95 nmol/L among the general adult population (28).

Pregnant and lactating women

A study among 95 pregnant fair-skinned Swedish women living at latitudes from 57° N to 58° N found that the mean serum 25OHD concentration during gestational weeks 35 to 37 was 47.4 nmol/L (29). About 65% had concentrations below 50 nmol/L, and use of vitamin D supplements was linked to higher mean vitamin D status (55 nmol/L) compared to non-use (37.7 nmol/L). Mean dietary vitamin D intake was 6.1 µg/d. Milman et al. (30) measured vitamin D status during pregnancy and at 8 weeks postpartum in 141 healthy, ethnic Danish women with normal pregnancies who were residents of greater Copenhagen (latitude 55° N). Mean serum 25OHD concentrations were 77, 98, 91, and 73 nmol/L at 18, 32, and 39 weeks gestation and at 8 weeks postpartum, respectively. About 20% had concentrations below 50 nmol/L at each time point. Median dietary vitamin D intake was 2.4 µg/d, and about one third of the participants were taking multivitamin supplements at the time of inclusion in the study. Results from a longitudinal study in two cohorts of pregnant Finnish women showed that the mean intake of vitamin D increased from a range of 6.2 µg/d to 6.4 µg/d during the years 1997 to 2002 to 8.9 µg/d in 2003–2004 (31). This increase was mainly due to increased fortification of foods and to a lesser extent from supplements.

Physiology and metabolism

Skin synthesis

Exposure of the skin to sunlight (the UV-B band with wavelengths of 290 nm–315 nm) is needed for the photo-conversion of 7-hydroxy-cholesterol to pre-vitamin D_3, which is then converted to vitamin D_3. The amount of vitamin D_3 produced depends on several factors such as exposed skin surface, season, latitude, skin pigmentation, and age (32). Dermal production of vitamin D_3 is reduced by pigmentation of the skin and with increasing age.

During the summer months (June–July) at latitudes around 60° N, expo-

sure of the face, arms, and hands (25% of body surface) to sunshine for 6–8 minutes 2 or 3 times a week is estimated to provide amounts equivalent to 5 µg/d to 10 µg/d vitamin D_3 in persons with fair skin pigmentation. About 10–15 minutes per day would be needed for persons with dark pigmentation (33). Datta et al. (34) investigated the effects of sun exposure on serum 25OHD concentrations from February to September in Danish subjects living at latitude 56° N. The results indicated that sun-induced changes in 25OHD concentrations might begin to occur already in early April and then peak by early August. The earliest period with a significant increase was seen at the beginning of May (weeks 17–19), which occurred after a mean of 2 days of exposing more than just the hands and face to the sun. Another one-year study among Danish adolescent girls and elderly women showed that the contribution from sun exposure to serum 25OHD concentration was considerable for both age groups (35).

Effect of Intake of vitamin D on serum 25OHD concentration

Absorption

The NNR SR (38) included one SR of good quality that evaluated the effect of supplements and foods fortified with vitamin D on serum 25OHD concentrations (39), one SR of low quality on fortified foods (40), and one SR of low quality on vitamin D supplementation (41).

Naturally occurring vitamin D is incorporated into chylomicrons and absorbed in the small intestine through the lymphatic system. It is estimated that about 80% of ingested vitamin D is absorbed via this route (1, 36). Experimental studies indicate that cholesterol transporters also play a role in vitamin D uptake (37).

Natural sources

There are limited data on the uptake of vitamin D from natural sources (36). No SR has been published on the relationship between dietary vitamin D from natural sources and serum 25OHD concentrations (38).

Fortified foods

The effect of intake of vitamin D from fortified foods on serum 25OHD concentration has been evaluated in an SR by Cranney et al. (39). Thirteen trials on food fortification and circulating serum 25OHD concentrations providing 5–25 µg vitamin D were included. Food fortification resulted in significant increases in serum 25OHD concentrations with the treatment effect ranging from 15 nmol/L to 40 nmol/L. The combined effect of forti-

fied food from two trials with vitamin D_3 doses equivalent to 10–12 µg/d was an increase in serum 25OHD concentration of 16 nmol/L (95% CI 12.9–18.5). Similar results were obtained in the SR by Black et al. (40). This SR included 16 studies in which fortified foods provided 3–25 µg/d (mean 11 µg/d), often in combination with calcium, and the mean observed increase in serum 25OHD concentration was 19.4 nmol/L. However, heterogeneity was high due to variations in dose, latitude, and baseline serum 25OHD concentrations. Only one study, in which bread was used as the carrier, was carried out in Nordic countries.

Supplements

Children, adolescents, and adults younger than 50 years of age

The SR by Cranney et al. (39) included four randomised controlled trials (RCTs) carried out in Denmark, Finland, France, and Lebanon on the effect of vitamin D intake on serum 25OHD concentrations in children and adolescents. Doses ranged from 5 µg to 50 µg of vitamin D_3/d and were given for durations of one month to over one year. The results showed increases in serum 25OHD concentrations ranging from 8 nmol/L with a daily dose of 5 µg of vitamin D_3, to 16.5 nmol/L with a daily dose of 15 µg, and to 60 nmol/L with a daily dose of 50 µg.

The SR by Cashman et al. (41) included studies carried out or evaluated in the winter season at latitudes north of 49.5° N (northern Germany). The studies included in the SR reported large differences in response to the doses (which ranged from 5 µg/d to 20 µg/d). These responses included decreases in serum 25OHD concentrations of 5–20 nmol/L (42), increases of 10–38 nmol/L (43–45), or no change (46). The study durations varied from 8 weeks to 56 weeks.

Adults ≥ 50 years of age

The SR by Cashman et al. (41) included three studies of older adults and the elderly. Vitamin D_3 doses of 5–45 µg/d resulted in increases in serum 25OHD concentrations of 9–30 nmol/L. Responses varied with dose and baseline serum 25OHD concentrations, and a greater effect was seen at lower baseline levels. In an SR by Autier et al. (47), 76 studies were included with subjects > 50 years of age given vitamin D supplementation. Doses ranged from 5 µg/d to 250 µg/d (median 20 µg/d) and the duration was 1 month to 60 months (median 8.5 months). Meta-regression of studies without concomitant calcium supplementation showed an increase in

serum 25OHD concentration of 1.95 nmol/L per 1 µg vitamin D among community-dwelling populations.

Comments

The SRs show substantial heterogeneity for the effects of vitamin D supplementation on serum 25OHD concentrations. There are no straightforward explanations for this, but factors such as prior vitamin D status, compliance, latitude, and season might have played a role. Grossman et al. (48) evaluated the effects of vehicle substances in vitamin D supplements in five studies and found that vitamin D in an oil vehicle produced a greater response in serum 25OHD concentrations in healthy subjects than vitamin D in a powder form or in an ethanol vehicle.

Determinants of vitamin D status

Major external determinants of vitamin D status are intake from foods and supplements and sun exposure (including season, latitude, and travels to sunny climates) (35). Cultural habits such as clothing are mainly related to sun exposure (27, 49–51). Subject-specific determinants are skin pigmentation, age, and genetic factors (38). The reported data on the disappearance of 25OHD in the serum suggests a half-life of about 15 days to 50 days (52).

The association between vitamin D status and BMI and adiposity was reviewed in the NNR SR (38). In mainly cross-sectional studies, an inverse association was found between BMI and serum 25OHD, while some – but not all – supplementation studies showed a lower response in serum 25OHD concentrations in obese persons than in normal-weight subjects. Moreover, weight loss led to an increase in serum 25OHD concentrations in some studies. The NNR SR. (38) concluded that there are some indications that adiposity should be considered a determinant of serum 25OHD concentrations, although so far there is so no evidence that higher intakes are needed in obese persons than in those with normal weight.

Metabolism

The liver rapidly takes up vitamin D_3 formed in the skin or absorbed from the gut where it is hydroxylated to 25OHD. This metabolite is transported in plasma bound to the vitamin D binding protein (also known as the group-specific protein, Gc). 25OHD is further converted into 1,25-dihy-

droxyvitamin D (calcitriol) in the kidneys. This is a calcium-regulating hormone that becomes active after binding to a nuclear vitamin D receptor. Together with parathyroid hormone and calcitonin, 1,25-dihydroxyvitamin D ensures that the concentration of calcium and phosphate in the plasma is maintained within narrow limits. Its main function is to stimulate the absorption of calcium from the intestine. In concert with parathyroid hormone, it also stimulates release of calcium from bone thereby increasing the concentration of calcium in the plasma. By contributing to the maintenance of normal concentrations of calcium (and phosphate) in the blood and the extracellular fluid, vitamin D is essential for normal mineralisation of the skeleton. Deficiency of vitamin D results in defective mineralisation leading to the development of rickets in children and osteomalacia in adults. The presence of vitamin D receptors in a number of tissues as well as epidemiological and experimental data indicate that vitamin D might play a role in cancer, autoimmune diseases, infections, and muscle strength in addition to the functions mentioned above.

Vitamin D and health

Total mortality

The NNR SR (38) included three SRs of high or good quality on the association between vitamin D status or intake and total mortality (39, 53, 54). The Cochrane Review by Avenell et al. (53) on vitamin D and fractures also included effects of interventions with vitamin D on total mortality as a secondary endpoint. Based on 23 trials, the relative risk (RR) of death was 0.97 (95% CI: 0.93–1.01) in those given vitamin D with or without calcium compared to those given placebo or calcium alone. However, in those given vitamin D plus calcium versus placebo or control (14 trials with 54,203 participants), the RR of death was 0.94 (95% CI 0.89–0.99).

Cranney et al. (39) included five prospective cohort studies. Four studies did not show an overall association between baseline serum 25OHD concentrations and total mortality, and one study reported a statistically significant inverse trend. In meta-analyses including four RCTs (13,899 participants), supplementation with vitamin D alone had no significant effect on all-cause mortality (RR = 0.97, 95% CI: 0.92–1.02), and supplementation with vitamin D and calcium (11 trials with 44,688 persons) did not show a significant reduction in mortality (RR = 0.93, 95% CI 0.86–1.0). The point estimate was, however, similar to that found by Avenell et al. (53).

The Cochrane Review by Bjelakovic (54) found that intervention with vitamin D_3 supplementation with or without calcium versus placebo or no intervention (32 RCTs with 74,789 participants) resulted in a 6% reduction in total mortality (RR = 0.94, 95% CI: 0.91–0.98). The effect was, however, only significant in RCTs giving vitamin D_3 in combination with calcium (range 300 mg to 1,600 mg, mean 929 mg, median 1,000 mg). Only eight trials tested supplementation with vitamin D_3 alone, and the difference between trials intervening with vitamin D_3 alone and trials intervening with vitamin D_3 and calcium was not significant. Significant effects were found in trials including participants with insufficient vitamin D status (serum 25OHD concentrations < 50 nmol/L) and in studies using daily doses lower than 20 µg/d. However, the differences from the other trials involving vitamin D adequacy (RR = 0.92, 95% CI: 0.7–1.07) and doses ≥ 20 µg (RR = 0.96, 95% CI: 0.92–1.01) were not statistically significant. Studies using vitamin D_2 (12 trials) did not show a significant reduction in mortality.

Based on the RCTs included in the aboveSRs, Lamberg-Allardt et al. (38) concluded that supplementation with vitamin D_3 at 10–20 µg/d combined with calcium significantly reduces total mortality. However, they note that it is still uncertain if co-supplementation with calcium is necessary to achieve this effect. Also, the threshold for serum 25OHD concentrations associated with reduced mortality is unclear.

In a meta-analysis of 18 RCTs (47), supplementation with vitamin D, often in combination with calcium, was associated with a 7% reduction in total mortality (95% CI: 1%–13%) compared to placebo. The mean study duration was 5.7 years and the mean vitamin D dose was 13 µg/d (range 7.5–50 µg/d). The calcium dose was generally around 1 g/d. A dose-response relationship could not be established. In studies where serum 25OHD concentrations were reported, these were generally below 50 nmol/L at baseline and increased to between 62 nmol/L and 105 nmol/L and a decrease was seen in the control group in several studies.

Larger prospective cohort studies, mainly from the US, generally show an increased risk of total mortality at serum 25OHD concentrations below 30–50 nmol/L (55–63). However, different categorization of serum 25OHD concentrations in the various studies precludes calculating a more precise cut-off for an increased risk.

In two cohort studies from Sweden and Denmark, both low and high serum 25OHD concentrations were associated with increased total mortality (60, 63). In the study by Michaëlsson et al. (60), increased all-cause

mortality was observed among men with 25OHD concentrations < 46 nmol/L (10% of subjects) as well as among those with serum 25OHD concentrations > 98 nmol/L (5% of subjects). Follow-up time was 13.7 years on average. In a Danish cohort study among almost 250,000 subjects from the Copenhagen general practice sector followed for 3 years, a J-shaped relationship was found with the lowest mortality at serum 25OHD concentrations of 50–60 nmol/L (63).

In summary, there is *convincing* evidence that combined supplementation with vitamin D and calcium is associated with reduced total mortality, especially at low serum 25OHD concentrations less than 30 nmol/L to 50 nmol/L. The findings from some prospective cohort studies of an increased risk at concentrations at the higher end in the study populations warrant further investigations.

Bone health

Rickets

Low serum 25OHD concentration increases the risk of rickets. The precise threshold is uncertain, but a number of studies suggest increased risk at serum 25OHD concentrations below 27.5 nmol/L. However, many studies were conducted in developing countries with low dietary calcium intake. Low calcium intake might influence the relationship between serum 25OHD concentrations and rickets, and the serum 25OHD concentration threshold for rickets in populations with high calcium intake is unclear. Vitamin D supplementation has been used as a prophylaxis in the Nordic countries for decades, and the currently recommended daily dose of 10 µg has been effective in preventing rickets (64). Still, cases of rickets in children have been reported that have been ascribed to lack of vitamin D prophylaxis during prolonged breastfeeding or insufficient dietary intake (20, 65, 66).

Fractures

The NNR SR (38) included two SRs of high or good quality (53, 67) and one of low quality (68). The authors concluded that there is *convincing* evidence that supplementation with vitamin D at a dose of 10–20 µg/d combined with calcium reduces the risk of total fracture and hip fracture. The effect is more pronounced in institutionalized elderly, and supplementation with vitamin D alone has not shown a significant effect (38). A precise threshold for serum 25OHD concentrations associated with reduced incidence has

not been established, but available data suggest that this might range from 40 nmol/L to 74 nmol/L (38). A Swedish cohort study in men found that a serum 25OHD concentration below 40 nmol/L was associated with an increased risk of fractures (69). Serum 25OHD concentrations were assessed at 71 years of age and the follow-up period was 11 years. However, only 5% of the cohort (20 subjects) had levels below 40 nmol/L.

Bone mineral density and bone mineral concentration

The NNR SR (38) included two SRs of high or good quality (67, 70) and one RCT (71). The overall conclusion was that supplementation with vitamin D alone in doses of 7.5 µg/d to 10 µg/d have no or limited effect on bone mineral density. Supplementation with vitamin D (10–50 µg/d) in combination with calcium (500–1,200 mg/d) prevented bone loss among Caucasians compared with placebo.

The serum 25OHD concentrations associated with maintaining adequate bone mineral density or bone mineral content varies among studies. The SR by Winzenberg et al. (70) found an effect of vitamin D supplementation only in children with low mean serum 25OHD concentrations at baseline (≤ 35 nmol/L). In observational studies among the elderly, bone loss at the hip was increased at serum 25OHD concentrations ranging from 30 nmol/L to 80 nmol/L in different studies.

Falls

The NNR SR (38) included four SRs of high or good quality (39, 67, 72, 73) and three of low quality (74–76). The definition of "falls" and "falling" varied among the included trials. It should be noted that the trials included in the different SRs were mostly the same with some variation due to different inclusion and exclusion criteria and timeframes.

The NNR SR (38) concluded that there is *probable* evidence that supplementation with vitamin D in combination with calcium is effective in preventing falls in the elderly, especially in those with low baseline serum 25OHD concentrations, among both community-dwelling individuals and those in nursing-care facilities. A dose greater than 20 µg/d in conjunction with calcium supplementation was effective in most cases. The threshold for an effect is unclear, but one study suggested that serum 25OHD concentrations below 39 nmol/L were associated with an increased risk of falls. The evidence for an effect of supplementation with vitamin D alone is *inconclusive*.

Muscle strength and function

The NNR SR (38) included two SRs of good quality regarding effects of vitamin D on muscle function in older subjects (77, 78). Stockton et al. (77) concluded that vitamin D supplementation does not have an effect at serum 25OHD concentrations above 25 nmol/L, but that vitamin D does have an effect in adults with vitamin D deficiency. Muir et al. (78) concluded that vitamin D doses of 20–25 µg/d showed beneficial effects on balance and muscle strength without taking baseline serum 25OHD concentrations into account. However, in most studies concentrations were 25–50 nmol/L.

There is *probable* evidence that vitamin D supplementation improves muscle function at low serum 25OHD concentrations, but the evidence for an effect at levels above 50–60 nmol/L is *inconclusive*.

Cancer

The association between vitamin D and cancer has been investigated in a number of cohort studies. Some RCTs have been performed, but they are secondary analyses of supplemental studies for the prevention of fractures (79, 80).

Total cancer. No consistent evidence was found for an association between vitamin D status and total cancer in SRs that include cohort studies and RCTs (38).

Colorectal cancer. The NNR SR (38) included four SRs of good quality (67, 81–83) that covered colorectal cancer. There is *suggestive* evidence based on prospective cohort studies of an inverse association between vitamin D status and risk of colorectal cancer (38), but the evidence for a causal relationship was judged as *limited*. A meta-analysis of observational studies by Touvier et al. (84) also assessed associations with vitamin D intake from foods and supplements. An increased intake of 2.5 µg/d from foods (10 studies) was associated with a small but significant reduction in risk (RR = 0.95, 95% CI: 0.93–0.98), but a corresponding increase in total intake (5 studies) did not have a statistically significant effect.

Breast cancer. The NNR SR included three SRs of good quality (67, 82, 83) that covered breast cancer. Based on these, there is *suggestive* evidence for an inverse association between vitamin D status and breast cancer risk, but good-quality studies are lacking and there is heterogeneity between studies (38).

Prostate cancer. The NNR SR included three SRs of good quality (67, 82, 83), and results of the studies showed that there is *inconclusive* evidence for an association between vitamin D and prostate cancer (38).

Some epidemiological studies indicate an increased risk of pancreatic cancer with high plasma 25OHD concentrations, but the overall evidence is *inconclusive* (38).

Hypertension and blood pressure

The NNR SR (38) included four SRs of good quality (67, 85) and two of low quality (86, 87) covering RCTs, one of which was of low quality, that investigated the relationship between vitamin D and blood pressure and hypertension. The results of that analysis showed that the evidence for an association is *inconclusive* (38). All SRs concluded that there was a need for further studies to explore this relationship for possible clinical significance.

The NNR SR (38) noted that low vitamin D status has been associated with a higher incidence of hypertension in population studies reviewed in two of the SRs (67, 85).

Cardiovascular disease (CVD)

The NNR SR (38) included two SRs of high or good quality (67, 88) and one of low quality (89) covering CVD outcomes and serum 25OHD concentrations. The SR of low quality focused on vitamin D supplementation and CVD (90) and one SR of good quality covered cardiometabolic outcomes (diabetes, hypertension, and blood pressure) and serum 25OHD concentrations (85).

The NNR SR (38) concluded that SRs based on cohorts or case-control studies have consistently found an association between low serum 25OHD concentrations, mostly below 37.5 nmol/L or below 50 nmol/L, and an increased risk of CVD. Evidence for an effect of vitamin D supplementation on CVD outcomes, however, is lacking because the trials in question were all designed for other health outcomes than CVD.

In a subsequent meta-analysis of 19 independent prospective cohort studies (6,123 CVD cases in 65,994 participants) an inverse association between serum 25OHD concentrations and risk of CVD outcomes was observed, but with considerable heterogeneity between studies. The pooled RRs, comparing the lowest serum 25OHD concentration categories with the highest, were 1.52 (95% CI: 1.30–1.77) for total CVD, 1.42 (95% CI: 1.19–1.71) for CVD mortality, 1.38 (95% CI: 1.21–1.57) for coronary heart disease, and 1.64 (95% CI: 1.27–2.10) for stroke (91). Associations

remained significant when analyses were limited to studies that excluded participants with baseline CVD and were better controlled for season and confounding. The CVD risk tended to increase monotonically for decreasing serum 25OHD concentrations below about 60 nmol/L with an RR of 1.03 (95% CI: 1.00–1.06) per 25 nmol/L decrease in serum 25OHD concentrations.

In summary, there is *probable* evidence for an inverse association between low vitamin D status and increased CVD risk. However, data are insufficient to establish a precise cut-off for an increased risk.

Diabetes

Type-1 diabetes

The NNR SR identified one SR of good quality that investigated the relationship between vitamin D and type-1 diabetes (92). Five studies were included, one cohort study and four case-control studies. The results show some evidence that supplementation with vitamin D in early childhood might offer protection against type 1 diabetes. Randomized controlled trials are lacking thus far.

Type-2 diabetes

The NNR SR (38) included one SR of good quality (85) and one of low quality (89) and one RCT of high quality (93) on the relationship between vitamin D and the risk for type-2 diabetes. Pittas et al. (2010) included both cohort studies and RCTs, and the latter showed no significant clinical effect of vitamin D supplementation. The RCT (93) found no protective effect of 20 µg/d of a vitamin D supplement. Type-2 diabetes was, however, not the primary outcome in this high-quality study. The SR by Parker et al. (89) included a meta-analysis of prospective cohort studies and showed an overall decrease in the prevalence of diabetes associated with higher serum 25OHD concentrations. However, no grading of scientific quality of the included studies was given.

In summary, the evidence for a causal relationship or an association between vitamin D and type-1 or type 2-diabetes is *limited and inconclusive* (38).

Body weight

The NNR SR (38) included one SR of good quality (67) that evaluated RCTs on the effect of supplementation with vitamin D alone or with calcium on body weight. No significant effects were seen (38), and the

evidence for an association between vitamin D intake and body weight is *inconclusive*.

Pregnancy outcomes

The NNR SR (38) included two SRs of high or good quality that covered maternal and neonatal outcomes (67, 94). The SR by De-Regil et al. (94) reviewed six RCTs including 1,023 pregnant women on the association between vitamin D supplementation and pre-eclampsia, preterm birth, low birth weight, and gestational diabetes and vitamin D status at term. In addition, there were a series of secondary intended outcome measures, including caesarean sections, maternal hypertension, and Apgar score. The vitamin D dose ranged from 20 µg/d to 30 µg/d, and three trials also included single high doses of 5,000 µg to 15,000 µg. Five of the studies (623 women) gave vitamin D alone, and one study (400 women) gave vitamin D in combination with calcium. Pre-eclampsia was reported by one study supplying both calcium and vitamin D, and no difference in risk was observed between the intervention and placebo groups. Vitamin D supplementation during pregnancy improved serum 25OHD concentrations at term. None of the included studies reported on gestational diabetes or preterm birth.

The SR by Chung et al. (67) included one small nested case-control study on the relation between vitamin D status and risk of pre-eclampsia. Lower adjusted mean serum 25OHD concentrations were associated with increased risk of pre-eclampsia, and early pregnancy serum 25OHD concentrations below 37.5 nmol/L were associated with a five-fold increased risk of pre-eclampsia.

In conclusion, vitamin D supplementation during pregnancy improves vitamin D status. There is *limited* evidence to assess the clinical significance at observed intakes.

Rickets

Two SRs of high or good quality were included in the NNR SR (38). The SR by Chung et al. (67) cited the previous SR by Cranney et al. (39) because no new studies were identified. The Cranney report included 13 studies regarding vitamin D status and rickets. In six studies, the mean or median serum 25OHD concentrations in children with rickets were < 27.5 nmol/L, but they were between 30 nmol/L and 50 nmol/L in the other seven studies. Most studies were conducted in developing countries with low calcium intakes. Low calcium intake can influence the relationship between serum

25OHD concentration and rickets, and the serum 25OHD concentration threshold for rickets in populations with high calcium intake (such as in North America) is unclear. Cranney et al. (39) concluded that there is fair evidence for an association between low serum 25OHD concentrations and the development of rickets, but that the evidence is inconsistent to determine a threshold serum 25OHD concentration above which rickets does not occur.

The SR by Lerch and Meissner (95) evaluated the effects of interventions for preventing nutritional rickets in children born at full term. The review was limited to studies performed in the last 50 years. Only four trials were included, of which three were carried out in China and Turkey and one among 10-year-old to 15-year-old children in France. The conclusions were focused on prevention of rickets in Africa, Asia, and the Middle East and in children who had migrated from these regions, and they stressed the importance of preventive measures including vitamin D supplementation.

In conclusion, risk of rickets increases with serum 25OHD concentrations below 50 nmol/L and the risk is high at concentrations below 27.5 nmol/L. The cut-off concentration depends on habitual calcium intake.

Other health outcomes

Infections

The NNR SR concluded that the evidence for an effect of vitamin D on infections is limited and that the reviewed trials were very heterogeneous (38).

Multiple sclerosis

The NNR SR concluded that there is insufficient data to draw any conclusion concerning the relation between vitamin D and multiple sclerosis (38).

Requirement and recommended intake

Criteria for setting reference values

In NNR 2004, serum 25OHD concentration < 40 nmol/L were judged to indicate moderate hypovitaminosis (96) and values > 50 nmol/L were considered to be desirable (97, 98).

The NNR SR on vitamin D found it difficult to establish an optimal serum 25OHD concentration or vitamin D intake based on the evaluated SRs (38) but noted that there is evidence that a concentration of 50 nmol/L would reflect a sufficient status. The IoM (32) considered calcium ab-

sorption together with bone mineral density, rickets, and osteomalacia to establish an optimal serum 25OHD concentration. The IoM found congruence among these outcomes with no additional benefits of serum 25OHD concentrations higher than 50 nmol/L and suggested that this level is consistent with an RDA-type reference value in that this level appears to cover the needs of 97.5% of the population. A serum 25OHD concentration < 30 nmol/L is regarded as indicating deficiency and between 30 nmol/L and 50 nmol/L is considered an insufficient vitamin D status (32).

The relationship between serum 25OHD and parathyroid hormone (PTH) concentrations has been considered in numerous studies, and based on these the proposed threshold for vitamin D sufficiency has varied between 25 nmol/L to 125 nmol/L. Using serum PTH as an outcome is difficult because the variation is large and because other factors have an effect on S-PTH. Sai et al. (99) concluded in a systematic review that "vitamin D insufficiency should be defined as serum 25OHD concentrations less than 50 nmol/L as it relates to bone". The IoM report stated that serum levels above 75 nmol/L are not consistently associated with increased benefit and that "there may be reason for concern at serum levels above 125 nmol/L" (32).

Assays for determining serum 25OHD concentrations might give different results, and this should be accounted for when interpreting results from studies linking status with health outcomes. Results from some immunoassay methods have been shown to give lower 25OHD values compared to, for example, HPLC or LC-tandem MS/MS (100, 101).

In NNR 2012, a serum 25OHD concentration of 50 nmol/L is used as an indicator of sufficiency, and a concentration of 30–50 nmol/L is considered to indicate insufficient status.

Infants

New-borns have a store of vitamin D that depends on the vitamin D status of the mother. During the first six weeks of life there is a rapid fall of serum 25OHD concentrations to a level seen in rickets (102). Human milk does not contain sufficient vitamin D to prevent rickets even if the mother takes vitamin D supplements (103). Sun exposure has a marked effect on vitamin D status in infants, and vitamin D supplementation might not be required provided exposure is sufficient. At northern latitudes, as in the Nordic countries, however, vitamin D supplementation is required in order to ensure that no infant develops rickets. During the first 6 weeks after birth, the serum 25OHD concentration falls to a range where there is a

high risk of rickets (< 27.5 nmol/L). Supplementation, therefore, should start during the first weeks of life.

A vitamin D intake of 2.5 µg/d might be sufficient to prevent rickets (16). In a Norwegian study by Markestad (102), a group of 8 infants were fed exclusively on milk formula containing 10 µg/L vitamin D. At 6 weeks of age, they all had serum 25OHD concentrations within the normal range (mean 92 ± 21 nmol/L), indicating that a mean intake of 7.5 µg (corresponding to an intake of 750 mL of formula) ensures satisfactory vitamin D status. In two previous Finnish studies, supplementation with 10 µg/d vitamin D from birth during wintertime resulted in mean serum 25OHD concentrations at 8 weeks (104) and 14 weeks (105) of age of about 45 nmol/L and >75 nmol/L, respectively, compared to about 14 nmol/L and 25 nmol/L in unsupplemented infants, respectively.

Based on these considerations, 10 µg/d is recommended for new-borns from the first weeks of age to 2 years.

Children and adults

Studies published during the last 10–15 years show large variations in vitamin D status among children and adolescents in the Nordic countries. These are mainly due to the degree of skin production of vitamin D from sun exposure during the summer and early autumn seasons, use of vitamin D supplements, and dietary intake. Serum 25OHD concentrations are generally lowest in late winter and early spring with exceptions due to occasional vacations to sunny climates.

The dietary requirement of vitamin D sufficient to maintain an adequate serum 25OHD concentration (≥ 50 nmol/L) throughout winter is partly dependent on the status in early autumn (35). Adequate sun exposure during the summer season is a suitable means to build up a body pool that can help maintain adequate status during the winter season. Engaging in outdoor physical activity in line with recommendations is one option.

Controlled intervention studies using vitamin D supplements carried out at latitudes covering the Nordic region show varying responses with respect to effects on serum 25OHD concentrations and the proportions of subjects below various cut-offs during the winter season.

In the NNR SR (38), results from an SR by Cashman et al. (41) were used as an approach to define dietary intakes that would maintain adequate serum 25OHD concentrations under various assumptions. The paper included meta-regressions of data from 12 intervention studies with vitamin D supplementation in children, adults, and the elderly carried out at lati-

tudes between 49.5° N and 63° N and one study carried out in Antarctica at 78° S. Depending on the statistical model used, the vitamin D intake needed to achieve wintertime serum 25OHD concentrations of at least 50 nmol/L for 95% of the population varied between 9.0 µg/d and 12.0 µg/d. However, the estimations were dependent on the analytical model used, and the studies included in the analysis gave highly variable results.

Results from studies conducted at similar latitudes as the Nordic countries with children aged 8–12 years showed increases of 10–25 nmol/L (43, 71) or no change (41) after supplementation with 10 µg/d vitamin D and with total intakes of 12.5–15 µg/d during the winter season.

Studies with adults aged 18–49 years also show divergent results with increases of 30–38 nmol/L (44, 45) or decreases of 7–12 nmol/L (42) after supplementation with 10–20 µg/d vitamin D (total intakes of 13.5–29 µg/d) during the winter season. The responses seem to be associated with several factors, and baseline concentrations are important. Because different analytical methods were used to assess serum 25OHD concentrations, it is difficult to compare the actual status between studies.

A combined analysis of the supplementation studies on children and adults (up to about 60 years of age) that measured serum 25OHD concentrations during wintertime with limited sun exposure is presented in an Appendix (42–46, 71, 106). In this analysis the study from Antarctica was excluded because it was not considered representative for the Nordic setting and because it administered high doses of vitamin D. The studies were carried out at latitudes within the Nordic region (55° N to 61° N) or at latitudes somewhat further south (50° N to 55° N). The supplementation studies suggest that the response to supplementation was dependent on baseline serum 25OHD concentration with no or limited increase when baseline levels were above 50 nmol/L. The analysis shows that an intake of 7.2 µg/d would maintain a mean serum 25OHD concentration during the winter season of about 50 nmol/L (Appendix, Figure 16.1.). Based on this evaluation, the average requirement (AR) is set at 7.5 µg/d. Results from the studies indicated relatively large inter-individual variations in response that partly depended on baseline concentration. Using the lower 95% confidence interval in the graph, an intake of about 10 µg/d would be sufficient for the majority of the population.

In NNR 2004, the recommended intake (RI) was set to 7.5 µg/d for the age group of 2 years to 60 years in order to diminish the seasonal drop in serum 25OHD concentration. Based on the combined results from studies with supplements, a further increase of the RI is warranted and

the RI is set to 10 µg/d. This RI considers some contribution of vitamin D from outdoor activities during the summer season (late spring to early autumn), which is compatible with normal, everyday life and also in line with recommendations on physical activity. Engaging in outdoor physical activity in line with recommendations is one option. A higher intake might be necessary for some parts of the population due to limited sun exposure or skin production related to cultural traditions, limited access to outdoor activities, or skin pigmentation.

Older adults and the elderly

Previous studies carried out in the Nordic countries showed that insufficient vitamin D status was common among the elderly, especially among those living in institutions (107–109). More recent studies give a more complex picture, and some studies have shown equal or higher serum 25OHD concentrations among the elderly (21, 23, 27, 110). However, elderly people living in institutions with little or no access to sun exposure are still at high risk of insufficient vitamin D status (24, 111). Apart from low dietary intake and limited time spent outdoors, the amount of 7-dehydrocholesterol in the skin epidermis diminishes with age and the efficiency of conversion of this precursor into vitamin D is less effective than in younger individuals (1). There is also some evidence that the PTH concentration tends to be higher among the elderly compared to younger adults at similar serum 25OHD concentrations. This might indicate less efficient bioconversion due to diminished kidney function resulting in secondary hyperparathyroidism (112–114).

A high incidence of osteoporotic hip fracture is seen in all Nordic countries, although a decrease has occurred in some countries in recent years (115–117). The more rapid bone loss and higher fracture rate in elderly women than in men is related to diminished oestrogen production in postmenopausal women.

The SR by Cashman et al. (41) included four RCT studies with mainly older adults (> 64 years of age) carried out at latitudes between 51° N (Ireland) and 63° N (southern Finland). In three studies, supplementation with 10–20 µg/d vitamin D (total intakes of 14–30 µg/d) resulted in increases in serum 25OHD concentrations of 12.5–39 nmol/L and mean concentrations of 60–88 nmol/L during wintertime (118–120). Supplementation with 5 µg/d (total intakes 9.1–14.7 µg/d) resulted in small changes (1–9 nmol/L) and mean concentrations of 53–55 nmol/L. In the fourth study, elderly women were given high doses of vitamin D (45 µg/d

for a total intake of ~55 µg/d) in combination with calcium (121). Results were comparable with the above studies. In a repeated crosssectional study by Sem et al. (109), which was not included in the SR by Cashman et al. (41), a daily supplement of 11–15 µg/d (total intake 14–19 µg/d) among elderly people living in Oslo (60° N) maintained serum 25OHD concentrations of around 90 nmol/L during winter. Compared to subjects with no supplementation, wintertime serum 25OHD concentrations were 35–60 nmol/L higher in the supplemented groups. Based on a regression analysis, it was calculated that an intake above 5–6 µg/d was required to ensure serum 25OHD concentrations above 50 nmol/L.

A combined analysis of results from the above studies (109, 118–120) was performed in which the study by Honkanen et al. (121) was excluded due to the high vitamin D dosing. The result of that analysis indicated that an intake of about 5 µg/d would maintain a mean serum 25OHD concentration of about 50 nmol/L during wintertime (Appendix, Figure 16.2.). This estimate is lower than for children and younger adults. However, confidence intervals are wider, and based on the lower 95% confidence interval in the graph an intake of about 10–11 µg/d would be needed to cover the majority of the population.

The NNR SR concluded that data from the reviewed SRs show that there is *convincing* evidence of a protective effect of vitamin D on bone health, total mortality, and the risk of falling (38). The effect was often only seen in persons with low basal serum 25OHD concentrations (< 50 nmol/L). In intervention studies, effects were mainly seen for combined supplementation with vitamin D and calcium. There is, however, some epidemiological evidence that high concentrations of 25OHD are associated with increased total mortality. Low serum 25OHD concentrations (mainly < 37.5 nmol/L) were associated with increased risk of CVD in epidemiological studies, but data from intervention studies are lacking (38).

A vitamin D intake of 10 µg/d is recommended for individuals 61–74 years of age. For people with little or no sun exposure, an intake of 20 µg/d is recommended.

For those aged 75 years and older, a total intake of 20 µg/d is recommended.

Pregnancy and lactation

There is a marked increase in 1,25-dihydroxyvitamin D in plasma during pregnancy (32). A close correlation has also been found between vitamin D status of the mother and the new-born (102). Serum 25OHD concen-

trations have been found to be low during winter in pregnant women under normal circumstances in the Nordic countries (29, 30, 122, 123). A Norwegian study from the 1980s showed that a supplement of 10 µg/d to pregnant women resulted in a serum 25OHD concentration in the upper normal range (124).

The NNR SR (38) concluded that vitamin D supplementation during pregnancy improved vitamin D status as measured by serum 25OHD concentrations at term (39, 94). However, the clinical significance of this remains uncertain. Data on health outcomes are *limited and inconclusive*.

Because no new strong evidence has emerged, the recommendation from NNR 2004 is maintained. An intake of 10 µg/d is recommended during pregnancy and lactation.

Reasoning behind the recommendation

New scientific data has emerged since the NNR 2004 was published, and evidence has accumulated that vitamin D intake and status is associated with total mortality, fractures, falls, and CVD outcomes. As in NNR 2004, a serum 25OHD concentration of > 50 nmol/L is used as an indicator of sufficient vitamin D status. Intervention studies with various doses of vitamin D show that an intake of 10 µg/d is needed to maintain serum 25OHD concentrations around 50 nmol/L among the majority of the population during wintertime at latitudes within the Nordic region. This RI considers some contribution of vitamin D from outdoor activities during the summer season (late spring to early autumn), and this is compatible with normal, everyday life and is also in line with recommendations on physical activity. For people with little or no sun exposure, an intake of 20 µg/d is recommended. For the elderly (>75 years of age), an intake of 20 µg/d is recommended, and this is mainly to account for the more limited solar-induced vitamin D synthesis and the evidence for the protective effect of such an intake against mortality, fractures, and falls.

Lower intake level

In NNR 2004, the lower intake level (LI) was set to 2.5 µg/d and this was mainly applicable to individuals > 60 years of age. Results from the RCTs using various doses of vitamin D supplements indicate that an intake of 2.5–3 µg/d would maintain serum 25OHD concentrations of about 30 nmol/L during wintertime provided that there was sufficient sun exposure

during the summer season (see Figures16.1. and 16.2.). However, for individuals with little or no sun exposure this intake might be insufficient to maintain this level. There is insufficient data to set an LI, for example, for infants under these circumstances. An intake below the LI might indicate deficient vitamin D status among children and adults especially in cases of little or no sun exposure.

Upper intake levels and toxicity

Large amounts of vitamin D are toxic and can lead to hypercalcaemia, nephrocalcinosis, and kidney failure. There are older reports of hypercalcaemia in connection with excessive supplementation of infant foods with vitamin D (125) and in connection with incidental over-enrichment of milk (126, 127). However, the exact ingested doses were not elucidated.

Relatively few RCTs included in the NNR SR report adverse effects of vitamin D (38). The adverse effects that were reported include milder transient and asymptomatic hypercalciuria or hypercalcaemia and gastrointestinal symptoms (67, 73, 128). Dose levels ranged from 10 µg/d to 143 µg/d vitamin D_3 and from 125 µg/d to 250 µg/d vitamin D_2. Other SRs found that vitamin D in doses of 10 µg/d given with calcium, but not vitamin D alone, moderately increased the risk of renal stones among postmenopausal women (39, 54). According to Bjelakovic et al. (54), the RR was 1.17 (95% CI: 1.02–1.34).

There are some observational studies suggesting that total mortality is increased at high serum 25OHD concentrations (60, 63, 83). Some studies have reported an increase in prostate cancer (129) or total cancer (60) at higher serum 25OHD concentrations ranging from 100 nmol/L to 150 nmol/L. A trial using large single yearly doses of vitamin D (corresponding to about 18 µg/d) reported increased incidence in fractures and falls in the elderly (130).

The EFSA (131) has set the tolerable upper level (UL) to 100 µg/d for adults and adolescents 11–17 years of age using hypercalcaemia as the criterion for adverse effects. For children 1–10 years of age, the UL was adjusted to 50 µg/d. For infants the UL of 25 µg/d was based on data relating high vitamin D intakes to impaired growth and hypercalcaemia.

The Institute of Medicine (32) also used onset of hypercalcaemia and related toxicity as basic criteria for setting ULs. For infants, the effects on growth were also included. The UL was set to 100 µg/d for adults and children older than 9 years of age. For younger children, ULs were

extrapolated to 25 µg/d and 38 µg/d for infants aged 0–6 months and 6–12 months, respectively.

Taking the new studies mentioned above into consideration, the UL for adults and adolescents 11–17 years of age is set at 100 µg/d. For younger children, the UL is set at 50 µg/d and for infants (0–12 months) the UL is set at 25 µg/d.

Appendix:
Vitamin D intake and serum 25OHD – results from supplement studies

Results from randomized controlled intervention trials using vitamin D supplements at various levels and carried out at latitudes covering the Nordic region were used to estimate overall association between intake and serum 25OHD concentrations (Table 16.1.). The included studies were selected mainly from the systematic review by Cashman et al (41) and the NNR 2004 edition. The studies were conducted during winter with limited sunexposure. Studies that administered high doses of vitamin D (> 30 µg/d) were excluded (121).

Children and adults

Data from randomized controlled intervention studies on children and adults (up to about 60 years of age) where serum 25OHD concentrations were measured during wintertime were used to estimate overall association between intake and serum 25OHD concentrations. The studies are listed in table 16.1. (42–46, 71).The studies were carried out at latitudes within the Nordic region (55° N to 61° N) or at latitudes somewhat further south (50° N to 55° N). The study by Meier et al. (106) included subjects with a wide age range (33–78 years), but as mean age was 55–58 years it was also included.

The relationship between vitamin D supplementation intake and serum 25OHD concentrations (log transformed) was analysed using fitted line plot (Minitab® 15.1.0.). The supplementation studies suggest that the response to supplementation was dependent on baseline serum 25OHD concentration with no or limited increase when baseline levels were above 50 nmol/L. The results show that an intake of 7.2 µg/d would maintain a mean serum 25OHD concentration in half of the subjects during the winter season of about 50 nmol/L (Figure 16.1.). Based on these data, the average requirement (AR) is set at 7.5 µg/d. Results from the studies

indicate relatively large inter-individual variations in response. Using the lower 95% confidence interval in the graph, an intake of about 10 µg/d was considered to be sufficient to ensure a serum 25OHD concentration in the majority of the population. Therefore the AR for these age groups was set at 7.5 µg/d and the RI at 10 µg/d.

Older adults and elderly

Data from randomized controlled intervention studies on older adults and elderly where serum 25OHD concentrations were measured during wintertime were considered too limited in number to use the same approach as above. The repeated cross-sectional study by Sem et al. (132) with elderly people living in their own homes or residents at old people's homes was therefore included as a basis to explore whether the same RI value would apply for the elderly as for the younger and adult groups. The studies were all carried out within latitudes 51° N to 61° N and listed in Table 16.1. (106, 109, 118–120). Based on the lower 95% confidence interval in the graph (Figure 16.2.) an intake of about 10–11 µg/d was considered to be sufficient to ensure a serum 25OHD concentration in the majority of this population group. Therefore the RI for this age group was set RI at 10 µg/d.

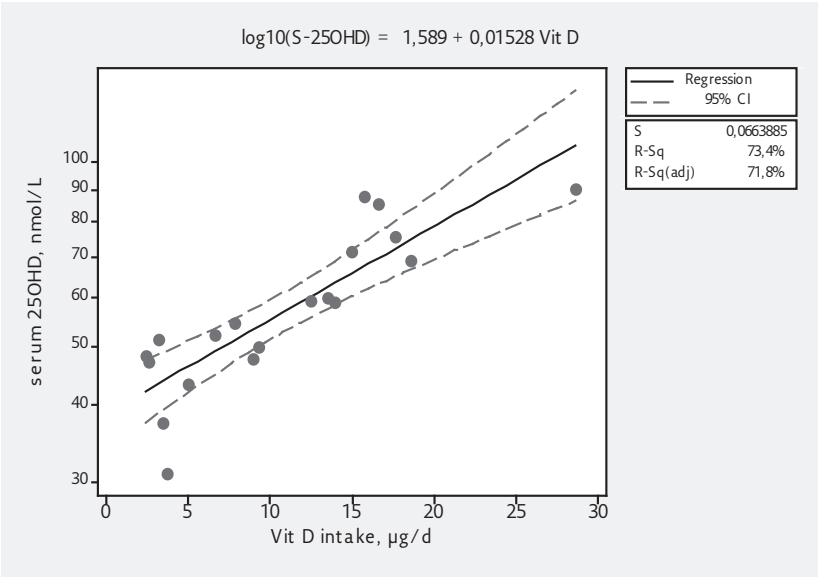


Figure 16.1. Effect of vitamin D supplementation on serum 25OHD concentrations during wintertime among children and adults up to about 60 years of age

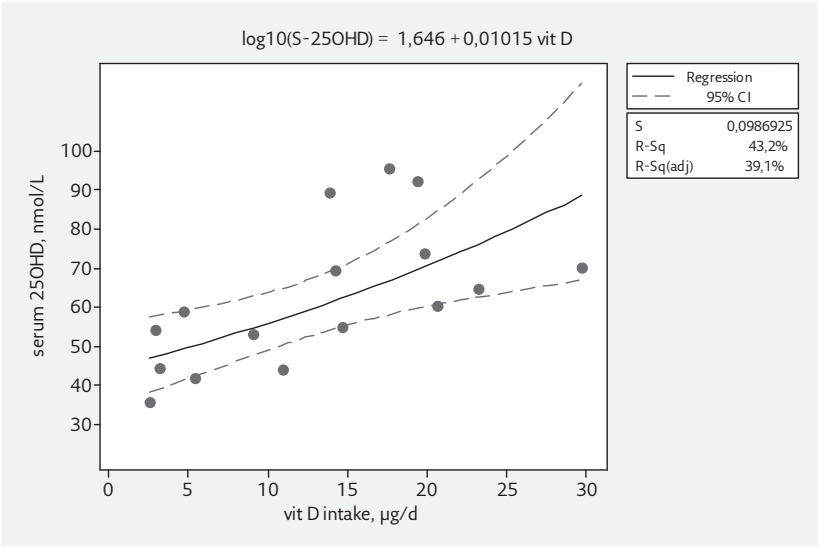


Figure 16.2. Effect of vitamin D supplementation on serum 25OHD concentrations during wintertime among the elderly (> 65 years of age)

Table 16.1. Vitamin D supplementation and serum 25OHD among children, adults and elderly during winter season

Reference	Country	Latitude	Season	Subject characteristics	Duration, wk	N	Suppl. Vit D_3 µg/d	Habitual vit D intake	Total vit D intake	Baseline S25OHD	Final S25OHD	SD	Mean change	Analytical method
Ala-Houhala et al. 1988 (43)	Finland	61 °N	Jan/Feb – Feb/ March	m, f, 8–10 y	56	24	10 µg D_2, 5–7 d/wk	5*	15	49.2	71.3 (77.9)	23.8	22.0 (28.7)	CPBA
						27	-	5*	5	45.9	43.2	19.5	-2.7	
Mølgaard et al. 2009 (133)	Denmark	55 °N	Nov-May	F, 11–12 y	~26	74	10	2.5	12.5	44.4	59.4	13.2	15.0	HPLC
						73	5	2.8	7.8	41.9	54.5	12	12.6	
						73	-	2.6	2.6	43.4	47.0	20	3.6	
Cashman et al. 2011b (46)	Finland, Denmark	61 °N, 55 °N	March – April	F, 11 y	52	49	10	3.9	13.9	58.4	58.8	10.9	0.4	HPLC
						49	5	3.9	8.9	57.4	47.6	8	-9.8	
						46	-	3.7	3.7	54.5	31.0	10	-23.5	
Barnes et al. 2006 (44)	UK	55 °N	March	M, f, 18–27 y	8	15	15	1.6	16.6	47.9	85.6	24.5	37.7	EIA
						12	-	2.4	2.4	55.5	48.3	16.8	-7.2	
Cashman et al. 2008 (42)	Ireland	51–55 °N	March	m, f, 20–40 y	22	53	15	3.6	18.6	75.9	69.0	18.6	-6.9	EIA
						57	10	3.5	13.5	72.2	60.0	13.4	-12.2	
						48	5	4.3	9.3	60.0	49.7	11.4	-10.3	
						57	-	3.4	3.4	65.7	37.4	12.2	-28.3	
Viljakainen et al. 2009 (45)	Finland	61 °N	April	m, 21–49 y	25	16	20	8.6	28.6	60.3	90.1	11.6	29.8	EIA
						16	10	7.6	17.6	62.3	75.6	13.6	13.3	
							-	6.6	6.6	64.7	52.2	18.5	-12.5	

Meier et al. 2004 (106)	Germany	49.5 °N	Feb/ March	m, f: 33–78 y	26	27	12.5	3.2	15.7	48.8	87.6	20.3	39.0	RIA
						16		3.2	3.2	61.5	51.2	21.3	-10.3	
Cashman et al. 2009 (119)	Ireland	51–55 °N	March	m, f, 64+	22	48	15	4.8	19.8	55.1	73.8	20	18.7	EIA
						53	10	4.2	14.2	54.3	69.5	17	15.2	
						48	5	4.1	9.1	51.8	53.2	17	1.4	
						55	-	4.7	4.7	58.8	58.8	17.1	0	
Viljakainen et al. 2006 (118)	Finland	61 °N	Jan -April	f, 65–85 y	12	13	20	9.7	29.7	44.1	70.2	13.5	26.1	HPLC
						11	10	10.6	20.6	46.5	60.4	10.2	13.9	
						13	5	9.7	14.7	46.0	55.0	10.2	9	
						12	-	10.9	10.9	52.2	43.9	19.9	-8.3	
Sem et al. 1987 (132) A=elderly homes B=free-living	Norway	60 °N	Feb – March	fA, 86 y		12		2.6	2.6	-	35.8	20.3		HPLC+ UV photo-metry
	Oslo			fA, suppl		23	15	2.6	17.6	-	95.5	30.3		
				mA, 80 y		13	21	-	5.4	-	42.0	13.8		
				mA, suppl		8	14	5,4	19.4	-	92.5	28.3		
				fB, 76 y		10	-	2.9	2.9		54.3	17.8		
				fB, suppl		14	11	2.9	13.9	-	89.3	20.0		
				mB, 79 y		2#	-	5.6	5.6		90.5	10.3		
				mB, suppl		4#	12	5.6	17.6	-	92.5	7.0		
Pfeifer et al. 2001 (120)	Germany	52 °N	March – May	f, 74 y	8	74	20 + Ca	3.2	23.2	25.7	64.8	25.8	39.1	RIA
						77	Ca	3.2	3.2	24.6	44.4	27.4	19.8	

* estimated # not included, too few subjects. CPBA: Competitive protein-binding assay, HPLC: High pressure liquid chromatography, EIA: Enzyme immunoassay, RIA: Radioimmunoassay.

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17 Vitamin E

Vitamin E α-TE/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y girls/boys
Recommended intake	RI	8	10	5	6	7/8
Average requirement	AR	5	6			
Lower intake level	LI	3	4			
Upper intake level	UL	300*	300*			

* mg/d from supplement (EFSA 2003).

Introduction

Vitamin E has traditionally been used as the common term for four tocopherols (α-, β-, γ-, and δ-tocopherol) and four tocotrienols (α-, β-, γ-, and γ-tocotrienol) that have been shown to have varying levels of biological activity in experimental animal studies (1). However, α-tocopherol is the only form that is recognized to meet human requirements. α-tocopherol is a required nutrient for humans because it is needed for prevention of vitamin E deficiency symptoms including neuropathy and haemolytic anaemia (2). In NNR 2012, vitamin E activity is confined to α-tocopherol. Vitamin E activity has previously been expressed as α-tocopherol equivalents (α-TE) that include the small amounts of activity suggested by animal experiments to be provided by other tocopherols and tocotrienols.

The naturally occurring form of α-tocopherol is RRR-α-tocopherol. Synthetic α-tocopherol (also known as all-rac-α-tocopherol or dl-α-tocopherol) contains an equal mixture of eight different stereoisomers. All of the stereoisomers have equal antioxidative activities, but only those with the 2R-configuration (RRR-, RSR-, RRS-, and SRR) have biologically relevant activities. Due to the lower affinity that α-tocopherol transport protein (α-TTP) has for 2S-isomers, the relative bioavailability of the synthetic form of α-tocopherol is suggested to be only half that of the naturally occurring α-tocopherol (3). This means that only α-tocopherol in foods and 2R-α-

tocopherols in vitamin E preparations contribute to vitamin E activity. For commercially available vitamin E preparations, the following conversion factors to α-TE have been suggested: 0.5 for all-rac-α-tocopherol, 0.455 for all-rac-α-tocopheryl acetate, and 0.91 for RRR-α-tocopheryl acetate (4, 5). In older literature, vitamin E activity was expressed as IUs. One IU is equivalent to 0.67 mg of the natural form and 0.45 mg of the synthetic form of the vitamin (6).

Dietary sources and intakes

Vegetable oils, vegetable oil-based spreads, nuts, seeds, and egg yolk are good food sources of vitamin E. The α-tocopherol content is highest in sunflower oil followed by corn and rapeseed oil, olive oil, and soybean oil. In addition, vegetable oils contain variable amounts of other tocopherols and tocotrienols. Corn oil, soybean oil, and rapeseed oil are high in γ-tocopherol. On average, approximately half of the α-tocopherol in the diet of Finnish adults was provided by cereal and bakery products and fat spreads, oils, and dressings (7). Among the EPIC study participants from the Nordic countries, added fats contributed the most to vitamin E (α-TE) intake followed by cereal, cereal products, and cakes (8). Other important sources were fruits, vegetables, and fish and shellfish.

In recent dietary surveys from the Nordic countries, the mean dietary intake of vitamin E (α-tocopherol) among adult populations varied between 7 mg and 10 mg per day (9–14). When expressed in relation to energy intake, dietary intake of α-tocopherol by adults in the Nordic countries ranges from 8 mg/10 MJ to 16 mg/10 MJ. During pregnancy, intake of vitamin E is higher and most of women use supplements containing vitamin E (15–18). α-tocopherol intake by children ranges from 7 mg/10 MJ to 11 mg/10 MJ and does not differ greatly from that of adults (18–20).

Physiology and metabolism

The uptake, transport, and tissue delivery of α-tocopherol involves molecular, biochemical, and cellular processes that are closely related with overall lipid and lipoprotein metabolism (21). The presence of bile salts and pancreatic enzymes and the formation of micelles are prerequisites for vitamin E absorption. In order to obtain maximal absorption, vitamin E should be given at meals. However, knowledge of vitamin E absorption is incomplete, and both the amount of fat and the food matrix influence

vitamin E absorption. In balance studies with small radioactive doses of α-tocopherol, absorption in normal subjects has ranged between 55% and 79% (2, 22), whereas a much lower figure of 33% was reported based on observed changes in plasma-labelled α-tocopherol after administration of a stable isotope-labelled dose of α-tocopherol (23). Large individual variation in vitamin E uptake has been reported.

Absorbed vitamin E is transported within chylomicrons or bound to HDL in the liver where α-TTP preferentially binds α-tocopherol and is essential for the selective resecretion of α-tocopherol (24). The metabolism of vitamin E is tightly regulated, and unlike other fat-soluble vitamins there is no toxic accumulation in the liver. α-tocopherol that is not released into circulation is excreted into the bile via transporters that are upregulated in the presence of α-tocopherol or it is metabolized via the cytochrome P450 system, also regulated with α-tocopherol, and excreted in bile or urine. The major route of excretion of α-tocopherol is in the faeces with small amounts excreted in urine (22). Turnover of vitamin E is slow; in a kinetic study with tracer-marked RRR-α-tocopherol tracked for 460 days in healthy men and women, the mean half-life of the dose was 44 days in plasma and 96 days in red blood cells (22).

Although no tissue serves to store vitamin E, depletion of body vitamin E takes decades rather than weeks (25). Non-α-tocopherols and tocotrienols are rapidly metabolized thereby preventing their tissue accumulation and limiting increases in their plasma concentrations (26). In human tissues, α-tocopherol is the most common tocopherol and contributes about 90% of the total amount of tocopherols and tocotrienols in plasma (27) and 50%–80% in other tissues (4). Recently, water-soluble α-tocopheryl phosphate has been shown to appear in minute amounts in foods and tissues (28).

The main biochemical function of α-tocopherol has been suggested to be its antioxidant activity. As a chain-breaking antioxidant, α-tocopherol might prevent the propagation of free radicals in membranes and in plasma lipoproteins (29). In addition, several other important biological functions, including modulation of cell signalling and gene expression, have been ascribed to vitamin E (30). α-tocopherol might modulate the activity of several enzymes. Most of these enzymes are membrane bound or activated by membrane recruitment, especially those affecting cell proliferation, membrane trafficking, and metabolism of xenobiotics (24). Genes involved in the metabolism and excretion of vitamin E are regulated by α-tocopherol itself. The ultimate biological function of vitamin E, however, remains to be elucidated (31).

Vitamin E is suggested to affect health through its antioxidant activity, immune system enhancement, inhibition of platelet aggregation, and anti-inflammatory function with much of this evidence coming from cell studies and the findings from animal experiments. Evidence for decreased oxidative stress with α-tocopherol supplementation in humans is inconsistent (32). The effect of vitamin E on biomarkers of oxidative stress appears to depend on the circumstances in which it is administered, most importantly on the level of baseline oxidative stress (33). Differences in the individual responses to α-tocopherol are also suggested to arise due to genetic factors (34, 35).

High vitamin E intake has been associated with prolonged bleeding suggesting that large amounts of vitamin E might interfere with the blood clotting system especially with simultaneous use of aspirin or treatment with anticoagulants (36, 37). It is hypothesized that vitamin E intake can affect vitamin K status because they share the same metabolic pathways (38, 39).

Vitamin E and chronic diseases

Vitamin E has been proposed to play a role in several chronic diseases such as cardiovascular diseases, cancer, dementia, and other diseases associated with increased oxidative stress and inflammation.

Observational studies have provided some evidence suggesting a lower risk of coronary heart disease with higher intake of vitamin E, but randomized clinical studies do not, in general, provide support for a significant or clinically important effect of vitamin E supplementation on coronary heart disease (40, 41) or stroke (42). However, some studies have reported specific beneficial and adverse effects. Supplementation of healthy women older than 45 years with 600 IU of a natural form of vitamin E every other day for 10 years did not affect the occurrence of cardiovascular events compared to placebo. It did, however, result in a significant 24% decrease in cardiovascular deaths in women over the age of 65 years at baseline (43). Results from the same study showed that women supplemented with vitamin E also had a 21% lower risk for vascular thromboembolism (44). Among women at high risk for cardiovascular diseases, such as those with prior cardiovascular disease, supplementation with 600 IU natural source vitamin E every other day for a mean of 9.4 years was associated with a marginal reduction of cardiovascular events (45). In another study of a high-risk population, daily supplementation with 400 IU natural

α-tocopherol did not prevent major cardiovascular events, and instead an increased risk for heart failure was found (46). In line with the results from the ATBC study (47), increased risk for haemorrhagic stroke was reported among healthy physicians who received 400 IU synthetic α-tocopherol every other day for 8 years (48).

The significance of vitamin E in cancer prevention has been investigated in several clinical trials, none of which has provided evidence for overall protection from cancer (49). The decreased prostate cancer risk associated with a 50 mg daily dose of synthetic α-tocopherol among middle-aged Finnish male smokers (50) has not been supported by findings from other large-scale controlled trials (51). On the contrary, in post-trial analyses increased risk of prostate cancer was reported among men who had received an average daily supplement of 400 IU synthetic α-tocopherol for 5.5 years (52). There is also no evidence from randomized controlled trials that vitamin E supplementation would be effective against other type of cancer when given for 5 to 10 years to middle-aged or elderly men and women in doses ranging from 50 mg of synthetic α-tocopherol per day to 400 IU of natural-form α-tocopherol per day (43, 46, 53–57). Results from observational studies on α-tocopherol in cancer prevention are inconsistent (58).

There is some evidence from observational studies to indicate a putative role of vitamin E in preventing cognitive impairment, but findings from a few intervention studies have provided little support for this (59). In observational studies, the reduced risk of type 2 diabetes due to higher intake of antioxidants was mainly attributed to vitamin E (60), but such a beneficial effect of vitamin E supplementation has not been confirmed in randomized trials (61). Observational studies of vitamin E and the risk of cataracts and age-related maculopathy have shown mixed results. Only a very limited effect of vitamin E supplementation alone or in combination with other antioxidants on the incidence or progression of cataracts or age-related macular degeneration has been reported (62).

Supplementation with α-tocopherol above the recommended levels is suggested to improve immune function and decrease respiratory tract infections, especially in the elderly (63), but the results of a few randomized trials are inconsistent. Individual differences in the effects of vitamin E supplementation on respiratory tract infections are suggested to be due in part to genetic factors (64).

Requirement and recommended intake

Vitamin E deficiency due to low dietary intake has not been described in normal, healthy individuals. However, deficiency can be caused by prolonged fat malabsorption, genetic defects in lipoprotein transport, or genetic defects in the hepatic α-tocopherol transfer protein. In addition, premature and very low birth weight infants are in danger of deficiency, and neurological disorders due to protein and energy malnutrition are suggested to be related to vitamin E deficiency (25). In premature children, symptoms such as haemolytic anaemia, thrombocytosis, and oedema have been reported (65). Clinical symptoms in adults include peripheral neuropathy, ataxia, and skeletal myopathy. In adults, prolonged low intakes of vitamin E have been shown to increase haemolytic tendency in vitro without any clinical symptoms (66) and this property can be used as a criterion of vitamin E adequacy.

A new approach to estimate the vitamin E requirement in humans was reported by Bruno et al. (23) based on a plasma α-tocopherol kinetics study among healthy adults given a 22 mg dose of stable isotope-labelled α-tocopherol with different amounts of fat. The estimated rate of α-tocopherol delivery to tissues was 5 mg per day. Using the observed absorption of 33%, the amount of dietary α-tocopherol needed daily to replace irreversible losses would be about 15 mg/d, which seems to support the current recommended daily allowance for vitamin E adopted by the US Institute of Medicine (3). However, absorption rates of 55–79% have been reported (2, 22), which, using the same approach, would lead to markedly lower estimates (6–9 mg/d).

In the absence of more specific measures, the plasma concentration of α-tocopherol is regarded as the most adequate indicator of vitamin E status (5, 67). Because the plasma lipid level influences the α-tocopherol concentration, correction for plasma lipids might be warranted in subjects with high lipid levels when assessing vitamin E status in populations. However, plasma levels might not necessarily display peripheral vitamin E status and might, therefore, be of limited validity (68).

The vitamin E requirement is partly related to the polyunsaturated fatty acids (PUFA) intake, because the antioxidant function of vitamin E is critical for the prevention of oxidation of tissue PUFA (69). In general, the need for greater amounts of vitamin E with higher intakes of PUFA is not a practical problem because most foods rich in PUFA are also rich in vitamin E.

Adults

Among adults, the criteria used for establishing the average requirements and recommended vitamin E intakes are the plasma concentration of α-tocopherol and the relationship to PUFA intake. Data from studies by Horwitt et al. (66) showed an increased haemolytic tendency in subjects with a plasma α-tocopherol concentration below 12 μmol/L, which corresponded to an α-tocopherol:total cholesterol ratio of 2.25 μmol/mmol (70). However, the in vitro haemolytic response was dependent on the PUFA content of the diet, and the limited number of subjects makes this limit uncertain. A plasma level above 16.2 μmol/L has been suggested as an indicator of acceptable vitamin E status (67).

Data from Nordic populations show that average α-tocopherol intakes of 6–10 mg per day are associated with mean plasma α-tocopherol concentrations of 23–28 μmol/L among adults (27, 71–73). Clearly higher concentrations with a range between 33–46 μmol/L have been reported among hyperlipidaemic subjects (74–78). Among a small group of subelite runners with irregular menstrual cycle, the serum concentration of α-tocopherol was low (15.7 μmol/L or 2.7 μmol α-tocopherol/mmol total lipids) apparently due in part to low vitamin E intake of only 5 mg/d (73). In these women, post-exercise osmotic erythrocyte fragility was increased at this low serum α-tocopherol concentration. Low vitamin E status has been observed in individuals who consume large amounts of alcohol (79), and occasional cases of neurological symptoms with ataxia due to vitamin E deficiency have been reported in the Nordic countries (80, 81). Other than these rare cases, the available data indicate that vitamin E status is sufficient in the Nordic populations at current vitamin E intakes. Results from a follow-up of the Finnish ATBC study among older male smokers showed that the lowest mortality during the 19 years of follow-up was among those whose serum α-tocopherol values, adjusted for cholesterol at baseline, were between 13 mg/L and 14 mg/L (30.2–32.5 μmol/L), and above this no further benefit was noted (82). These serum values correspond to a daily intake of approximately 13 mg vitamin E, and this might indicate the vitamin intake level that is sufficient to give protection from chronic diseases and protect from premature death (2). However, these findings might not be generalizable to other groups.

The US Institute of Medicine (3) derived an estimated average requirement (EAR) for adults on vitamin E intakes sufficient to prevent hydrogen peroxide-induced haemolysis mainly based on a study on men by Horwitt (66). However, the study diets contained high amounts of corn oil and

estimates indicate that the proportion of linoleic acid was 11–12 E%, which is above the upper recommended range for PUFA in NNR 2012.

The relationship between vitamin E and PUFA intake could also be used as a criterion for the recommended intake. Based on a suggested requirement of 0.6 α-TE/g PUFA (69) and an average PUFA level of 5% of energy intake (E%), an intake of 7 and 9 mg α-tocopherol/d for women and men, respectively, would be sufficient. The Scientific Committee on Food considered a ratio of 0.4 α-TE/g total PUFA to be adequate (70) for adults provided vitamin E does not fall below 4 mg/d for adult men and 3 mg/d for adult women. Based on this ratio, the estimated average requirement would thus be 5 and 6 mg α-tocopherol/d for women and men, respectively. These values are used as average requirements (ARs) in NNR 2012.

In the absence of signs of vitamin E inadequacy in the general Nordic population and because no new data supporting changes have emerged, the recommended intake (RI) from 2004 is maintained in NNR 2012. The RI of vitamin E is set to 8 α-TE/d for women and 10 α-TE/d for men. Because no human data are available on the biopotency, apart from antioxidative activity, of tocopherols and tocotrienols other than the 2R-isomers of α-tocopherol, the reference values only apply to the 2R-isomers. A number of studies suggest that besides α-tocopherol, other tocopherols and tocotrienols might have important functions and beneficial effects (58, 83) but thus far evidence of their importance in human health is limited.

Children

The recommended intakes for infants and children are generally based on the vitamin E content in breast milk and the relationship between α-tocopherol and linoleic acid or total PUFA (84). The Scientific Committee on Food considered a ratio of 0.4 α-TE/g total PUFA to be adequate also for children (70). In NNR 2012, the recommended intakes are based on a ratio of at least 0.6 α-TE/g total PUFA and a mean intake of PUFA corresponding to 5 E%.

Pregnancy and lactation

The recommended intake value for pregnancy is set to 10 α-TE/d, which is applicable in the last two trimesters and covers the increased intake of energy and PUFA. The recommended intake during lactation is set to 11 α-TE/d and also includes the extra requirement to cover secretion in breast milk.

Reasoning behind the recommendation

In the absence of signs of vitamin E inadequacy in the general Nordic population, and because no new strong evidence supporting changes since NNR 2004 have emerged, the recommended intakes of vitamin E remain unchanged.

Upper intake levels and toxicity

The toxicity of natural vitamin E is low, and this is apparently due to efficient metabolic control that prevents any excess accumulation of the vitamin in the body. No adverse effects have been described from intakes provided by food sources. In a review of 24 clinical trials with vitamin E supplementation published between 1974 and 2003, Hatchcock et al. (85) concluded that few adverse effects have been reported and that doses ≤1,600 IU (1,073 mg RRR-α-tocopherol) were suggested to be safe for most adults. This amount corresponds to the upper safe limit set at 1,000 mg α-tocopherol per day by the US Institute of Medicine (3). The Scientific Committee on Food (86) has proposed an upper level of α-tocopherol of 300 mg/d for adults. This level is mainly based on effects of increased intakes of vitamin E supplementation on blood clotting and includes an uncertainty factor.

Concern regarding potential harm of long-term vitamin E supplementation was initially raised by findings from the ATBC study suggesting increased mortality due to haemorrhagic stroke (47). A meta-analysis of nine RCTs that investigated effects of vitamin E supplementation on stroke risk, which included the ATBC study, showed no association for risk of total stroke (seven studies), a reduced risk for ischaemic stroke (five studies), and an increased risk for haemorrhagic stroke (five studies) (87). Doses ranged from 50 to 300 mg/d. The effects were mainly seen in men, and no significant association for haemorrhagic stroke was seen in the one study of women. Five of the RCTs were secondary prevention studies and two included subjects with high cardiovascular disease risk. Thus, high intakes of supplemental vitamin E might interfere with the blood clotting system, especially with simultaneous use of aspirin.

A small but statistically significant increase in mortality was seen among those supplemented with vitamin E in two meta-analyses of randomized clinical trials (88, 89). Increased mortality was suggested among subjects supplemented with doses of 400 IU per day or higher, and a dose-response

analysis showed progressively increased all-cause mortality even at vitamin E doses of 150 IU/d (88). However, generalization of these findings, which were largely based on studies in patients with chronic diseases compared to healthy adults, is uncertain. Although the causal relationship between vitamin E supplementation and increased mortality remains unclear, this possibility is a reason to be cautious in relation to vitamin E supplementation.

Taken together, the available scientific data suggest that there are no overall benefits of prolonged high intakes of supplemental vitamin E in the general population. The UL established by EFSA for vitamin E as supplement, 300 mg/d, was included in NNR 2004. In the absence of clear risks associated with long-term high supplemental intakes of vitamin E this UL is maintained in NNR 2012. However, additional, long-term studies are warranted.

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18 Vitamin K

No recommendation given due to lack of sufficient evidence

Introduction

Vitamin K is the collective term for compounds with vitamin K activity and having the common 2-methyl-1,4-naphtoquinone ring structure. Vitamin K occurs naturally in two forms. Phylloquinone, or vitamin K_1 (2-methyl-3-phytyl-1,4-naphtoquinone), is synthesised by plants. Menaquinones, or vitamin K_2 (multi-isoprenylquinones, several species), are primarily produced by bacteria. Both forms are found in animal tissues.

Dietary sources and intake

Leafy green vegetables, vegetable oils, and vegetable oil based fat spreads are the main sources of phylloquinone (1–3). Menaquinones, especially MK-4, are found in liver, meat, egg yolk, and dairy products (4). Natto, a fermented soybean preparation, is particularly rich in menaquinone-7. Based on HPLC analyses of vitamin K in a large number of food products and food intake data from various sources in Finland, an average intake of 120 µg/d has been calculated (2, 5). In a nationally representative nutrition monitoring study in Finland, it was estimated that the mean vitamin K intake is 90 µg/d in women and 100 µg/d in men aged 25–64 years (6). In the Norwegian Hordaland study, it was estimated that intake of phylloquinone is 130 µg/d and that of menaquinones is 15–20 µg/d in women and men aged 47–50 years based on food frequency data (7). Using food records, smaller phylloquinone intakes (60–70 µg/d) have been reported in Danish women aged 45–58 years (8).

Physiology and metabolism

Compounds with vitamin K activity are required as cofactors for the carboxylation of glutamic acid to γ-carboxyglutamic acid (Gla) that is needed for the synthesis of factors II (prothrombin), VII, IX, and X, and proteins C, S, and Z that are involved in the coagulation of blood (9). The presence of Gla in these proteins enables them to bind calcium. Several Gla-containing proteins have been identified in bone, including osteocalcin, matrix Gla protein, protein S, and growth-arrest-specific gene (Gas6) protein. Osteocalcin is most likely involved in the regulation of bone mineral maturation, but otherwise the exact function of these proteins in bone is not known. Matrix Gla protein is involved in regulation of soft-tissue calcification. In addition, a number of other Gla-containing proteins with unknown functions have been identified in several tissues (3, 10, 11).

Vitamin K is absorbed in the jejunum and ileum, and it is estimated that 80% of purified phylloquinone is absorbed (12). However, bioavailability from food sources is considerably less, and absorption of phylloquinone from food sources was found to be 10–15% that of phylloquinone absorbed from tablets or suspensions (13, 14). Bioavailability of phylloquinone from kale was approximately 5% as assessed using a stable isotope (15). Fat malabsorption decreases the absorption of vitamin K significantly, and bleeding is an early sign of secondary vitamin K deficiency.

Absorbed vitamin K is transported by chylomicrons in the lymph and is taken up primarily by the liver. In addition to the liver, vitamin K is also stored in bone tissue, the heart, the pancreas (3), and fat tissue (16). Compared to other fat-soluble vitamins, the total body pool is small. Turnover of phylloquinone is rapid, but the turnover of most menaquinones is somewhat slower. Hepatic reserves are rapidly depleted when dietary vitamin K is restricted, and a more or less continuous supply is required to maintain satisfactory body stores.

Because of poor placental transport of vitamin K and consequent deficiency in new-borns, haemorrhage, sometimes intracranial, can occur during the neonatal period.

Vitamin K and bone health

The association between phylloquinone intake or status and the risk of fracture has been investigated in several observational studies, and the majority of them show an inverse association (11). The association between

phylloquinone intake and bone mineral density has been less consistent. Several randomized clinical trials have assessed the effect of phylloquinone supplementation with doses ranging from 200 µg/d to 5 mg/d on bone mineral density and hip fracture, and the majority have reported no effect of the supplementation (1, 17–19). A three-year RCT found that supplementation with phylloquinone, in combination with a mineral + vitamin D supplement, reduced bone loss of the femoral neck in postmenopausal women (20). A one-year RCT in post-menopausal women found that supplementation with calcium and vitamin D alone or in combination with either phylloquinone or menaquinone-7, increased total-body BMD, while significant increases in lumbar spine BMD were only seen in the groups receiving additional vitamin K (21). Earlier interventions using pharmacological doses of menaquinone-4 carried out in Japan supported prevention of fractures, but the quality of those trials has been criticised (22). Recent trials in other populations have not indicated a significant effect of menaquinones on bone mineral density (18, 23, 24). In a meta-analysis of the effect of long-term treatment with oral anticoagulants on bone density, no differences were found at any site other than lower bone density in the ultradistal radius (25). Furthermore, poorer health of the anticoagulant users as compared to non-users could be an important confounder in the association between oral anticoagulants and bone health (26).

Vitamin K and atherosclerosis

Vitamin K-dependent matrix Gla protein inhibits vascular calcification suggesting a role for vitamin K in atherosclerosis. However, human data from observational studies have been inconsistent (27, 28). High phylloquinone intake can reflect a generally heart-healthy diet instead of a direct effect. A randomized clinical trial has suggested that phylloquinone supplementation slows the progression of coronary artery calcification among healthy adults who have existing calcification (29), but no effect has been observed on carotid intima-media thickness (30). A few prospective cohort studies have reported a reduced risk of coronary heart disease at higher dietary menaquinone intakes (31, 32), but more studies are needed before recommendations can be made based on cardiovascular health outcomes.

Vitamin K and other health effects

Anticarcinogenic effects of vitamin K have been reported in animal and cell studies, and an observational study has suggested an association between menaquinone intake and reduced risk of cancer (33). In addition, a role for vitamin K against insulin resistance has been proposed, but human data are still limited (34, 35). Vitamin K is also suggested to reduce inflammation (3, 11).

Requirement and recommended intake

Clinical deficiency is normally not detected after the first few months of life in otherwise healthy individuals. Deficiency has been seen in connection with malabsorption, antibiotic treatment, and parenteral nutrition without vitamin K supplementation.

Determination of the requirement for vitamin K has been difficult because it is not possible to induce clinical deficiency symptoms with a vitamin K depletion diet. Bacterial synthesis in the intestine is not sufficient, however, to maintain normal serum levels of vitamin K. The traditional, insensitive method to evaluate vitamin K status has been to determine the concentration of coagulation factors, most often measured with the prothrombin time test. Newer biomarkers of vitamin K status include serum concentrations of phylloquinone, the degree of carboxylation of vitamin K-dependent proteins, and urinary vitamin K metabolites (1, 11, 36). The U.S. Institute of Medicine (37) determined, however, that these methods could not be used in the assessment of requirements because of uncertainty surrounding their true physiological significance and the lack of sufficient dose-response data. Therefore, the U.S. Institute of Medicine set an adequate intake (AI) of 120 and 90 µg/d for men and women, respectively, based on self-reported median vitamin K dietary intakes in apparently healthy population groups (37).

A depletion-repletion study on 10 young men showed that a reduction of phylloquinone in the diet from the normal level of 80 µg/d to about half that level for 3 weeks resulted in reduced plasma phylloquinone, an increase in undercarboxylated prothrombin in plasma, and reduced urinary excretion of Gla (38). Supplementation with 50 µg/d reversed these changes. However, in another study a similar supplementation did not bring the plasma phylloquinone levels back to original levels after the depletion diet (39). Healthy young individuals with intakes of about 60 to

80 µg/d (corresponding a daily intake of 1 µg/kg) have shown no signs of clinical deficiency, indicating that this intake is adequate for the majority of individuals based on our current understanding of vitamin K's function in blood coagulation (38, 40–42). However, studies indicate that this amount might be insufficient to support adequate carboxylation of extrahepatic vitamin K-dependent proteins (43–48). However, available data to base recommendations are not sufficient.

In NNR 2004 a provisional recommended intake of 1 µg/kg body weight per day was given for both children and adults. This level is maintained in NNR 2012, since no strong scientific evidence for change has emerged.

Breastfed new-borns are at risk of haemorrhage. Vitamin K concentrations in human breast milk have ranged from 0.85 µg/L to 9.2 µg/L with a mean of 2.5 µg/L (37). Using the average concentration as a basis, and average intake of milk, the U.S. Institute of Medicine set an AI at 2 µg/d for infants 0–6 months of age. It is recommended that all new-borns should routinely be given vitamin K (as a 1 mg intramuscular dose or as weekly oral doses) to avoid haemorrhage during the neonatal period, and oral prophylaxis should be continued for the first three months (49, 50).

Upper intake levels and toxicity

No evidence of toxicity associated with high intakes of any form of natural vitamin K has been reported. The Scientific Committee on Food of the European Commission concludes in their report that there is no evidence of adverse effects associated with supplementary intakes of vitamin K in the form of phylloquinone of up to 10 mg/d for limited periods of time (51). This is supported by Cheung and co-workers (19) who reported no increased adverse effects in women receiving 5 mg phylloquinone daily for 4 years. Synthetic analogues such as menadione have been associated with liver damage and haemolytic anaemia and should not be used therapeutically.

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19 Thiamin

Thiamin mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y girls/boys
Recommended intake	RI	1.1	1.4	0.6	0.9	1.0/1.2
Average requirement	AR	0.9	1.2			
Lower intake level	LI	0.5*	0.6*			
Upper intake level	UL	– **	– **			

* 0.8 mg at energy intakes <8 MJ/d and 1.0 mg/d for elderly.
** Not established.

Introduction

Thiamin (vitamin B_1) is essential for the utilisation of carbohydrates and branched-chain amino acids in the body. Thiamin participates in metabolism in the form of thiamin pyrophosphate (TPP, also known as thiamine diphosphate) as a coenzyme for pyruvate dehydrogenase, transketolase, and α-ketoglutarate dehydrogenase in the oxidative decarboxylation of α-keto acids to aldehydes and in the utilisation of pentoses (1, 2). TPP is also a coenzyme for keto acid dehydrogenase in the metabolism of branched chain amino acids (1). Thiamin triphosphate is involved in nerve and possibly muscle function (1).

Dietary sources and intakes

Major food sources of thiamin in the Nordic diet are cereals and cereal products, meat and meat products, and milk and dairy products. The dietary supply of thiamin in the Nordic countries is 1.4–1.7 mg/10 MJ (see chapter on intake of vitamin and minerals in the Nordic countries).

Physiology and metabolism

In vegetable foods, thiamin occurs mainly in the free form and in animal foods mainly in phosphorylated forms that are converted to free thiamin prior to absorption (3, 4). Absorption takes place in the small intestine, generally via an active, carrier-mediated system involving phosphorylation. At high intakes, passive diffusion also takes place (5, 6). Thiamin is also obtained from the normal bacterial microflora of the large intestine and it is absorbed in that region of the gut (4), but the quantitative importance of this source is uncertain. Studies with ^{14}C-labelled thiamin in young men (7) showed that more than 95% of the vitamin was absorbed at intakes of 1–2 mg/d. At intakes above 5 mg/d, the relative absorption rapidly decreases.

After absorption, thiamin is transported to the liver where it is converted to its biologically active form, TPP (2). The total body pool of thiamin in an adult is about 30 mg and most of this is found in the muscles and liver (2, 7). The metabolism of thiamin in the body is relatively fast, and the half-life of ^{14}C-labelled thiamin is estimated to be 9–18 days (7).

Thiamin deficiency causes beriberi. In adults, symptoms include disturbances in the peripheral nervous system and heart function. Early deficiency symptoms can include anorexia, weight loss, mental changes, and muscle weakness. In alcoholics, conditions such as Wernicke's encephalopathy and Korsakoff's psychosis can occur and these are strongly related to insufficient thiamin intake and/or malabsorption (8). Among children, symptoms appear more quickly and are generally more severe and can lead to heart failure.

Commonly used indicators of thiamin status include the enzymatic activity of transketolase in the erythrocytes (ETK_{AC}). The NNR reference values for thiamin consider urinary excretion relative to ETK_{AC} and to thiamin intake. The activity coefficient represents the degree of enzyme activity stimulation in vitro, and the activity of this enzyme depends not only on TPP availability but also on glucose phosphate availability. An activity coefficient below 1.15 is regarded as an indicator of sufficient status, and an activity coefficient of 1.15–1.25 indicates marginal status (9). The concentration of free thiamin and its phosphate esters in blood or erythrocytes has been shown to be a good indicator of thiamin status (10), especially among subjects at risk for thiamin deficiency (10, 11). The usefulness of the activity coefficient as an indicator of thiamin status in population surveys has been questioned, mainly due to its low correlation with erythrocyte thiamin (12).

Thiamin and chronic diseases

Several epidemiological studies have investigated the relationship between intake of thiamin and other B-vitamins (folate, riboflavin, vitamin B_6, and B_{12}) and various cancers, particularly colorectal and breast cancer. No clear evidence for a relation between thiamin intake and different cancer forms has been found (13–15). Thiamin has also been related to neurodegenerative disorders in the elderly such as Alzheimer's disease (16), but evidence for a role in preventing neurological disorders is limited (17).

Requirement and recommended intake

The requirement of thiamin has been related to energy and carbohydrate intake (18, 19), and a clear relationship was shown by Sauberlich and co-workers (20). The current U.S. dietary reference intakes are, however, based on absolute intakes (21). Generally, thiamin intakes are related to energy and protein intakes in the normal intake ranges of populations such as those of the Nordic countries.

Clinical signs of deficiency have been observed at intakes below 0.5 mg/d, which corresponds to 0.05 mg/MJ (0.2 mg/1000 kcal) (18, 21). In other studies, thiamin excretion in the urine and ETK_{AC} were normalised at intakes of 0.07–0.08 mg/MJ (0.30–0.33 mg/1000 kcal).

In the absence of new data, the reference intakes set in NNR 2004 (22) are kept unchanged. The average requirement for adults and children is thus set at 0.10 mg/MJ and the recommended intake is set at 0.12 mg/MJ. However, when planning diets with energy levels below 8 MJ/d the thiamin content should be at least 0.8 mg/d. The recommended intake for infants 0–12 months old is set at 0.10 mg/MJ. The lower limit of intake is estimated at 0.05 mg/MJ.

Studies on pregnant and lactating women indicate a higher requirement as assessed by biochemical parameters (21). An additional intake of 0.4 mg/d during pregnancy and 0.5 mg/d during lactation is recommended.

A few studies indicate that thiamin utilisation is impaired among elderly subjects (23). Therefore, when planning diets for elderly with energy levels below 8 MJ/d, the thiamin content should be at least 1.0 mg/d.

Reasoning behind the recommendation

The reference intakes set in NNR 2004 (22) are kept unchanged. A few studies have explored relationships between thiamin intake and function and a few studies have examined the effects of supplements on various clinical or biochemical outcomes, but these studies do not make a useful contribution to understanding requirements in healthy populations (24). Thus, there is no strong evidence to support a change of the recommendation.

Upper intake levels and toxicity

The EU Scientific Committee for Food (25) concluded that it was not possible to set a safe upper intake level for thiamin due to a lack of data. Habitual thiamin intakes up to 6–7 mg/d have not been associated with negative effects. Oral intakes up to 500 mg/d for periods up to one month have not been associated with toxic effects (25).

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20 Riboflavin

Riboflavin, mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y girls/boys
Recommended intake	RI	1.3	1.7	0.7	1.1	1.2/1.4
Average requirement	AR	1.1	1.4			
Lower intake level	LI	0.8	0.8			
Upper intake level	UL	– *	– *			

* Not established.

Introduction

Riboflavin, formerly known as vitamin B_2, functions as a precursor for the coenzymes FMN (flavin mononucleotide) and FAD (flavin adenine dinucleotide) and as covalently bound flavin. These are necessary components of a number of oxidative enzyme systems and participate in electron transport pathways (1).

Dietary sources and intake

Major sources of riboflavin in the Nordic diets are milk and dairy products, meat, and meat products. The average dietary intake according to national dietary surveys is in the range of 1.8 mg to 2.4 mg/10 MJ (see chapter dietary intake in Nordic countries).

Physiology and metabolism

Riboflavin occurs in foods as a free molecule or as FAD or FMN complexed with proteins. Protein-bound riboflavin is hydrolysed to free riboflavin in the gastrointestinal tract and absorbed via a specific transport mechanism (1–4). This mechanism is saturated at doses of about 30–50 mg. Absorption rates of free riboflavin are reported to be 50–60% at doses

of 2–25 mg (4), and studies on whole foods have shown absorption rates of 60–70% (5).

Riboflavin is mainly stored in the body as flavoproteins and to a lesser degree as free riboflavin. As a consequence, urinary excretion can be affected by changes in nitrogen balance. The urinary excretion of riboflavin can increase under conditions of negative nitrogen balance or during infections, but the opposite can be seen during periods of rapid growth (6). No consistent relationship has been found between riboflavin requirement, measured by urine excretion or retention, and protein intake in situations of positive protein balance. Riboflavin is also involved in folate metabolism because FAD is a co-enzyme for methylenetetrahydrofolate reductase (MTHFR), which influences the metabolism of homocysteine. Low riboflavin status, assessed by erythrocyte glutathione reductase activity (EGRAC), has been associated with increased plasma homocysteine levels in subjects with a specific genotype of MTHFR (7).

Biomarkers of riboflavin status include the activity coefficient of EGR (EGRAC) and the urinary excretion of riboflavin (8). At habitual intakes, urinary excretion is proportional to the intake because the body has a limited ability to store riboflavin (4). Depletion-repletion studies show that the urinary excretion of riboflavin increases gradually with increasing intakes, and a sharp increase at intakes of about 1 mg/d indicates tissue saturation. The EGRAC represents the degree of enzyme stimulation in vitro after addition of FAD. A ratio of 1.0 indicates an absence of stimulation. There is a general relationship between the activity coefficient and the riboflavin intake, which is clearest at intakes up to about 1 mg/d. Different criteria for normal EGR activity have been suggested, and this can complicate the interpretation of results from studies on riboflavin status (1, 8, 9). EGRAC ratios above 1.3–1.4 have been suggested to indicate deficiency and ratios of 1.0 to 1.2 indicate adequate status (1).

Although the metabolic effects of riboflavin deficiency are profound, there are only a few clear-cut clinical symptoms. These include various skin changes, including angular stomatitis and seborrheic dermatitis, and glossitis. Severe riboflavin depletion has been associated with impaired iron status, anaemia, and mental disturbances (13). Isolated dietary riboflavin deficiency does usually not occur, and deficiency is normally seen in association with other nutritional deficiencies.

Clinical signs of riboflavin deficiency have been observed in men at intakes of 0.6 mg/d or less, which corresponds to 0.06 mg/MJ (0.25 mg/1000 kcal) (1, 10–13). In a long-term study, consumption of a diet containing

0.75–0.85 mg/d (0.3–0.4 mg/1000 kcal (4.2 MJ) for up to two years resulted in certain clinical symptoms in one subject.

Powers and co-workers (14) found that supplementation with riboflavin improved some markers of iron status in women with biochemical signs of riboflavin deficiency based on EGRAC (>1.40). However, significant improvements were seen only in those women with EGRAC ratios above 1.65 indicating that the upper threshold for inadequacy might be too low.

Riboflavin and chronic diseases

Several epidemiological studies have investigated the relationship between intake of riboflavin and other B-vitamins (folate, vitamin B_6, and B_{12}) and various cancers – in particular colorectal and breast cancer. Results from prospective or nested case-control studies published between 2000 and 2012 have found no association (15–21). A few retrospective case-control studies have found an inverse relationship (22, 23), but others have found no association (15, 24–27). Results of studies using biomarkers of riboflavin intake are inconclusive (28–32).

Requirement and recommended intake

In setting dietary reference values, previous expert groups have related riboflavin intake to either energy or protein intake (10, 12, 13). The U.S. dietary reference intakes are based on absolute intakes (1). Generally, riboflavin metabolism and intake are related to energy and protein intake at normal intake ranges in populations such as those of the Nordic countries. However, at low energy intakes (below 8 MJ/d) the requirement expressed per MJ might be higher and the opposite might be the case at energy intakes well above 12 MJ/d.

In NNR 2004 (33) the average requirement (AR) was estimated to be 0.12 mg/MJ based on older studies in which riboflavin status was assessed using primarily urinary excretion of riboflavin and to a lesser extent using the EGRAC. There are limited new scientific data for setting reference values for riboflavin.

Few controlled studies in healthy adults in Western populations, and generally with few subjects, have assessed the effects of graded intakes of riboflavin on EGRAC ratios (9, 34, 35). Cut-off ratios used to estimate adequacy were around 1.2–1.25, and recent data indicate that the commonly used EGRAC ratio threshold for inadequacy (1.3–1.4) might be too low (14).

There is insufficient data to change the reference values from NNR 2004 (33). Thus, an RI of 0.14 mg/MJ is maintained, and this applies to both children and adults. This level corresponds to an intake of about 1.5–1.6 mg/d for adult men and 1.2–1.3 mg/d for adult women with moderate physical activity. However, when planning diets the riboflavin content should not be lower than 1.2 mg/d, even at energy intakes below 8 MJ/d (8). For pregnant and lactating women, an extra 0.3 and 0.4 mg/d, respectively, is recommended.

The lower intake level (LI) is estimated to be 0.8 mg/d based on earlier depletion-repletion studies.

Reasoning behind the recommendation

In NNR 2004 (33) the average requirement (AR) was estimated to be 0.12 mg/MJ based on older studies in which riboflavin status was assessed using primarily urinary excretion of riboflavin and to a lesser extent using the EGRAC. There are limited new scientific data for setting reference values and the values from NNR 2004 are therefore maintained.

Upper intake level and toxicity

There are no reports of adverse effects of high riboflavin intakes from dietary sources. The limited studies in which large doses (100–400 mg/d) of supplemental riboflavin have been administered do not indicate any adverse effects (4). There are insufficient data to set a UL for riboflavin.

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21 Niacin

Niacin NE/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y girls/boys
Recommended intake	RI	15	18	9	12	14/16
Average requirement	AR	12	15			
Lower intake level	LI	9*	12*			
Upper intake level	UL	35**	35**			

* 8 NE/d at intakes < 8 MJ/d.
** as nicotinic acid.

Introduction

Niacin is the common term for nicotinic acid, nicotinamide, and derivatives that exhibit the biological activity of nicotinamide. The main function of niacin is in the form of the coenzymes NAD (nicotinamide adenine dinucleotide) and NADP (nicotinamide adenine dinucleotide phosphate) that are involved in a number of redox reactions in the metabolism of glucose, amino acids, and fatty acids.

Dietary sources and intake

Preformed niacin occurs in foods such as meat, fish, and pulses. Protein-rich foods also contribute to the niacin intake through conversion from tryptophan. The diet in the Nordic countries provides 33–43 niacin equivalents (NE)/10 MJ (see chapter on dietary intake in Nordic countries).

Physiology and metabolism

In foods, niacin occurs mainly as NAD and NADP, and these are effectively hydrolysed and absorbed in the intestine (1, 2). Data from human studies indicate near complete absorption of up to 3 grams of nicotinic acid.

In cereals such as maize, niacin can be esterified to polysaccharides and this form is considered to be less available (3). Alkaline treatment during preparation of these foods releases much of the niacin.

In the body, niacin can be formed from the conversion of tryptophan. On average, 60 mg of dietary tryptophan is estimated to yield 1 mg niacin (60 mg tryptophan = 1 niacin equivalent (NE)). Niacin status can be measured by urinary excretion of certain metabolites, including N'-methylnicotinamide and methyl pyridone carboxamides. The body has a limited capacity for storing niacin nucleotides and deficiency symptoms can occur after 50–60 days of consuming a low-niacin, corn-based diet (4).

Niacin deficiency results in pellagra and is mainly observed in populations consuming a diet predominantly based on maize or other cereals with a low protein content and low bioavailability of niacin. Few controlled studies, with few subjects, have investigated the effects of niacin-restricted diets (4, 5). In one controlled study, pellagra developed at an intake of 8.8 NE/d (4). In two other studies, no clinical symptoms were seen in subjects with an intake of 9.2–12.3 NE per day, which is the equivalent to about 1 NE/MJ (4).

Requirement and recommended intake

In the absence of new scientific data, the reference values for niacin given in NNR 2004 remain unchanged. The average requirement is set at 1.3 NE/MJ based on studies in which niacin status has been assessed using urinary excretion of niacin metabolites, which is considered to be an appropriate marker (5). The recommended intake is set at 1.6 NE/MJ. This corresponds to an intake of 16–19 NE/d for adult men and 13–15 NE/d for adult women. However, when planning diets the niacin content should not be lower than 13 NE/d, even at an energy intake below 8 MJ/d. For pregnant women and lactating women, an extra 1–2 NE/d and 4–5 NE/d, respectively, is recommended. This is based on the niacin content of breast milk and the increased energy requirement.

For infants and children over 6 months of age, the recommended intake for adults is applied.

The lower limit of intake is estimated to be 1 NE/MJ, and at energy intakes below 8 MJ/d the lower limit is estimated to be 8 NE/d.

Reasoning behind the recommendation

The focus of interest for niacin requirements over the last decade has been as a "drug" for the treatment of various dyslipidaemias. The reference values for niacin given in NNR 2004 (6) are kept unchanged because there are no new scientific data to suggest a change.

Upper intake levels and toxicity

There are no studies indicating adverse effects of consumption of naturally occurring niacin in foods. Intakes of nicotinic acid, but not nicotinamide, as a supplement or fortificant in the range of 30 mg/d to 1000 mg/d can result in mild symptoms such as flushing. Higher intakes have been reported to induce liver damage. The U.S. Food and Nutrition Board (4) set an upper limit of 30–35 mg/d for adolescents and adults based on the risk of flushing. For children 1–3 years old, they set the UL to 10 mg/d, for children 4–8 years old they set the UL to 15 mg/d, and for children 9–13 years old they set the UL to 20 mg/d. The EU Scientific Committee for Food (1) has proposed an upper limit for nicotinic acid of 10 mg/d and for nicotinamide of 900 mg/d for adults. These levels are also used in the NNR 2012.

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22 Vitamin B_6

Vitamin B_6 mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y girls/boys
Recommended intake	RI	1.2	1.5	0.7	1.0	1.1/1.3
Average requirement	AR	1.0	1.3			
Lower intake level	LI	0.8	1.0			
Upper intake level	UL	25	25			

Introduction

Vitamin B_6 is the common term for pyridoxine, pyridoxal, and pyridoxamine. Pyridoxal phosphate (PLP) and pyridoxamine phosphate function as coenzymes for a number of enzymes that mainly participate in amino acid metabolism (1, 2). PLP is regarded as the most biologically active form and is a co-enzyme for glycogen phosphorylase.

Dietary sources and intake

Important sources of vitamin B_6 are fish, meat, offal, potatoes, and milk and dairy products. The average content in the Nordic diet is 1.6–2.5 mg/10 MJ (see chapter on dietary intakes in Nordic countries).

There is limited information on vitamin B_6 status in Nordic populations (3). Studies on the elderly show good status on average, but up to 30% of 80-year-old Danes had plasma PLP levels below 20 nmol/L. This indicates insufficient intake despite an acceptable reported dietary intake.

Physiology and metabolism

The absorption of the different vitamers takes place via a passive process in the gut. The bioavailability of vitamin B_6 in foods varies and depends on the chemical form of the vitamin (4). Studies indicate that pyridoxal and pyridoxamine raise the PLP concentration by about 10% less than pyridoxine. In most fruits, vegetables and grains, a portion of the pyridoxine occurs as a glucoside, which is considered to be less bioavailable than other non-glucoside forms (4, 5). The content of pyridoxine-glucoside in a mixed American diet has been estimated to be about 15% of the total vitamin B_6 content (6). The bioavailability of vitamin B_6 in a mixed American diet (as assessed by plasma PLP levels and urinary pyridoxine excretion) was estimated to be 71%–79% of the ingested pyridoxine (as hydrochloride), but the design of the study was not optimal (7).

The body stores of vitamin B_6 have been estimated to be approximately 1,000 µmol (170 mg), of which 80%–90% is found in the muscles. The turnover of the vitamin is relatively fast with a half-life of 25–33 days for PLP in plasma (1).

Vitamin B_6 status can be assessed using a variety of biochemical indicators, of which the plasma PLP level is considered one of the most reliable (8, 9). PLP makes up 70%–90% of the total vitamin B_6 in plasma, and this level reflects both the tissue stores and intake of vitamin B_6. PLP levels might also be affected by factors independent of the dietary supply such as age, pregnancy, and physical exercise.

The PLP concentrations among adult subjects with clinical symptoms of vitamin B_6 deficiency have been reported to be less than 10 nmol/L. PLP levels indicative of adequate tissue stores and enzyme functionality have been suggested to be 20 nmol/L or 30 nmol/L (8, 9). Available studies show a direct relationship between vitamin B_6 intake and PLP, but the data are less consistent with respect to the relationship between measured vitamin B_6 intake, PLP, and other biochemical indicators of adequacy such as urinary pyridoxine excretion or xanthurenic acid excretion after a tryptophan load.

The vitamin B_6 status is to a certain extent influenced by the protein intake. In two controlled studies in adult men and women in which a constant vitamin B_6 intake was administered, protein intakes of 1.5 g/kg body weight resulted in approximately 40% lower PLP levels than a protein intake of 0.5 g/kg (10, 11). However, in another study the PLP levels did not vary systematically with the protein intake (12).

Some studies (12, 13) indicate that the PLP level decreases with age, which would suggest an increased vitamin B_6 requirement among elderly subjects. However, some recent longitudinal studies of 2–5 years duration actually found a weak increase in the PLP status of elderly Europeans (14, 15) despite observation of an apparent decrease in vitamin B_6 intake (16). In a study by Pannemans et al. (12), the PLP levels were 30%–40% lower among a group of elderly subjects (27–32 nmol/L) than among young subjects (45–47 nmol/L) after consuming a controlled diet with similar vitamin B_6 content (1.5–1.8 mg/d). At these intakes of vitamin B_6, both young and elderly participants had PLP levels above 20 nmol/L. However, other studies have failed to detect any major difference in vitamin B_6 metabolism due to age (17, 18), although these were of short duration. Thus, the relationship between protein and vitamin B_6 intake in the elderly has so far been difficult to estimate, and the data to establish a vitamin B_6 requirement are conflicting.

The intake of riboflavin might also influence the vitamin B_6 status because flavin enzymes are involved in the formation of PLP. Severe riboflavin deficiency might, therefore, affect PLP levels.

Vitamin B_6 intake might influence the plasma homocysteine level via the trans-sulphuration pathway, and this has been proposed to be a risk factor for coronary heart disease (19). However, homocysteine levels are more strongly influenced by folate status (19, 20). In a randomized controlled trial (RCT) (20) on healthy elderly subjects (mean age 70 years) with PLP levels of 28–30 nmol/L, six weeks supplementation with 1.6 mg vitamin B_6 per day only marginally reduced homocysteine levels after repletion of folate and riboflavin status. Metabolic studies in young, healthy adults using controlled diets with restricted vitamin B_6 contents (<0.5 mg/d) for 30 days did not influence homocysteine levels, although these levels were already low (7 µmol/L) at baseline (21, 21a). In another study, serum concentrations of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) decreased somewhat, but whether this effect was due to the vitamin B_6 restriction or to changes in dietary intake is not clear (21).

Deficiency

Dietary deficiency of vitamin B_6 is rare and is usually seen in combination with a lack of other B-vitamins. Clinical symptoms seen in infants and children include epileptiform convulsions, weight loss, gastro-intestinal problems, and microcytic anaemia (8, 22). Experimentally induced deficiency

among adults leads to various mental disturbances, abnormal EEGs, and various types of skin changes in the face. Among adults, clinical symptoms have generally only been seen with diets containing 0.1–0.2 mg/d or less of vitamin B_6 (8). Insufficient intake of vitamin B_6 also induces certain biochemical disturbances such as increased excretion of xanthurenic acid in the urine and decreased transaminase activity in the erythrocytes.

Health effects

Several clinical and epidemiological studies have been published during the last decade on the relationships between vitamin B_6 intake or biomarkers of intake and various health outcomes including cardiovascular disease (CVD), cancer, and cognitive function.

CVD

Low vitamin B_6 status has been associated with low-grade inflammation and risk of cardiovascular outcomes, including coronary artery disease, myocardial infarction, and stroke (23–27). Results from more recent epidemiological studies in healthy populations are conflicting. No association between dietary vitamin B_6 intake and stroke was found in prospective cohort studies on men (28, 29). An inverse association between plasma PLP and myocardial infarction was found in the US Nurses Health Study (30), but no association was found in men or women in a Dutch nested case-control study (31). PLP levels in the lowest reference quartile of both studies were <27.9 nmol/L with a mean of 16 nmol/L.

Reported intake ranges for vitamin B_6 vary considerably in the literature, mainly due to the use of supplements and, to some extent, to the dietary assessment method used. Although reported intakes from dietary sources seem to be relatively similar in Europe and the US, total intakes in several US studies are higher due to the use of supplements. Inclusion of supplements introduces uncertainties in the interpretation of results because most supplements contain a variety of B-vitamins and other micronutrients. Results from RCTs with supplements containing different combinations of large doses of vitamin B_6, B_{12}, and folic acid or vitamin B_6 alone are mostly negative (23, 32, 33). Study populations have usually included subjects with prior heart disease or who are at high risk for CVD. Studies in which baseline intakes of vitamin B_6 or plasma PLP levels were reported have indicated high or adequate vitamin B_6 intakes (2.5 mg/d) and PLP levels (30–50 nmol/L).

Cancer

Colorectal cancer

Several studies have investigated an association between vitamin B_6 intake or status and the risk of colorectal cancer. Vitamin B_6 is involved in cell proliferation, oxidative stress response, and angiogenesis. A systematic review (SR) and meta-analysis of nine prospective studies from Europe, the US, and Asia (including both cohort and nested case-control studies) showed a marginal and non-significant risk reduction when extreme intakes (quartiles or quintiles) were compared. Heterogeneity among the studies was large, but one Dutch study showed an increased risk of colon cancer among women in the highest intake category (34). Exclusion of this study yielded a pooled risk reduction of 20% (95% CI: 8–31%) (35). In five studies reporting both age-adjusted and multivariate risk estimates, the relative risks (RRs) were 0.79 (95% CI: 0.70–0.90) and 0.85 (95% CI: 0.68–1.07), respectively. Subsequent cohort studies from the US and Europe have either found an inverse association between vitamin B_6 intake (36) or found no significant associations (37–39).

The SR by Larsson et al. (35) also included four studies on the association between blood PLP levels and colorectal cancer and reported a pooled relative risk reduction of 48% (95% CI: 29–62%) when highest intake categories (quartiles or quintiles) were compared to the lowest intake categories. Results from a nested case-control study with the EPIC cohort including 1,365 cases and 2,319 controls showed a risk reduction with increasing quintiles of PLP concentrations (RR per quintile = 0.89, 95% CI: 0.84–94) (40). However, the mean follow-up time was relatively short at 3.6 years.

An RCT from the US in which female health professionals with high risk of CVD were given a daily supplement with folic acid (2.5 mg/d), vitamin B_{12} (1 mg/d), and vitamin B_6 (50 mg/d) did not find any difference compared to placebo in colorectal adenoma incidence during 9 years of intervention (41).

Other cancers

Results from recent prospective studies do not support an association between vitamin B_6 intake or status and breast cancer (42–48), endometrial cancer (49), prostate cancer (50–52), or pancreatic cancer (53, 54). Results from a nested case-control study within the EPIC study found a reduced risk of gastric adenocarcinoma (RR per quartile = 0.78 (95% CI: 0.65–0.93)) with increasing levels of the vitamin B_6 plasma markers

(plasma PLP, pyridoxal, and 4-pyridoxic acid) (55). The association with PLP alone was non-significant.

Cognitive function

A Cochrane Review identified only two RCTs investigating the association between vitamin B_6 and cognitive impairment or dementia, and these studies were only among healthy elderly men and women (55a). The authors found no evidence for any short-term benefit from vitamin B_6 supplementation in improving cognitive functions or mood. This conclusion is supported by prospective cohort studies that found no statistically significant associations between risk of dementia or Alzheimer's disease and total intake of dietary vitamin B_6 and supplements (56–58) or between cognitive function and plasma PLP (59). Only one study (60) found higher plasma PLP to be related to better cognitive performance (memory). Thus, at present there is no evidence for an association between cognitive function and vitamin B_6.

Other health effects

There are some observations implying a role for vitamin B_6 in diabetes (2). An RCT from the US in which female health professionals with high risk of CVD were given a daily supplement with folic acid (2.5 mg/d), vitamin B_{12} (1 mg/d), and vitamin B_6 (50 mg/d) did not find any difference in type-2 diabetes incidence compared to placebo during 7.3 years of intervention (61). However, the reported baseline mean intake of vitamin B_6 was high, about 5 mg/d.

Requirement and recommended intake

In infants, symptoms such as convulsions have been seen with the consumption of formula containing vitamin B_6 at a concentration of 0.06 mg/L (22). Among adults, clinical symptoms of deficiency have not been observed at intakes above 0.5 mg/d. The available controlled studies suggest that PLP levels are related to the level of protein intake in both men and women, but the effect is estimated to be rather limited within the usual range of protein intakes (1.0–1.5 g/kg body weight) seen in the Nordic countries.

Results from epidemiological studies indicate that vitamin B_6 status might be related to certain cancers, especially colorectal cancer, but associations with reported dietary intakes are less conclusive. RCTs have shown that supplements including high doses of vitamin B_6 do not consistently

reduce the incidence of CVD outcomes or colorectal adenomas. Reported intakes and plasma PLP levels at baseline have varied considerably between studies, and this limits the interpretation of their results.

In NNR 2004, the estimated average requirement (AR) of vitamin B_6 for adult men and women was set at 0.013 mg/g dietary protein. This value was based on the results from depletion-repletion studies with controlled intakes of vitamin B_6 (expressed as free pyridoxine) that indicated that PLP levels above 20 nmol/L could be reached at intakes of 0.6–1.0 mg/d or around 0.01 mg/g dietary protein (62–67).

The recommended daily intake (RI) is maintained at 0.015 mg/g protein. However, when planning diets the daily intake of vitamin B_6 should not be lower than 1 mg/d. The values for the RIs for each sex and age group, up to 60 years of age, are calculated based on the reference value for energy intake and the assumption that the protein content of the diet provides 15 E%. For older age groups, RIs are calculated assuming a protein content of 18 E%.

The basic requirement for vitamin B_6 is increased for pregnant women, especially during the last trimester, to cover the extra needs of the foetus. For lactating women, an increased intake is necessary to cover the needs for vitamin B_6 in breast milk. Assuming an increased energy requirement during the last two trimesters of pregnancy and during lactation, an additional intake of 0.2 mg/d and 0.3 mg/d, respectively, is recommended. Although there are data indicating that plasma PLP levels decrease throughout pregnancy, there are insufficient data to support higher intakes (68–70).

For infants and older children, the reference intakes are based on the same value as for adults due to a lack of scientific data to suggest otherwise.

The lower intake level (LI) for adults is set to 0.01 mg/g protein. However, the scientific basis for this LI is weak.

In earlier studies, consumption of high-dose oral contraceptives was found to influence biochemical vitamin B_6 status in some women due, for example, to increased excretion of xanthurenic acid after a tryptophan load (8). The clinical relevance of this effect is uncertain, however, and this observation has not been included when setting the reference values.

Some epidemiological studies have suggested an association between low vitamin B_6 status and/or intake and increased risk of CVD and some cancers, especially colorectal cancer. However, most RCTs using supplements with high doses (50 mg/d) have not shown any major protection against these diseases. The available data are considered insufficient as a basis for setting reference values.

Reasoning behind the recommendation

In NNR 2004, the recommendations were based on depletion-repletion studies among adults using a cut-off for PLP levels of 20 nmol/L. Results from epidemiological studies indicate that low vitamin B_6 status might be related to increased risk of certain cancers. RCTs with supplements including vitamin B_6 have shown no benefits with respect to CVD or cognitive function. The recommendations from NNR 2004 are maintained.

Upper intake levels and toxicity

Adverse effects of high vitamin B_6 intakes have been observed at intakes above 50 mg/d consumed for prolonged periods of months to years. Symptoms include minor neurological symptoms and, at higher levels of 500 mg/d or more, neurotoxicity (71). The EU Scientific Committee on Food concluded that adverse effects are unlikely to occur at doses below 100 mg/d and proposed an upper safe intake level (UL) for adults of 25 mg/d (71). This level is also adopted in the NNR 2012.

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23 Folate

Folate µg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	300 (400[1])	300	80	130	200
Average requirement	AR	200	200			
Lower intake level	LI	100	100			
Upper intake level	UL	–	–			

1 Women of reproductive age are recommended to consume 400 µg/d.
2 There is no evidence for adverse health effects associated with high intakes of folates from natural sources.

Introduction

Folate is a generic term for a group of compounds that includes folic acid and derivatives having nutritional properties similar to folic acid. Folacin is sometimes used synonymously with folate. Folic acid (pteroylmonoglutamic acid, PGA) consists of three parts, a pteridine ring, p-aminobenzoic acid, and glutamic acid. Folic acid is the synthetic form of the vitamin and is not found naturally in foods. Folates in foods consist of the pteroylpolyglutamates that contain one to six additional glutamate units.

Dietary sources and intake

Folate is present in most foods, and high concentrations are found in liver, green vegetables, and legumes. The most important food groups contributing to folate intake are cereal products (including bread) and vegetables, but dairy products, fruits, and berries are also significant sources. The folate content in foods might be underestimated in food composition databases and food tables mainly because common methods of analysis fail to open up the food matrix and liberate all of the folate (1).

Folates are labile, and significant losses in the cooking process are common. However, the cooking losses are dependent on both the food in question and method of processing (2).

The average dietary intake in the Nordic countries is 280–350 µg/10 MJ (see the chapter on dietary intakes in Nordic countries).

Physiology and metabolism

The metabolically active forms of the vitamin are reduced folate – THF – coupled to additional glutamate molecules. These serve as coenzymes in the transport of one-carbon units in amino acid metabolism and nucleic acid synthesis. The carbon can be carried as a methyl group (CH_3-THF), a formyl group (CHO-THF), a methylene group (–CH_2-THF), a methenyl group (–CH^+-THF), or a formimino group (CHNH-THF). Folate coenzymes are required for normal cell division, and deficiency appears first in fast-growing tissues such as the formation of blood cells in bone marrow. A central folate-dependent reaction in amino acid metabolism is the re-methylation of homocysteine to methionine. The methyl donor is 5-CH_3-THF, the synthesis of which is catalysed by the enzyme methylenetetrahydrofolate reductase (MTHFR) and requires vitamin B_{12}. Homocysteine is also removed by a reaction that requires vitamin B_6. Elevated levels of homocysteine in serum can indicate low folate status, thus a normal serum homocysteine level is a measure of adequate folate supply. Other markers of folate status are erythrocyte (or RBC) folate and serum folate concentrations. Erythrocyte folate levels reflect tissue stores and are an indicator of long-term dietary intake. Unlike serum folate, erythrocyte folate is not affected by recent or transient changes in intake and thus might reflect actual intake. However, serum folate is strongly correlated to intake in population studies (3).

Bioavailability

Food folates must be hydrolysed by brush border folate conjugase to monoglutamates prior to absorption in the upper part of the small intestine (4). The degree of absorption varies from one food to another and depends on the chemical form of the vitamin and the presence of absorption inhibitors or enhancers in the meal. Another important factor is the food matrix in which the folate is entrapped (5, 6). It is not possible to predict the overall bioavailability of folates from the composition of a diet (4), and there are few studies on absorption of food folate from composite meals. Bioavailability of folates has traditionally been estimated to be approximately 50% (7), but this level should only be considered a rough estimate. The value

differs among populations and ethnic groups depending on the dietary composition, genetics, and a variety of other factors (1). Furthermore, natural food folate from a diet rich in fruit, vegetables, and liver products was estimated to have a bioavailability of 80% compared to supplemental folic acid (8).

Very few data are available from well-controlled intervention trials with diets naturally rich in folate or with foods fortified with folic acid. Interventions with folic acid-fortified breads or breakfast cereals (9, 10), as well as with meals and foods high in natural folate (11), have resulted in improvement of folate status indicators. In intervention trials with synthetic folate compounds, the natural folate form 5-methyl tetrahydrofolate was shown to be similarly effective or even more effective than the common fortificant folic acid in improving folate status (12, 13). Consumption of leafy green vegetables in the NHANES cohort (prior to mandatory fortification) was associated with higher serum folate levels, and promoting the consumption of fruits and vegetables was considered an effective strategy for enhancing nutritional adequacy (14).

Not enough data exist comparing the bioavailability of different forms of natural folate with each other or estimating folate bioavailability from different food matrices or meals. One study showed that female volunteers with a normal folate status could maintain their status during a 12-week intervention by adding five slices of wholegrain bread to their habitual diet. The women could also improve their status by adding a breakfast meal containing an additional 125 µg of folate for a total folate intake of about 310 µg/d, and such an intake complied with the recommended intake for folate (11). However, no additional improvement in folate status was observed during a 4- to 8-week intervention with an additional 150 µg folate from food (11, 15).

Based on the available literature, it can be concluded that long-term interventions with folates from natural foods and folic acid from supplements or fortified foods in physiological doses (up to 400 µg/d) improve folate status. However, due to a lack of studies, inconsistencies in the available data, and possible limitations in the experimental designs (e.g., unsuitable reference doses) there is not enough evidence for a quantitative estimation of the bioavailability of natural folates and synthetic folic acid (16).

Health outcomes

Pregnancy outcomes

There is convincing evidence that maternal folate status and intake is inversely associated with neural tube defects (NTD). A Cochrane Review found consistent results showing prevention of NTD from daily folic acid supplementation (alone or in combination with other vitamins and minerals) compared with no intervention/placebo or to vitamin and mineral supplements without folic acid. However, there was no statistically significant evidence for any effects on prevention of cleft palate, cleft lip, congenital cardiovascular defects, miscarriages, or any other birth defects (17). With respect to non-neural birth defects, the evidence is *inconclusive*.

In addition, low maternal folate status or inadequate use of folic acid supplements during early pregnancy has been reported to be associated with a higher risk of behavioural problems in the offspring (18–20). Use of folic acid supplements during pregnancy was associated with improved neurodevelopment in 4-year-old Spanish children when adjusting for socio-demographic and behavioural factors (20). The absence of folic acid supplementation in early pregnancy was associated with a higher risk of behavioural problems in the offspring at 18 months of age (18). In Swedish adolescents, higher folate intake and lower homocysteine status have been associated with improved achievement in school and this effect was consistent after correcting for parental education and other confounders (21).

Neurological outcomes in adults

There is *probable* evidence that an adequate folate intake or folate status (i.e. according to the recommendations) protects against poor cognitive function and potentially against some of the neurological disorders that tend to develop in the elderly. However, individuals deficient in vitamin B_{12} might be at risk for cognitive impairment even when serum folate levels are elevated (16).

Cancer

The NNR systematic review (SR) concluded that there is *limited-suggestive* evidence for a protective association between dietary folate at recommended intake levels (>300 µg/d) and risk of colorectal cancer (16). Similar conclusions are found in the report by the WCRF/AICR (22) regarding colorectal cancer. That report also found *limited* evidence that foods containing folate protect against cancers of the pancreas and the oesophagus.

In contrast, the NNR SR identified too few studies to draw any conclusions on associations between folate intake or folate status and cancers of the pancreas, the bladder, or the prostate (16). According to the NNR SR, the overall evidence regarding dietary folate and breast cancer risk is *inconclusive*, and most studies reported no significant associations (16). Although a meta-analysis of epidemiological studies reached similar conclusions regarding overall risk for breast cancer, that report concluded that adequate folate intakes might protect against breast cancer in women with moderate to high alcohol intakes (23). In addition, women of the Malmö Diet Cancer cohort with high folate intakes (i.e. in the highest quintile of the population and at the recommended level of folate intake) had a lower risk of postmenopausal breast cancer compared to the lowest quintile of folate intake (24).

Folate plays an important role in the proliferation of both normal and tumour cells. This has been demonstrated by animal experiments using very high doses (megadoses) of folic acid that resulted in enhancement of tumour formation from pre-carcinogenic stages (25). Because intake levels are generally higher in populations with mandatory folic acid fortification compared to populations with no fortification, there are concerns that the use of folic acid supplements and fortification might have population-wide adverse health effects (26, 27). However, the NNR SR identified too few studies regarding folic acid supplementation and cancer risk, and thus the evidence was graded *insufficient* (16).

Because the need for folate (and methyl groups) is greatest in rapidly growing cells, the potential influence of high folic acid doses on protection from, or stimulation of, tumour formation varies between different types of cancer. Also, inconsistencies and non-significant findings across epidemiological studies might depend not only on differences in study design but also on population differences regarding background diet, lifestyle, and genetic predisposition. For instance, recent SRs and meta-analyses from China, Norway, and the US regarding folic acid supplementation and risk of total cancer separately concluded that there is no significant association (28), a borderline increased risk (29), or a significantly increased cancer risk (30). One of these studies also reported protection of folic acid supplementation against melanoma skin cancer (28), but another reported an increased risk of prostate cancer (29).

Many studies have examined variations in the genes coding for enzymes of key importance for the metabolism of folate such as MTHFR. A meta-analysis that found support for folate in protecting against cancers of the

oesophagus, pancreas, and stomach also indicated that the MTHFR 677TT genetic variant was linked to reduced risk for several cancers (31).

Cardiovascular disease

An adequate dietary folate intake (i.e. according to the recommendations) has been shown to be inversely associated with both severe and subclinical cardiovascular disease (CVD) outcomes (16). Elevated concentrations of homocysteine in the blood have been associated with increased risk of CVD (32, 33). Mild hyperhomocysteinaemia can be caused by a combination of low folate intake and disruption of homocysteine metabolism. A common mutation in MTHFR makes the enzyme less stable and thus lowers its activity. Several studies show that if folate status is low homocysteine is elevated in the less common homozygous TT genotype compared to the heterozygous CT genotype and the more common homozygous CC genotype. If plasma folate is in the upper range of intake, there are little or no differences between the three genotypes (34–38). The frequency of TT-homozygotes in studies of Nordic populations is 5%–8.4% (34, 39). These frequencies are below earlier reported figures – average ≈12% (range 5.4%–16%) – in the Caucasian population (40). In general, men have higher concentrations of homocysteine than women, and the plasma homocysteine concentration tends to increase with age in both sexes (34, 41). The cause and significance of homocysteine increasing with age is not well understood, but the physiological decline in renal function might partly explain this age effect (42).

The effects on disease rates of supplementation with folic acid to lower plasma homocysteine levels are uncertain. A review by Clarke and coworkers (43) showed that dietary supplementation with folic acid (doses ranged from 0.8 mg/d to 5.0 mg/d except for one trial in which 40 mg/d was given) had no significant effects within five years on cardiovascular events or on overall cancer or mortality in the populations studied. A meta-analysis by Clarke et al. (44) further confirmed that available evidence does not support the routine use of B-vitamins to prevent CVD.

Requirement and recommended intake

Adults

The minimum dietary requirement to prevent folate deficiency anaemia in adults has been estimated to be 50–100 µg/d (45), or 50 µg/d of absorbed folate as judged from a daily parenteral dose of this amount (46).

On a virtually folate-free diet, the daily losses from stores in the liver and extrahepatic tissues are about 60 µg/d (47). The daily excretion of folate catabolites is around 0.3%–0.8% of the folate body pool (48, 49). Excretion of intact folate in the urine is between 1% and 5% of the ingested folates (7, 48, 49), but excretion increases at higher intakes (48, 49). Well-nourished individuals excrete 5–40 µg/d in the urine, and the losses from the enterohepatic circulation are similar (47). Based on these criteria, the lower intake level (LI) of dietary folate for adults is set to 100 µg/d.

Assessment of average requirements (AR) and recommended intakes (RI) are based on a combination of indicators reflecting folate status including the concentrations of serum or plasma folate, erythrocyte folate, and serum or plasma homocysteine. Serum and erythrocyte folate concentrations below 6.8 nmol/L and 317 nmol/L, respectively, are considered low (50). Because deficiency of folate is one of several causes of hyperhomocysteinaemia, the total plasma homocysteine concentration is regarded as a functional index of folate status. There is no consensus with regard to the definition of normal or elevated plasma homocysteine levels. The upper limit of the reference range is proposed to be 12 µmol/L (41, 51).

Results from well-controlled intervention trials with diets naturally rich in folate or with foods fortified with folic acid have shown that intakes of 200–300 µg/d are associated with adequate folate status, i.e., erythrocyte or plasma folate levels above the cut-off values (9–11).

Intervention with 120–400 µg/d supplemental folic acid or folic acid fortified foods over a period of 4 weeks to 14 weeks resulted in improvements of several or all folate status indicators, including the concentrations of plasma folate, erythrocyte folate, and plasma/serum homocysteine (9, 52–57). However, while reduced 5-methyl-THF is the dominant folate form in circulating blood, un-metabolized folic acid was detected in circulating plasma after ingestion of folic acid doses of around 400 µg but not doses of 150–200 µg (54). No studies regarding the implications of un-metabolised folic acid on human health are available (16).

An average dietary intake of 200 µg folate every day for 6–8 months maintained normal levels of serum and erythrocyte folate in adult men staying in a metabolic unit and consuming a controlled diet (58). In a study of women aged 17–40 years (n = 45), a calculated mean intake of 190–200 µg/d was sufficient to maintain levels within the normal reference range of serum and erythrocyte folate concentrations over a period of 12 weeks (59).

Results from a depletion-repletion study in 10 women housed in a metabolic unit for 92 days found that a daily intake of 200 µg/d from

food folates resulted in erythrocyte folate levels of above 300 nmol/L, and an intake of 300 µg/d resulted in an additional small rise in plasma folate levels (7).

Observational studies linking dietary intake and levels of plasma and erythrocyte folate are less precise because of possible underestimation of intake due to misreporting and/or inadequate food composition data (1, 60). However, this is counteracted if intake estimates are not corrected for losses during cooking. Despite these reservations, observations of intake and folate status in an apparently healthy population can give useful additional information on folate requirements.

Results from dietary surveys indicate that reported mean or median intakes of folate of 270–316 µg/d were associated with erythrocyte folate levels above 676–959 nmol/L (41). Intakes of 240–325 µg/d were associated with plasma folate levels of 11.3–14.2 nmol/L (34, 61, 62). In the study by Brussaard and co-workers (62), the prevalence of serum folate levels below 7 nmol/L (value indicating adequate folate status (63)) was 6% among those with a mean intake of 325 µg/d and 13% among those with a mean intake of 270 µg/d.

The above-cited studies indicate that intakes around 300 µg/d are sufficient to keep serum and erythrocyte folate levels well above cut-off values.

Keeping the possible underestimation of folate intake in mind and the fact that only a few of the cited studies found individuals with very low intakes, the AR with respect to maintaining normal blood levels is estimated to be 150–200 µg/d. An intake of 300 µg per day should keep folate concentrations in the blood above accepted cut-off values and homocysteine concentrations below accepted cut-off values. Therefore, the estimated AR for adults in the NNR is set to 200 µg/d and the RI to 300 µg/d.

Women of reproductive age represent a specific challenge because there is convincing evidence that an adequate supply of folate before and up to 12 weeks after conception reduces the risk of NTD. However, far from all pregnancies are planned. Therefore, an RI of 400 µg/d for all women of reproductive ages should provide adequate folate supply to women experiencing unplanned pregnancies. Currently, most women in the Nordic countries do not meet the RI for folate. In the Swedish national survey "Riksmaten" 2010–2011, less than 20% of the adult female population reached the RI (64). About 10% of women of childbearing age in Iceland have intakes lower than the AR of 200 µg/d. The average daily intake is 304 µg for men and 248 µg for women. Finnish studies report mean folate intakes in women of reproductive ages ranging from 215 µg/d to 230 µg/d (65, 66).

Pregnancy and lactation

Because folate requirements increase during pregnancy, especially in the last trimester, the risk of deficiencies in women with low folate stores also increases. When folate intake is inadequate, maternal serum and erythrocyte folate concentrations decrease and megaloblastic anaemia can develop. Caudill and colleagues (67) compared pregnant (second trimester) and non-pregnant women on controlled intakes of dietary folate plus folic acid and concluded that 450 µg/d (judged to be equivalent to ~600 µg/d from diet alone) was sufficient to maintain folate status in pregnant women. Both serum and erythrocyte folate concentrations were high at the end of the 12-week study indicating that a lower intake might be sufficient. In NNR 2004, the recommended intake during pregnancy was set to 500 µg per day. This was based on previous studies indicating that 400–500 µg/d is considered sufficient to meet the increased requirement from fast growing tissues during pregnancy (67). Because there are no new scientific data, this recommendation is kept unchanged in NNR 2012.

The concentration of folate in human milk varies throughout the lactation period and is highest between 3 and 6 months (68). Smith and coworkers (69) reported the average concentration of folate in human milk to be 85 µg/L. Based on a daily milk production of 0.75 L and a bioavailability of 50%, the diet should contain approximately 100 µg of extra folate. Lactating women are thus recommended 500 µg/d, and this amount will allow replenishment of stores before a possible new pregnancy.

Infants and children

In NNR 2004, infants were recommended to consume 5 µg folate per kg body weight. A diet that supplied 3.5–5.0 µg/kg maintained growth, haemopoiesis, and clinical well-being in 20 infants aged 2–11 months over a period of 6–9 months (70). Slightly higher serum and erythrocyte folate concentrations were found in infants at the upper end of the intake range. Because no new data on the requirements in children have been identified, the recommendations for children in the age group 1–14 years are kept unchanged in NNR 2012 and are based on 5 µg folate per kg body weight.

Reasoning behind the recommendation

According to the NNR SR, there is *probable* evidence that an adequate folate intake or status protects against poor cognitive function and *limited-suggestive* evidence for a protective effect against some neurological disor-

ders. Folate intake and folate status have also been shown to be inversely associated with CVD outcomes. Folate intake from foods and folate status are also inversely associated with the risk for colon cancer, but findings are less clear regarding other cancers. Long-term intervention trials with natural food folate and folic acid from supplements and fortified foods improve folate status. However, studies and data on quantitative estimation of the bioavailability of various natural folates and synthetic folic acid are sparse and inconsistent. This is partly due to limitations in experimental design.

No evidence emerged from the NNR SR to prompt a change in the current recommendations of 300 µg folate per day for adult women and men and 400 µg/d for women of reproductive age (16). No published data provide evidence regarding the specific folate intake level required to maintain an optimal folate status. There is also no evidence in the evaluated articles to motivate changing any of the other folate dietary reference values (DRV).

Upper intake levels and toxicity

There is no evidence for adverse health effects associated with high intakes of folates from natural sources. However, a high intake of folic acid (either supplemental or from fortification) can mask haematological symptoms caused by deficiency of vitamin B_{12}. The Scientific Committee on Food (71) has set the upper level of intake (UL) of folic acid to 1000 µg/d for adults. The UL for children and adolescents is adjusted on the basis of bodyweight and is 200, 300, 400, 600, and 800 µg per day for children aged 1–3, 4–6, 7–10, 11–14, and 15–17 years, respectively (71). The NNR SR found no evidence to support a change to the UL (16).

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24 Vitamin B_{12}

Vitamin B_{12} µg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	2	2	0.8	1.3	2.0
Average requirement	AR	1.4	1.4			
Lower intake level	LI	1	1			
Upper intake level	UL	[a]	[a]			

[a] Not established.

Introduction

Vitamin B_{12} is the common term for a group of cobalt-containing compounds (corrinoids) that are biologically active in humans. Cobalamin can be used synonymously with vitamin B_{12}. Inactive compounds analogous to vitamin B_{12} are found in the diet, especially in plant foods (1).

Dietary sources and intake

Vitamin B_{12} is mainly found in foods of animal origin. Plant foods might contain trace amounts from bacterial contamination or as a result of fermentation, but the adequacy of these sources is questionable (2). Meat, liver, dairy products, fish, and shellfish, are particularly good sources and are main sources in the average diet (3, 4). Seaweeds and algae contain biologically inactive vitamin B_{12} analogues as well as a few active vitamin B_{12} compounds. However, the adequacy of these sources is uncertain (5). Some seaweeds and seaweed products also contain high amounts of iodine, and this can lead to excessive intake of dietary iodine with adverse effects on thyroid function (2, 6–8). Some plant-based milk substitutes (e.g. soy milk, oat milk, and rice milk) might be enriched with vitamin B_{12} and, therefore, might be an important source of vitamin B_{12} in vegans. The diet in the Nordic countries has a mean vitamin B_{12} content of 6–8 mg/10 MJ.

Vegetarian diets, especially vegan diets, tend to contain low or minimal amounts of vitamin B_{12} (9–11).

Physiology and metabolism

Absorption of vitamin B_{12} is a multistep process. Protein-bound vitamin B_{12} in foods is cleaved from the protein through the action of hydrochloric acid and pepsin in the stomach and then re-bound to haptocorrin (transcobalamin I, TC I). The absorption requires a glycoprotein – intrinsic factor – secreted by the parietal cells of the stomach. In the small intestine, vitamin B_{12} is released from haptocorrin and binds to the intrinsic factor and the resulting complex is absorbed via special receptors in the ileum. Vitamin B_{12} is linked to transcobalamin II in the enterocytes, and the TC II-vitamin B_{12} complex, also called holotranscobalamin (holoTC), enters the blood circulation and is rapidly taken up by the liver, bone marrow, and other tissues (12, 13). Most of the circulating vitamin B_{12} is bound to transcobalamin I (TC I) and has a half-life of several days compared to the half-life of about an hour for holoTC (13). The ileal receptors are saturated at intakes of 1.5 µg to 2.0 µg per meal (12, 14). As the intake increases, the percentage of absorbed vitamin B_{12} decreases. Bioavailability of vitamin B_{12} from various foods, as assessed by whole-body retention or faecal excretion, ranges from about 20% up to 90% at single doses of 0.25 µg to 5 µg (12). It is estimated that approximately 50% of dietary vitamin B_{12} is absorbed by healthy adults with normal gastric function (15, 16).

The function of vitamin B_{12} is related to the metabolism of methyl groups. Methylcobalamin is a cofactor for methionine synthase – the enzyme that catalyses the conversion of homocysteine to methionine. This reaction is closely related to folate function. Adenosylcobalamin is a cofactor for methylmalonyl-CoA mutase in the isomerization of methylmalonyl-CoA to succinyl-CoA. Intracellular deficiency of vitamin B_{12} results in increased plasma concentrations of methylmalonic acid (MMA) and homocysteine.

Total body stores of vitamin B_{12} are reported to be 2–5 mg, of which about a half is in the liver (13). The daily loss of vitamin B_{12} is about 0.1% of the total body pool (14, 17). Clinical symptoms of vitamin B_{12} deficiency generally develop only after several years of insufficient dietary intake or decreased absorption (13).

The most common biochemical markers for assessing vitamin B_{12} status are the mean corpuscular volume of red blood cells (MCV) and the concentrations of plasma vitamin B_{12}, holoTC, and serum MMA. Serum

homocysteine can also be used, but this is more strongly influenced by folate status and only to some extent by vitamin B_6 and riboflavin status. A plasma vitamin B_{12} concentration below 150 pmol/L is considered an indicator of vitamin B_{12} deficiency, although levels between 150 pmol/L and 220 pmol/L can indicate insufficient supply. A decreased level of plasma holoTC is an early sign of negative vitamin B_{12} balance and has been used as a complementary indicator of vitamin B_{12} status together with an increased MMA concentration (13). Both holoTC and MMA levels are increased when kidney function is impaired. During pregnancy, plasma holoTC is considered to be the most suitable marker of maternal supply of vitamin B_{12} to the foetus (18).

An adequate supply of vitamin B_{12} is essential for normal blood formation and neurological function. Vitamin B_{12} deficiency results in macrocytic, megaloblastic anaemia and/or neurological symptoms due to degeneration of the spinal cord, brain, and optic and peripheral nerves. Deficiency caused by inadequate dietary intake is only observed in adults who have been eating vegan diets for many years without taking vitamin B_{12} supplements or including products enriched with vitamin B_{12}, or in infants and children from families following such a dietary pattern (2, 19–21).

Elderly people frequently have low vitamin B12 levels (22) that cannot be attributed to poor intake of vitamin B_{12} (23). A major cause of vitamin B_{12} deficiency is vitamin B_{12} malabsorption, which usually results from atrophic gastritis and hypochlorhydria. This disorder is defined as the inability to absorb protein-bound vitamin B_{12} by a person who is fully capable of absorbing free vitamin B_{12}. Pernicious anaemia, which is a disease caused by a low or missing secretion of intrinsic factor, accounts for only a small fraction of people with low vitamin B_{12} concentrations (22).

A systematic review found inconclusive evidence for an association between subnormal blood levels of vitamin B_{12} and anaemia (24). The result was weakened by the fact that the included studies used different tests to measure the blood levels and used different cut-off points to define vitamin B_{12} deficiency. However, even the studies with the lowest cut-off points for deficiency in which the strongest associations would be expected did not report clear associations.

There are limited data on vitamin B_{12} status in Nordic populations. Results from population surveys among adults have shown a prevalence of low plasma vitamin B_{12} concentrations (<150 pmol/L) of 1%–6% at mean dietary intakes of 5–7 µg vitamin B_{12} per day (25–27). A higher prevalence of low plasma vitamin B_{12} concentrations was found in an earlier study

on a population of Danish 80 year olds (28). In the study by Vogiatzolou et al. (26), 5% had levels below 200 pmol/L and in the study by Loikas et al. (27) among persons aged 65–100 years 32% had concentrations of 150–250 pmol/L.

Health effects

Several randomized controlled trials (RCTs) have tested the effect of supplemental intake of B-vitamins (folic acid, vitamin B_6, and B_{12}) on the risk of cardiovascular disease (CVD) and cancers. Doses of vitamin B_{12} in the studies ranged from 0.4 mg/d to 1 mg/d (29, 30). In addition, cohort studies have investigated the association between vitamin B_{12} intake or status and CVD and cancers.

CVD

Results from a few recent cohort studies show no consistent association between CVD and dietary intakes (31, 32) or plasma concentrations of vitamin B_{12} (33). In the study by Weikert et al. (33), a significantly increased risk of ischaemic stroke (RR = 1.57, 95% CI: 1.02–2.43) was found in the lowest tertile of plasma vitamin B_{12} (median 191 pmol/L) compared to the upper tertile (median 394 pmol/L) in the German cohort of the EPIC study. Among elderly subjects, no association was found between plasma concentrations of vitamin B_{12} and coronary heart disease mortality or all-cause mortality (34).

RCTs using supplements containing combinations of folic acid, vitamin B_6, and vitamin B_{12} (with doses of vitamin B_{12} ranging from 0.4 mg/d to 1 mg/d) did not show significant reductions in the risk for myocardial infarction or angina pectoris, but one of the four studies showed a reduced risk of stroke (35, 36).

Cancer

Results from cohort and nested case-control studies have generally shown no associations between intake or status of vitamin B_{12} and breast cancer (37–40), endometrial cancer (41, 42), or colorectal cancer (43–47). A positive association between plasma levels of vitamin B_{12} and the risk for prostate cancer has been indicated, and a meta-analysis of five cohorts found an odds ratio of 1.10 (95% CI: 1.01–1.19) for each 100 pmol/L increase in plasma vitamin B_{12} concentrations (48). Results from the Finnish ATBC study among heavy smokers (47) found a significantly increased

risk of prostate cancer in the highest quintile of total vitamin B_{12} intake (>14 µg/d) after up to 17 years follow-up.

Cognitive function

Some prospective cohort studies have examined the relationship between cognitive function and vitamin B_{12} intake and/or status among the elderly. The Chicago Health and Aging Project included men and women aged 65 years and older and found that total dietary and supplementary intake of vitamin B_{12} (49) as well as plasma levels of vitamin B_{12} (50) were inversely related to cognitive decline, but the study found no relation between total intake and risk of Alzheimer's disease (51). A prospective study from Oxford University also found that vitamin B_{12} status was inversely associated with cognitive decline (52), but other prospective cohort studies found no association between cognitive decline and vitamin B_{12} status (53–55) or total vitamin B_{12} intake (56).

Intervention studies that have examined the relationship between vitamin B_{12} and cognitive function have used a combination of vitamin B_6, vitamin B_{12}, and folate (57, 58), and a Cochrane Review found that the evidence for any effect of vitamin B_{12} on improving the cognitive function of people with dementia and low serum vitamin B_{12} levels was insufficient (59). Thus, the evidence based on intervention studies of the effect of vitamin B_{12} *per se* among the healthy elderly is limited, and the results from prospective cohort studies are inconclusive.

Requirement and recommended intake

The requirement for vitamin B_{12} to prevent anaemia can be estimated from studies of patients with pernicious anaemia (60). In a study on 20 patients, an intramuscular dose of 0.5–2.0 µg vitamin B_{12} per day was needed for normalizing and maintaining haematological status, and 0.5–1.0 µg was sufficient for most subjects (60). Because these patients are unable to reabsorb vitamin B_{12} excreted in the bile, the physiological requirement for healthy individuals is somewhat lower.

In NNR 2004, an average physiological requirement of vitamin B_{12} was set to 0.7 µg/d based on the above and other studies (1, 15). With correction for absorption losses (50%) the average requirement (AR) was set to 1.4 µg/d for adults. By assuming a coefficient of variation of 15% and adding two standard deviations to allow for individual variation, the recommended dietary intake for adults was set to 2 µg/d.

The US IoM used a similar approach for setting the DRIs. The estimated AR was set to 2.0 µg/d and the RDA to 2.4 µg/d assuming a coefficient of variation of 10%. Herbert (1) calculated the average dietary requirement to be 1.4 µg/d based on the assumptions that adequate body stores were 1,000 µg, the mean half-life was 1,000 days, and the mean absorption was 50%.

In NNR 2004, the recommended intake (RI) for the elderly was the same as for younger adults. Increasing the RI is not considered likely to overcome malabsorption of food-bound vitamin B_{12} or lack of intrinsic factor.

Pregnant women usually have adequate stores to cover the estimated additional requirements of 0.1–0.2 µg/d (15). In NNR 2004, the RI was the same as for non-pregnant women. The RI is maintained in NNR 2012 because there are no new scientific data to suggest a change.

Lactating women are recommended an additional 0.6 µg/d to compensate for the content of vitamin B_{12} in breast milk. This recommendation is maintained in NNR 2012.

For children, the recommended intake in NNR 2004 was based on 0.05 µg/kg body weight, and this is also used as the basis for setting the RI in NNR 2012.

Results from cross-sectional population studies have shown that biochemical indicators of vitamin B_{12} status are stabilised at intakes of about 4–10 µg/d among adults (26, 61, 62). Whether intakes in the above range are associated with long-term benefits is unclear.

The lower dietary intake needed to prevent anaemia is 1 µg/d.

Reasoning behind the recommendation

The reference values for vitamin B_{12} are kept unchanged from NNR 2004 because there are no strong scientific data to suggest that changes are needed. The AR and RI are based on studies on patients with pernicious anaemia. Results from intervention and epidemiological studies do not support benefits of higher intakes for the prevention of common diet-related diseases such as cancer, CVD, or cognitive impairment. There is insufficient evidence for an association between subnormal blood levels of vitamin B_{12} and anaemia among the elderly. However, many elderly persons with impaired gastric function might need supplementing with vitamin B_{12} due to food-vitamin B_{12} malabsorption.

Upper intake levels and toxicity

There are no clearly defined adverse effects of excess vitamin B_{12}, and data are insufficient to establish an upper intake level (UL). There is no evidence that intakes up to 100 µg/d from foods and supplements represent a health risk (63).

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25 Biotin

No recommendation given due to lack of sufficient evidence

Introduction

Biotin is a water-soluble heterocyclic compound formerly known as vitamin H that belongs to the group of B-vitamins. Biotin is essential to all known organisms and is synthesized by plants and microorganisms, but animals, including man, lack the ability to synthesize biotin (1). Biotin in foods exists in free or protein-bound forms.

Dietary sources and intake

Biotin is found in most foods at low concentrations. Offal meats such as liver and kidney, egg yolks, rolled oats, and wheat bran are rich sources (2). The average intake in Danish adults is estimated at 40 µg per day and approximately 70% of this intake is provided by bread and other cereal products, dairy products, and eggs (2).

Physiology and metabolism

Protein-bound biotin is digested in the gut prior to absorption and requires the enzyme biotinidase (1) to cleave the covalent bond between the biotin and the protein (1). Bioavailability of biotin in different foods varies from very low to almost complete utilisation. In general, however, less than half of the biotin in foods is available (3). Raw egg white contains the glycoprotein avidin that binds to biotin and prevents its absorption, but the biotin binding capacity of egg white is lost upon cooking. A potential source of biotin is microbial synthesis in the large intestine, but the quantitative contribution of this source to biotin metabolism is unclear (4).

Biotin functions as a cofactor in carboxylation reactions and assists in the transfer of one-carbon units in the form of activated carboxyl groups during intermediary metabolism. These reactions are important in fatty acid synthesis, in the conversion of pyruvate into oxaloacetate (an intermediate in the citric acid cycle), and in degradation of branched amino acids and odd-chain fatty acids.

When the activity of 3-methylcrotonyl-CoA carboxylase decreases, its substrate is shunted to an alternate metabolic pathway that produces 3-hydroxyisovaleric acid (3-HIA). 3-HIA is excreted in the urine, and an elevated urinary concentration of 3-HIA is regarded as an early and sensitive indicator of biotin deficiency (1, 5). Dietary deficiency of biotin is rare and has only been conclusively demonstrated in individuals on parenteral nutrition without biotin or on diets with chronic ingestion of raw egg white. Biotin deficiency has also been demonstrated in cases of inherited biotinidase deficiency (1). Increased excretion of 3-HIA is frequently seen during normal pregnancy and is reflective of reduced biotin status (6). However, no untoward effects of a marginally reduced biotin status in pregnancy have been documented (7).

Requirement and recommendation

Data providing an estimate of biotin requirements are scarce, and no recommendation is given in NNR 2012. The U.S. Food and Nutrition Board set an adequate intake (AI) for adults of 30 µg/d (8). This reference intake is based upon the intake of biotin in breast-fed infants and is extrapolated to adults by body weight.

Upper intake levels and toxicity

Data on adverse effects from high biotin intake are not sufficient to set a tolerable upper intake level (UL). Although no numerical UL can be established, existing evidence from observational studies indicates that current levels of biotin intake from all sources do not represent a health risk for the general population (9).

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26 Pantothenic acid

No recommendation given due to lack of sufficient evidence

Introduction

Pantothenic acid belongs to the group of B-vitamins. The vitamin is water-soluble and has an important role in intermediary metabolism as part of coenzyme A (1, 2). Pantothenic acid is widely distributed in nature as its name implies (from the Greek *pantos* meaning "everywhere").

Dietary sources and intake

Pantothenic acid is found in many foods. Rich sources of pantothenic acid are offal, dried legumes, and wholegrain products. Data on dietary intakes in the Nordic countries are scarce. The content of pantothenic acid in the average Danish diet is estimated to be approximately 5 mg per 10 MJ (3). The majority (~ 75%) of this amount comes from milk and cheese, cereal products (including bread), meats, and vegetables (3).

Physiology and metabolism

As a constituent part of coenzyme A and acyl-carrier protein, pantothenic acid plays a central role in both catabolism and anabolism as a carrier of acyl groups. The bioavailability of pantothenic acid from foods is 40%–60% (1).

Deficiency of pantothenic acid is rare because of the widespread nature of the vitamin, and deficiency has only been observed in individuals on a diet free of pantothenic acid or given an antagonist to pantothenic acid (4). Deficiency-induced greying of the hair in mice can be reversed by administration of pantothenic acid, but the once popular idea that pantothenic acid might restore hair colour in humans proved fruitless (5, 6).

Requirement and recommended intake

There is insufficient information for estimating the requirement of pantothenic acid, and no recommended intakes are included in NNR 2012. In the U.S., the recommendation for an adequate intake (AI) for adults was set to 5 mg/d (4). This reference intake is mainly based upon estimated usual intakes of pantothenic acid in the US population, and there is no evidence to suggest that this level of intake is inadequate.

Upper intake levels and toxicity

The toxicity of pantothenic acid is very low, and due to a lack of systematic oral intake dose-response studies no upper intake level can be derived. The evidence available from clinical studies using high doses of pantothenic acid indicates that intakes considerably in excess of current levels of intake from all sources do not represent a health risk for the general population (7).

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27 Vitamin C

Vitamin C mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	75	75	30	40	50
Average requirement	AR	50	60			
Lower intake level	LI	10	10			
Upper intake level	UL	–	–			

Introduction

The term vitamin C refers to both ascorbic acid and dehydroascorbic acid because both forms have an anti-scorbutic effect. Although the classical vitamin C deficiency, scurvy, is prevented by small daily intakes (about 10 mg/d) (1), current knowledge of the antioxidant functions of vitamin C has recently had a great influence on the research into daily vitamin C allowances.

Dietary sources and intake

The concentration of vitamin C is high in many vegetables, berries, and fruits (especially citrus fruits). Moreover, intake from vitamin C-enriched products (e.g. juices) can be considerable. The average intake of vitamin C in the Nordic countries is 123–152 mg/10 MJ. The plasma level of vitamin C is a biomarker of fruit and vegetable consumption (1), and the observed associations between plasma (and dietary) vitamin C and health might at least partly reflect other health-enhancing components in fruit and vegetables or even other lifestyle variables.

Physiology and metabolism

Vitamin C is a cofactor for several enzymes involved in the biosynthesis of collagen, carnitine, and neurotransmitters (2). In all these functions, the effects of ascorbic acid are based on its ability to be an electron donor. Consequently, ascorbic acid is oxidised to dehydroascorbic acid. The vitamin is also involved in the biosynthesis of corticosteroids and aldosterone and in the microsomal hydroxylation of cholesterol in the conversion of cholesterol to bile acids. Due to its reducing power, ascorbic acid also improves absorption of non-haem iron.

Ascorbic acid is a potent antioxidant. The vitamin readily scavenges reactive oxygen species and reactive nitrogen species in addition to singlet oxygen and hypochlorite. It is evident that ascorbic acid provides meaningful antioxidant protection in neutrophils, semen, and plasma (e.g. protection against Low density lipoprotein (LDL) oxidation) (2, 3). Ascorbic acid can also regenerate other antioxidants such as vitamin E. As a reducing agent, ascorbic acid can also inactivate carcinogenic substances such as nitrosamines.

Ascorbic acid is absorbed from the intestine by a sodium-dependent, active process that is saturable and dose-dependent. The bioavailability (the efficiency of gastrointestinal tract absorption) is at least 80% for doses of 100 mg or less, 60–70% for doses of 200–500 mg, and less than 50% for doses exceeding 1,000 mg (3). Unabsorbed ascorbate is degraded in the intestine and this process can lead to diarrhoea and intestinal discomfort that are sometimes reported by persons ingesting very large doses from supplements (4).

Vitamin C undergoes glomerular filtration and renal reabsorption. When the transport protein reaches saturation, the remaining vitamin C is excreted in the urine. For doses up to 60 mg no ascorbic acid is excreted (3), for doses of 100 mg about 25% is excreted, for doses of 200 mg about 50% is excreted, and for doses of 500 mg about 80–90% is excreted. The estimated threshold for excretion is about 80 mg/d meaning that essentially no vitamin C is excreted in the urine if the daily intake is lower than the threshold (5).

The body pool of ascorbic acid increases up to a daily intake of approximately 100 mg (6) at which point neutrophils, monocytes, and lymphocytes become saturated (3, 7). When white blood cells become saturated, the plasma ascorbic acid concentration is approximately 50–60 mmol/L but very large doses (2,500 mg/d) are capable of increasing plasma levels

up to 80 mmol/L (3, 7). However, above a daily intake of about 100 mg ascorbic acid, further increases in vitamin C intake lead to gradually smaller increases in plasma vitamin C levels (9). Plasma ascorbic acid concentrations below 23 mmol/L are indicative of marginal vitamin C status (8). This level is reached with an estimated daily intake of 41 mg, but this exact value depends on body size (8). Marginal status can present as decreased antioxidant capacity, fatigue, and irritability (3). Symptoms of scurvy are observed when plasma levels are below 11 mmol/L (8) or the total body pool is below 300 mg (9). Scurvy is very uncommon, but cases have been reported even in Nordic countries (10).

Prospective cohort studies

One way to study the associations between vitamin C and chronic diseases is to use longitudinal population samples, or cohort studies. Unfortunately, these are not ideal for many reasons, the most important of which is that it is almost impossible to make precise estimations of vitamin C intake by using the methods available in studying large populations (mainly food-frequency questionnaires).

Another approach is to study the association of plasma ascorbic acid concentration and disease outcomes. The advantage of this approach is that plasma vitamin C measurements are more accurate and reliable than estimates of dietary vitamin C intake. The drawback to this approach is that plasma vitamin C levels reflect many other dietary and lifestyle variables than just vitamin C intake from the diet. For example, consumption of fruits and vegetables correlates with plasma ascorbic acid concentration (1) but fruits and vegetables also have positive health effects that are not explained by their vitamin C content. In addition, even after multiple adjustments a high intake of fruits and vegetables can still be associated with some unmeasured lifestyle variables that are positively related to health (11, 12).

Eight large prospective studies have found an inverse association between plasma ascorbic acid concentration and cardiovascular and/or all-cause mortality (13–20). Moreover, five prospective cohort studies, all using the EPIC data (European Prospective Investigation into Cancer and Nutrition), have reported on associations between plasma ascorbic acid concentration and type 2 diabetes (21), coronary artery disease (22), stroke (23), blood pressure (24), and heart failure (25). All of these studies showed that the risk for mortality and morbidity was highest in subjects with the lowest plasma concentrations. In contrast, Lawlor et al. (12) did not find

an association between plasma vitamin C concentration and coronary heart disease even after adjustment for socioeconomic conditions.

The relationship between plasma vitamin C concentration and morbidity was curvilinear in most of the above studies, that is, the largest decrease in risk (compared to, for example, the adjacent lower quartile), was observed for those between the 20th and 40th percentile. Studies with cancer mortality as the outcome have also identified the lowest plasma ascorbic acid category as being clearly associated with increased risk (20, 26). However, in some studies (13, 14, 17, 18, 20), decreased risk for cardiovascular mortality (significantly different from the category with highest risk) was only seen in categories with higher plasma ascorbic acid concentration (e.g. above 40th percentile). The same variation was seen in studies using disease incidence as outcome: in some cases, those above the 25th percentile had similarly reduced risk ratios (22, 25), but other reports showed that the risk was still reduced at least up to the median plasma ascorbic acid concentration (21, 23, 24).

Supplementation studies

Supplementation studies are controlled interventions. The definite advantage – compared to observational cohort studies – is that the additional intake of vitamin C is known. However, the estimation of dietary intake (without supplements) is as difficult to assess as in observational studies. Another more principal problem is that the amount of supplemented vitamin C is often significantly higher than the assumed average and recommended intakes (27). Therefore, these studies do not provide much information about variations of intakes that are closer to what can be achieved from ordinary diets.

Bjelakovic and co-workers (27) published a meta-analysis on mortality in randomized trials of antioxidant supplements for the prevention of diseases. They identified only three trials with vitamin C as the single supplement, and only one of these trials (28) had an outcome with major relevance to the NNR. Although Salonen and co-workers (28) reported that vitamin C slowed down atherosclerotic progression in hypercholesterolemic persons, the overall conclusion in the meta-analysis was that vitamin C alone or in combination with other antioxidants had no significant effect on mortality (27).

More recently, two papers based on the Physicians' Health Study II (a randomized controlled trial) concluded that vitamin C did not reduce the

risk of prostate or total cancer (29) or cardiovascular disease (30) in middle-aged and older men. In contrast, a meta-analysis of clinical trials concluded that vitamin C supplementation (median dose 500 mg/d) lowered blood pressure in both hypertensive and normotensive participants (31). However, most trials were short in duration (median 8 weeks) and the trial sizes were rather small and ranged only from 10 to 120 participants. Therefore, larger studies of longer duration are needed to get more insight into the potential blood pressure lowering effects of vitamin C supplementation.

Dietary micronutrient recommendations are typically based on data on deficiency symptoms (lower intake level) and on associations with, and effects on, chronic diseases such as cardiovascular disease, type 2 diabetes, cancer, and osteoporosis. In addition to chronic diseases, vitamin C has a potential effect in the prevention and treatment of the common cold. However, a meta-analysis has concluded that there is no scientific evidence supporting a protective role of vitamin C supplementation in reducing the incidence of colds in normal populations (32). In contrast, randomized trials suggest that vitamin C supplementation might reduce the incidence of the common cold in athletes and other individuals who are under extreme physical stress (33, 34). Moreover, high daily intakes of vitamin C (200–1,000 mg) might reduce the duration of the common cold by approximately 10% (32).

Requirement and recommended intake

Earlier Nordic recommendations (35), as well as the U.S. RDIs from 1989 (9), were based on an estimated adequate body pool (1,500 mg) that would give an ample safety margin against scurvy (36). It was estimated that a daily intake of approximately 30–40 mg would provide a body pool of 900 mg and prevent scurvy for 30–40 days after cessation of this daily intake (9). This intake would also lead to plasma ascorbic acid concentrations above 23 mmol/L (8). By assuming a large inter-individual variation (50%) and to ensure adequate iron absorption, the NNR 1996 was set at 60 mg for both men and women.

Based on the increased recognition of the antioxidant property of vitamin C, it has been proposed that the daily recommendations should be based on its antioxidant activity rather than on antiscorbutic activity or body pool (2). Moreover, it seems clear that the maximal antioxidant activity is reached after higher intakes than the levels needed to prevent scurvy (3). Based on these arguments, the recommendations for vitamin

C intake in NNR 2004 (37) were grounded mostly on the role of ascorbic acid in preventing morbidity and mortality from chronic diseases such as cancer and cardiovascular diseases (37). This reasoning could obviously be challenged because it is mostly based on population studies with the limitations noted earlier in this chapter.

By using the cut-off points in population studies for clearly lowered risk to morbidity and mortality from chronic diseases, such as cancer and cardiovascular diseases (in relation to the lowest 20%), the mean cut-off point was an ascorbic acid concentration of 32 mmol/L (unweighted mean of the eight studies with mortality as outcome) (13–20). This plasma level was chosen as the basis for the average requirement in NNR 2004 (37). The more recent studies on morbidity could indicate a slightly higher optimal level of roughly 40–50 mmol/L as a basis for the average requirements (21–25). However, the evidence might be biased due to the fact that all identified cohort studies relied on the same data.

Using the pharmacokinetic data of Levine et al. (3, 7), a 32 mmol/L concentration of ascorbic acid in the plasma corresponds to a daily vitamin C intake of approximately 60 mg/d in men and 50 mg/d in women. This is close to the intake at which vitamin C begins to be excreted in the urine (3) and corresponds to a body pool of approximately 1,000–1,200 mg (36). By giving a conservative 25% allowance for the inter-individual variation, the daily recommendation is set to 75 mg. Hence, this recommendation can be seen as the meeting point of two approaches: one from population studies and the other from pharmacokinetics (the excretion of vitamin C into the urine). In addition, an intake of 75 mg/d would lead to a plasma vitamin C concentration of around 40 mmol/L (3, 38), which is a level that has already been associated with inhibition of LDL oxidation in vitro (39).

The pharmacokinetics of vitamin C in women appear to be similar to those in men (7). However, at daily intakes below 100 mg, women have slightly higher plasma vitamin C concentrations for a given level of intake. These data suggest that the average requirements are slightly lower in women, which might be due to their smaller body size (9). However, to ensure adequate non-haem iron absorption, the coefficient of variation for women was assumed to be double that for men, and hence the same recommendation is applied for both sexes. Smokers might need about 30 mg more vitamin C daily to reach plasma vitamin C levels comparable to non-smokers (40).

The recommended intake is increased by 10 mg/d during pregnancy to cover the increased needs due to the growth of the foetus and catabolised

vitamin C (9). Breast milk contains approximately 30 mg vitamin C per litre (9). If the average milk production is 750 mL/d, up to 25 mg/d of additional vitamin C would be needed during lactation. This, then, increases the daily vitamin C recommendations during pregnancy to 85 mg/d and during lactation to 100 mg/d.

The average requirements for children were extrapolated from the adult values by assuming growth factors of 1.3 for children younger than 2 years old and 1.15 for children 2 to 13 years old. The recommended intake was calculated as 1.25 times the estimated average requirement.

Reasoning behind the recommendation

The 2004 Nordic Nutrition Recommendation (37) was based on a mean ascorbic acid cut-off point of 32 mmol/L, which was the unweighted mean of the eight studies with mortality as the outcome. The average dietary vitamin C intake leading to this plasma ascorbic acid concentration was estimated to be 60 mg. When adding an estimation for the intra-individual variance (2 SD = 15 mg), the recommendation was set at 75 mg/d for adults. The more recent studies on morbidity could indicate a slightly higher optimal level, roughly 40–50 mmol/L, as a basis for the average requirement. However, the evidence for this might be biased due to the fact that all of the identified cohort studies relied on the same data. Therefore, these data were not regarded as sufficient for raising the average requirement or the recommended intake.

Upper intake levels and toxicity

There is no evidence that high intakes (>1,000 mg/d) of vitamin C are carcinogenic or teratogenic (40). However, high intakes might cause diarrhoea and other gastrointestinal disturbances and possibly also increased oxalate formation and kidney stone formation in susceptible individuals.

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28 Calcium

Calcium mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	800	800	600	700	900
Average requirement	AR	500	500			
Lower intake level	LI	400	400			
Upper intake level	UL	2,500*	2,500*			

* EFSA 2012.

Introduction

The amount of calcium in the body at maturity is approximately 1,200 g and 1,400 g in adult women and men, respectively. Over 99% is found in teeth and bones, and the remainder is present as an easily exchangeable pool in the blood, extracellular fluid, and in all cells in the body. This free calcium plays vital roles in signal transduction both within and between cells, neuromuscular transmission, glandular secretion, and in a large number of enzymatic reactions. The concentration of calcium in plasma is kept constant within narrow limits (2.1–2.6 mmol/L). About half of this is in an ionised form and the other half is bound to albumin. Parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D$) are the most important hormones in the regulation of calcium homeostasis. They contribute to the maintenance of a constant calcium concentration in the plasma by regulating the influx and efflux of calcium in the intestine, bones, and kidneys. Maintenance of a constant concentration of ionised calcium is of vital importance, and calcium homeostasis is probably the most tightly regulated homeostatic mechanism in the body.

In bones, calcium is almost exclusively in the form of hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$). Adult bone tissue undergoes continuous remodelling through resorption by osteoclasts and formation of new bone by osteoblasts. The rate of exchange of calcium between bone and the exchangeable

pool has been estimated to be about 700 mg/d. Bone formation exceeds bone resorption in children, and the rate of remodelling is higher in children than in adults and it is higher in trabecular bones than in cortical bones.

Dietary sources and intake

Milk and dairy products are main sources of calcium in the Nordic countries. Other sources of calcium are fish and fish products, especially when eaten with the bones intact. Pulses, nuts, seeds, and green vegetables have variable amounts of calcium. Mean calcium intakes are 995–1,417 mg/10 MJ.

Physiology and metabolism

In the intestine, dietary calcium is mixed with calcium in the digestive juices. From this mixture, absorption takes place mostly in the upper part of the ileum by passive diffusion or by an active energy requiring process. The latter is dependent on the action of $1,25(OH)_2D$, the hormonal form of vitamin D. Calcium absorption is thus decreased in vitamin D deficiency. The difference between dietary calcium and that lost in faeces is termed net absorption. True absorption is much higher because of reabsorption from, and secretion into, the intestinal juices. The per cent net absorption (or fractional absorption) increases with decreasing amounts of calcium in the diet and also with increased physiological needs such as during infancy, during puberty, and during pregnancy. This adaptation of calcium absorption according to varying intakes and varying physiological needs is of primary importance when assessing the dietary calcium requirement.

Balance studies have shown that when calcium intake is reduced, a period of up to several weeks of negative balance is observed in most individuals before a new steady state is reached (1). The ability to adapt might be reduced by advancing age (2). However, in the extensive balance study by Malm it was shown that adaptation in men might still be efficient at least up to the age of 70 (1). Thus calcium absorption per se seems to be unaffected by ageing (3).

The absorption of calcium can be inhibited by foods containing such factors as phytic acid and oxalic acid in plant foods and phosphates. Because calcium intake in the general Nordic population is generally sufficient and derived from a variety of dietary sources, and because of adaptation, these factors probably play only a minor role in an ordinary mixed diet. This situation might be different in populations with low calcium intake and

consuming large amounts of fibre-rich food such as unfermented bread (4). The net calcium absorption is reported to range from about 30% to 60% in infants and between 25% and 40% in older children depending on absolute intake (5). The net absorption is relatively high during puberty (about 34% from an intake of 925 mg/d (5)) and then declines to 20%–25% in adulthood and even lower at advanced age (4, 6). The varying degree of absorption, both because of adaptation and varying dietary compositions, add uncertainty to the use of net absorption estimates as a basis for determining requirements.

Calcium is lost from the body via the faeces, urine, and skin. Non-absorbed calcium is lost with faeces. In adults with intakes of about 1,000 mg, the loss amounts to about 70% to 80% of the intake, but an appreciable amount is recovered as calcium soaps. Loss via the skin and sweat is generally small, about 20–50 mg/d (7, 8). Under warm conditions or high physical activity, the loss might be appreciably greater.

Loss via urine varies appreciably from person to person. It is generally between 100 and 400 mg/d in adults and is relatively constant within individuals even if the intake varies. In the balance study by Malm (1), the urinary loss decreased from 231 mg/d to 201 mg/d (not significant) upon reduction of the intake from 940 mg/d to 450 mg/d. This finding indicates that the urinary loss of calcium is only affected to a minor degree by the intake and can almost be considered an individual constant. Adaptation to low intake thus does not involve the kidneys to any significant degree. Similar findings have been observed in children (9, 10).

Dietary factors such as intakes of sodium, potassium, and phosphorus as well as acid-base balance have been reported to affect calcium balance (11–14). The long-term effect on bone health, however, is unclear. Inactivity increases bone resorption and loss of calcium. Conversely, weight-bearing exercise contributes to higher bone mineral density (15–17). Post-menopausal women have a higher rate of bone resorption during the night than during the day (18).

Health effects of calcium intake

In connection with the formulation of NNR 2012, a systematic review (SR) was carried out to update the scientific evidence for requirements and for the favourable or harmful health effects of calcium (19). Medline and Swemed+ were searched for publications from 2000 to December 2011 and included all SRs that reported on calcium supplementation or habitual

dietary calcium intake on health outcomes. Meta-analyses, randomized controlled trials (RCTs), and cohort studies were included in a second search covering publications from May 2009 up to March 2011 and in an additional search covering studies until the end of 2011. The SR concentrated on studies reporting on independent effects of calcium, although few recent trials reported solely on the effects of calcium on health outcomes and most trials used calcium together with vitamin D compared to placebo.

Bone health

Children

The NNR SR (19) identified one high-quality SR (20, 21) and one low-quality meta-analysis that covered effects on bone health in children (22). The SR by Winzenberg et al. included 19 RCTs of calcium supplementation either with calcium supplements or dietary calcium in doses of 300–1,200 mg/d compared with placebo over a treatment period of at least three months. The studies included healthy children aged 3 to 18 years (the mean ages of the studies were 4–17 years) from Europe, Israel, the US, China, and Africa, and bone outcomes were measured after at least six months of follow-up. Calcium was provided in the studies as various calcium compounds, milk extracts, or milk minerals. The combined results showed a small, but significant, increase in bone mineral density (BMD) in the upper limb, but this seems mainly have been driven by studies including children from Hong Kong and the Gambia with habitually low calcium intakes. However, the results did not differ by baseline dietary calcium intake when using higher or lower values than the median value (794 mg/d) of the individual study means as the cut-off. The authors state that the finding is unlikely to result in a clinically significant decrease in fracture risk.

A low-quality meta-analysis by Huncharek et al. (22) included 12 RCTs from Hong Kong, the US, Europe, and Israel on the effects of calcium/dairy supplementation on bone health. The calcium supplements in the studies ranged from 300 mg/d to 1,300 mg/d, and the studies used bone mineral content (BMC) in grams as the primary outcome. Initial pooling of 12 RCTs (2,460 subjects) yielded a summary mean difference in BMC of 2.05 g (95% CI: −3.26 to 7.36 g) between the calcium-supplemented and placebo arms. Due to the heterogeneity of the pooled data, the calculated summary mean difference in BMC was considered to be of dubious validity (19). Baseline calcium intakes in studies from Europe and the US were

700–1,200 mg/d, thus an additional intake may have had limited effect on bone health measures.

In an 18-month RCT, 96 girls aged 11–12 years were randomised to receive a calcium supplement or placebo as a beverage (23). Baseline calcium intake was 636 mg/d. After 18 months, the calcium intake was 946 mg/d in the intervention group and remained at the baseline level in the control group (mean 658 mg/d). There were no group differences in BMC or BMD measures at 18 months in intention to treat analyses. However, the absolute gains in BMC were generally significantly greater at most sites, e.g. lumbar spine region (~5% at 18 mo), and bone resorption markers and PTH were significantly lower in the intervention group. At follow-up 42 months after the start of the study, the differences between groups were no longer evident. Vitamin D intake and status were not reported.

The results from RCTs show no or only small effects on bone mineral measures after increasing calcium intakes by 300–1,200 mg/d above habitual intakes (20–23). However, habitual calcium intakes were in general relatively high (> 700 mg/d), and this might have influenced the results. The study by Lambert et al. (23) indicates that an intake of around 900 mg/d would lead to small increases in BMC and BMD compared to an intake of about 600 mg/d in prepubescent girls aged 11–12 years.

Uusi-Rasi et al. (19) concluded that it is likely that calcium intake is a necessary, but not sufficient, condition for the development of a strong skeleton. Adequate vitamin D intake might be a crucial factor when assessing the role of calcium intake because vitamin D status interacts with calcium uptake and metabolism.

Pregnancy and foetal growth

The NNR SR (19) did not identify any SRs regarding calcium intake and bone health during pregnancy. One RCT and one prospective study, both of low methodological quality, that assessed bone health in the offspring were included. The RCT included healthy primiparous women (< 20 weeks gestation) with calcium intakes below 600 mg/d. The results showed that supplementation with 1,500 mg/d compared to placebo throughout the rest of the pregnancy did not impact on foetal somatic and skeletal growth, nor on neonatal characteristics and anthropometric measurements at delivery (24). In a prospective study, Yin et al. (25) found no significant association between maternal calcium intake in the third trimester of pregnancy and bone mass in children at 16 years of age. Calcium intake was assessed with a food frequency questionnaire and mean intake was high at 1,670 mg/d.

In summary, the available data are insufficient to draw conclusions on potential associations between calcium intake during pregnancy and bone health in the offspring (19).

Adults

After puberty and throughout most of adulthood, bone mass is consolidated and calcium requirements are relatively stable. Peak bone mass – the maximum amount of bone that can be accumulated – is reached in early adulthood (26, 27). The peak bone mass that can be attained is affected by genetic background and by lifestyle factors such as physical activity and total calcium intake.

Bone is a dynamic tissue, and a number of clinical studies suggest that increasing bone mass early in life has a transient effect but does not confer protection against later bone loss and osteoporosis (28). The total calcium content of bone at maturity is approximately 1,200 g in women and 1,400 g in men (29, 30). In men, this level remains relatively constant until the onset of age-related bone loss later in life, and in women until the onset of menopause. Caucasian women appear to lose as much as 3%–10% of their trabecular bone per year during the first few years after menopause and about 1% of their cortical bone per year during the first decade after menopause. After this accelerated bone loss period, the loss again levels off during the postmenopausal years. Lifetime losses can reach 30% to 40% of peak bone mass among women and 20% to 30% among men (31).

Women

The NNR SR did not identify any SR published since 2000 reporting on the effects of calcium supplementation on bone health in premenopausal women (19). For postmenopausal women, the SR by Uusi-Rasi et al. (19) included one high-quality (32) meta-analysis, one low-quality (33) meta-analysis) regarding calcium intake and bone health (bone mass and fractures).

The meta-analysis by Chung et al. (32) covered studies from a previous review by Cranney et al. (34). Trials using calcium supplements only and trials with calcium plus vitamin D were analysed together. The supplements typically provided 500–1,200 mg calcium per day and 10–20 µg vitamin D_3 per day. Chung et al. (32) concluded that there was no evidence to change the findings by Cranney et al. (34) that there is good evidence that combined vitamin D_3 and calcium supplementation results in small increases

in BMD of the spine, total body, femoral neck, and total hip. However, no trials that included an intervention group with calcium supplement alone were included.

Men

Data evaluating the effect of calcium intake on bone health in men are scarce and inconclusive (19). Only one low-quality SR was identified (35) that covered assessment of BMD by five prospective and nine cross-sectional studies. Results were inconsistent regarding the association between calcium intake (dietary or supplements) and subsequent bone loss.

Conclusions

In postmenopausal women, calcium supplementation of 500–1,200 mg/d increased BMD in most studies. Calcium plus vitamin D_3 supplementation resulted in small increases in BMD of the spine, femoral neck, and total hip. The data evaluating the effect of calcium intake on bone health in men are scarce and inconclusive.

Fractures

The NNR SR (19) included one high-quality SR (32), one high-quality meta-analysis (36), two low-quality meta-analyses (33, 37), and one low-quality cohort study (38) on the association between calcium intake and fractures. Data reporting the effects of calcium supplementation on bone fractures in children were not identified.

The SR by Chung et al. (32) covered studies from a previous review by Cranney et al. (34) and two additional RCTs identified among studies published after that up to 2009. The SR by Cranney et al. (34) concluded that calcium supplementation (500–1,600 mg/d) with vitamin D (10–20 µg/d, mainly as D_3) is effective in reducing fractures and falls in institutionalized populations, but that evidence for reducing falls in postmenopausal women and older men was inconsistent. However, the only trial that included an intervention group with calcium supplement alone showed no effect on secondary fracture risk (39). This was a secondary prevention.

The meta-analysis by Tang et al. (36) included 29 randomised trials on the effects of supplementation with calcium or calcium in combination with vitamin D on fractures and bone loss. Seventeen trials reported all types of fractures as an outcome. In total 64,897 individuals 50 years or older, 92% of them women, were included. In 16 trials, participants received

calcium-only supplements (500–1,200 mg/d). Effect of supplementation with calcium only on fracture risk showed a borderline significant reduced risk (relative risk (RR) = 0.90, 95% CI: 0.80–1.00). The difference in RR between calcium-only supplementation and calcium combined with vitamin D was small (0.90 vs. 0.87) and not significant. Risk reduction was significantly higher with doses at or above 1,200 mg/d than with lower doses in individuals who were elderly (> 70 years), had low dietary calcium intake (< 700 mg/d), or were compliant with calcium supplementation (> 80%).

The remaining studies included in the SR by Uusi-Rasi et al. (19) did not show any consistent association between calcium intake from the diet or from supplements and fracture risk (33, 37, 38). The meta-analysis of Bischoff-Ferrari et al. (37) included five RCTs that provided 800–1,600 mg/d calcium as a supplement. The pooled results from these studies showed no reduction in hip fracture risk with calcium supplementation, and there was even the possibility of an increased risk. In a Swedish prospective cohort study by Warensjö et al. (38), calcium intakes in the lower quintile (< 751 mg/d) were associated with an increased risk of any fractures and hip fracture as well as osteoporosis compared to the third quintile (882–992 mg/d). Intakes in the upper quintile (> 1,137 mg/d) did not further reduce the risk of fractures but were instead associated with an increased risk of first-ever hip fracture.

In summary, the evidence that calcium supplementation alone reduces fracture incidence is *limited and inconclusive* (19). Calcium supplementation in combination with vitamin D might be effective in reducing fractures in institutionalized populations, but the effect in the general population is unclear.

Pregnancy related outcomes

The NNR SR included two high-quality SRs (40, 41) and one good-quality SR (42) on the effects of calcium during pregnancy (19).

Offspring

The SR by Buppasiri et al. (40) reviewed 21 RCTs involving 16,602 pregnant women. Results showed a significant increase in birth weight of about 65 g (95% CI: 16–114 g) in children whose mothers had used calcium supplements ranging from 300–600 mg/d to 1,000–2,000 mg/d during pregnancy compared to babies of non-supplemented women (19 trials, 8,287 women). However, no significant differences were found for the

proportions of low birth weight infants between the two groups. Dietary calcium intakes were not reported so total intakes cannot be estimated.

In the SR by Bergel et al. (42), including two RCTs and three observational studies, no consistent effect was found on blood pressure in infants. However, in children aged 1–9 years, higher maternal calcium intake (dietary or from supplements) was associated with lower systolic blood pressure (mean 1.92 mmHg, 95C% CI: 0.71–3.14 mmHg). Calcium intakes from supplements were 2 g/d in the RCTs, and the mean total intake was 1.7 g/d in the included observational study. No association with diastolic blood pressure was found. The SR by Hofmeyr et al. (41) included one RCT that found that calcium supplementation with 2 g/d during pregnancy was associated with lower risk of having systolic blood pressure greater than the 95th percentile in children at 5–9 years of age compared to placebo (RR = 0.59, 95% CI: 0.39–0.91). Reported dietary intake at baseline was about 450 mg/d.

In conclusion, there is *probable* evidence for an association between supplemental calcium intakes during pregnancy and birth weight. Because there is no information on total calcium intakes, the relevance with respect to setting DRVs is limited.

No conclusions can be drawn with respect to effects on blood pressure in the offspring.

Mother

Hofmeyr et al. (41) also included 13 randomized trials comparing calcium supplementation of at least 1 g per day (typically 1.5–2 g/d) during pregnancy with a placebo. Meta-analysis of 12 trials including 15,730 women showed that the risk of high blood pressure was reduced by 35% (RR = 0.65, 95% CI: 0.53–0.81), and the effect was greatest in women with low baseline calcium intake (as defined by the trial authors or, if not defined, a mean intake < 900 mg/d). High blood pressure was defined as diastolic blood pressure ≥ 90 mmHg, or an increase in diastolic blood pressure of 15 mmHg or more or an increase in systolic blood pressure of 30 mmHg or more. In four small trials with women at high risk of developing preeclampsia (568 women), the risk of preeclampsia was reduced by 55% (RR = 0.45, 95% CI: 0.24–0.83).

The results on preterm birth were inconsistent. Hofmeyr et al. (41) reported that the overall average risk of preterm birth was reduced in the calcium supplementation group (11 trials, 15,275 women: RR = 0.76, 95% CI: 0.60–0.97). The SR by Buppasiri et al. (40) found no statistically signifi-

cant differences between women who received calcium supplementation and non-users for preterm births < 37 weeks gestation (RR = 0.90; 95% CI: 0.73–1.11; 12 studies with 15,615 women) or < 34 weeks gestation (RR = 1.11; 95% CI 0.84–1.46; 3 trials with 5,145 women).

In summary, There is *suggestive* evidence that calcium supplementation during pregnancy reduces the risk of developing hypertension. However, the effect seems to be dependent on baseline calcium intake, which was not specified, and this limits the interpretation of the results.

Lactation

The NNR SR did not identify any SR regarding calcium intake and lactation (19).

Cancer

The NNR SR (19) included nine articles of which two were SRs of high quality (32, 43) and three were cohort studies of good quality (44–46).

Breast cancer

The SR by Chung et al. (32) concluded that higher calcium intakes were associated with a lower risk of breast cancer in premenopausal women only. In the prospective cohort study by Hjartaker et al. (44) including 64,904 Norwegian women, calcium intakes in the upper category (> 800 mg/d, 4th quartile) tended to be associated with lower risk of pre-menopausal breast cancer compared to the lower category (< 550 mg/d). Mean follow-up was 8.6 years.

Colorectal cancer

Calcium intake as a supplement (1,200–2,000 mg/d), alone or with other agents, was associated with lower risk of recurrence of colorectal adenomas in two SRs of RCTs (43, 47).

The high-quality SR by Chung et al. (32) included the SR by Weingarten et al. (43), 19 prospective cohort studies, and one nested case-control study. The studies included men and women older than 45 years, and follow-up time ranged from 1.4 years to 11.3 years. Of the five cohort studies and the nested case-control study with good methodological quality, two of the cohort studies showed a significant inverse association between total calcium intake and risk of colorectal cancer. In general, risk reductions were observed in intake categories above the lower reference category in

the cohort, which varied between about 500 mg/d and 800 mg/d. Five of the cohort studies included Nordic populations in which calcium intakes in the low and high categories were 500–860 mg/d and 740- >1,420 mg/d, respectively, among women and 760–1,180 and 1,070- >1,950 mg/d, respectively, among men (48–52). Results were mixed, and three studies showed an inverse association (48, 50, 51).

Prostate cancer

The SR by Chung et al. (32) included 12 prospective cohort studies among men with mean ages ranging from 53 years to 67 years. Five studies found a higher risk (adjusted OR 1.2–2.2) among subjects in the highest calcium intake categories (quintile/quartile, 921 to >2,000 mg/d) compared to subjects in the lowest intake categories (455–1,000 mg/d). Seven studies did not find an association between calcium intake and the risk of prostate cancer. Only one cohort study included Nordic populations (heavy smokers in Finland) in which calcium intakes in the low and high reference categories were 1,000 mg/d and ≥ 2,000 mg/d, respectively (53). The results of that study showed an increased risk of prostate cancer with increasing calcium intakes during a mean of 17 years follow-up.

Other cancers

No significant associations were found with endometrial cancer in a low-quality SR (54), with lung cancer in a good-quality prospective cohort study (46), or with total cancer in the SR by Chung et al. (32).

Summary

The NNR SR concluded that there is *suggestive* evidence that higher calcium intakes might be associated with a decreased risk of colorectal cancer (19). Higher calcium intakes have also been associated with an increased risk of prostate cancer. Based on the SR by Chung et al. (32) the evidence is *limited-suggestive*. The evidence for an association with total cancer is sparse and *inconclusive*. The interpretation of the findings is complicated by large variations in habitual calcium intakes in the study populations, the use of calcium-containing supplements, and differences in dietary assessment methods.

Cardiovascular outcomes

The NNR SR included 13 studies (6 SRs, 1 meta-analysis, 3 RCTs, and 3 cohort studies) that addressed different types of cardiovascular outcomes (19). The methodological quality of the SRs was generally high or good except for one (55). Two of the RCTs (56, 57), the meta-analysis (58), and two of the cohort studies (59, 60) were graded as low quality.

Cardio-metabolic markers

Calcium intake and calcium supplementation were not significantly associated with progress of aortic valve calcification, coronary artery calcification (CAC) (59), serum lipids (57, 59), atherosclerosis vascular disease (61), abdominal aortic calcification, or coronary aortic calcification (56). All studies were of low quality.

Blood pressure

Results from three SRs of high quality showed that calcium supplementation lowered systolic blood pressure by 2–4 mmHg in hypertensives and in pregnant women, but no significant effect was seen among normotensives (32, 41, 62). Doses varied from approximately 400 mg/d to 2,000 mg/d with most studies using 1,000 mg/d to 1,500 mg/d.

Cardiovascular disease events

In the SR by Uusi-Rasi et al. (19), calcium intake or calcium supplementation was not significantly associated with stroke (58, 60), cardiovascular events (55), or cardiovascular disease mortality (63). In one study (58), calcium supplementation was associated with increased risk of myocardial infarction but not in the others (55, 61).

Summary

The SR by Uusi-Rasi et al. (19) did not find any consistent evidence for an association between calcium intake and cardiovascular outcomes. The low-quality meta-analysis by Bolland et al. (58) suggested an upward trend in cardiovascular events in older people receiving calcium supplements. However, cardiovascular events were not a primary outcome, the studies were small, and the event frequency was low. Doses ranged mainly from 1,000 mg/d to 1,200 mg/d, but total calcium intake was not reported. The adverse events might, therefore, be associated with calcium intakes of 2,000 mg/d or more. The implications for habitual calcium intakes from

foods are probably limited. No increase in cardiovascular events was found in the good-quality studies (61, 63) or in the low-quality SR of RCTs by Wang et al. (55). The results of the high-quality SR by Dickinson et al. (62) showed that calcium supplementation might improve some vascular risk factors, such as blood pressure, in hypertensives.

Diabetes

The NNR 2012 SR (19) identified one SR of low methodological quality that had type-2 diabetes as an outcome (64). The results showed that a higher calcium intake from supplements, with or without vitamin D or dairy, was associated with reduced risk of type-2 diabetes.

Obesity and body weight control

The NNR SR (19) included three SRs, of which two were of high methodological quality (32, 65) and one was of low quality (66). Two RCTs of low quality were also included (57, 67). No consistent association was found. In the SR by Onakpoya et al. (65), which included seven RCTs with 794 subjects in total, calcium supplementation was associated with a mean difference of −0.74 kg body weight and −0.93 kg body fat compared to placebo. Interventions included calcium supplements of 1,000–1,500 mg/d with a duration of 6–24 months.

The evidence for an effect of calcium intake on body weight is *inconclusive*.

Total mortality

The NNR SR (19) included two SRs, one of high methodological quality (32) and one of low quality (58). The SR by Chung et al. (32) showed no association between calcium intake and mortality from cardiovascular causes. In the SR by Bolland et al. (58), including 15 RCTs, calcium supplementation was not associated with total mortality, but an increased risk of cardiovascular death was observed. In three prospective studies, higher calcium intake was associated with about a 10% to 25% decreased risk in all-cause mortality (60, 63, 68).

In conclusion, no consistent association was found between calcium intake and total mortality or death from various causes.

Requirement and recommended intake

It has been difficult to reach agreement on what should be considered the physiological requirement of calcium. This is because we have no clear deficiency criteria at low intakes due to the slow turnover of bone. When assessing the dietary requirement for calcium, one condition is that vitamin D status should be sufficient because vitamin D influences calcium bioavailability.

In NNR 2004, calcium requirements and recommendations were based on different criteria for various age and sex groups. For children and adolescents, recommendations were based on calcium retention in the skeleton during growth in addition to the requirement for losses in faeces, urine, skin, and sweat. For adults, data from balance studies were used and supplemented with evidence regarding the role of calcium in maintaining a healthy skeleton and preventing fractures.

Children and adolescents

Because over 99% of body calcium is in the skeleton, an adequate calcium intake during the growth period might be critical in maximising BMC. During growth, bone formation exceeds bone resorption. The NNR 2004 reported that the estimated net retention in the skeleton was 160 mg/d during the first year of life, between 70 mg/d and 150 mg/d during the period of 1–10 years of age, and 250 mg/d and 300 mg/d during pubertal growth for girls and boys, respectively (69). These estimates are in line with a recent longitudinal study in adolescent Caucasian boys and girls aged 9–18 years that measured calcium accrual in the skeleton (70). Boys accrued bone mass equivalent to 175 mg calcium per day with a maximum accrual of 296 mg per day at age 14. Girls accrued 122 mg calcium per day with a maximum 235 mg per day at age 13. A previous study in Danish children 6–19 years old found that median annual calcium accretion in pubertal stage III (median age 13 years) was 220 mg/d in girls and 317 mg/d in boys, which were close to the maximum annual BMC increase (71).

Controlled balance studies have been used to estimate calcium needs during growth. The studies have generally been of short duration (2–6 weeks) and measured net retention of calcium calculated from intake and losses in urine and faeces (72–76). Adaptation to low calcium intakes is generally efficient in children and adolescents (72, 73). At intakes of 300–400 mg/d, fractional absorption was around 60% compared to 26%–43% at intakes of 1,200–1,400 mg/d. However, the total absorbed amount is

higher at higher intakes. Maximal net calcium retention has been reported to occur at intakes of 1,100–1,500 mg/d in children aged 9–18 years (74).

A limitation of these studies for setting DRVs is that adaptation, especially to lower intake levels, had probably not yet taken place. Other factors also influence bone growth and calcium accretion, including vitamin D status and physical activity. Insufficient vitamin D status can impair calcium absorption from the gut, but the serum 25OHD concentration below which a significant effect occurs is uncertain. According to the US Institute of Medicine (77) report, an effect is generally seen at serum 25OHD concentrations below 30 nmol/L (77), but a level of 20 nmol/L is reported by Lips (78). Data on vitamin D status are, however, reported in relatively few of the studies.

Results from the SR by Winzenberg et al. (20, 21) included in the NNR SR (19) showed that calcium supplementation among children with a mean age ranging from 4 years to 17 years was associated with a small increase in the upper limb BMD and total body BMC, but the long-term effects on future risk for fractures were uncertain. Overall, baseline dietary calcium intake was relatively high with a median of the individual study means of 794 mg/d. The 18-month study by Lambert et al. (23) showed some improvements in BMC and BMD at a mean intake of about 950 mg/d compared to around 650 mg/d among girls aged 11–12 years. At follow-up 42 months after the start of the study, the differences were no longer evident. Vitamin D intake or status was not reported.

The US IoM (77) used a factorial approach for setting an estimated average requirement (EAR) among children and adolescents up to 18 years of age. Based on several studies, mean calcium accretion or retention estimates were 100 mg/d for infants and 100–210 mg/d for older children up to 18 years (70, 76, 79, 80). However, the resulting EARs are dependent on estimates of fractional absorption and losses via urine, faeces, and skin. Ideally, results from more long-term studies on balance and bone development should be used to establish EARs.

In NNR 2004, no average requirements (ARs) were established. The recommended intake (RI) for children 1–5 years of age was set to 600 mg/d based on estimates for calcium accretion and absorption. The SR by Uusi-Rasi et al. (19) concluded that no strong evidence has emerged to support a change in the recommendation. In the study by Lynch et al. (76), net calcium retention was estimated to be 160 mg/d at an average intake of 550 mg/d. An advantage of this study is that calcium intake during the study period did not differ from the previous habitual calcium intake. The

calcium accretion in the skeleton during this period has been estimated to be 100–120 mg/d (c.f. (76)). Adding losses in sweat of about 30 mg/d results in a net balance of 130 mg/d. An intake of about 500 mg/d is estimated to cover the average requirement and an intake of 600 mg/d the majority. Thus the RI is maintained in NNR 2012.

In NNR 2004 the RI for the age group 6–9 years was set to 700 mg/d. There are limited new data for this age group. In the study by Vatanparast et al. (70), calcium accretion was 100–120 mg/d among boys and 88–99 mg/d among girls aged 9–10 years and these are similar to the estimates for younger children. The IoM used an estimated calcium accretion of 140–160 mg/d for children aged 4–8 years and set an EAR of 800 mg/d and an RDA of 1,000 mg/d. However, these data were based on short-term balance studies and no data on skeletal accretion were reported (80, 81).

Because there is no new strong scientific evidence, the RI of 700 mg/d is maintained in NNR 2012.

Calcium retention is very high during puberty, and the maximum rate of retention coincides with the maximum growth velocity. In the study by Vatanparast et al. (70), mean skeletal calcium accrual among children aged 9–18 years was 121 mg/d and 175 mg/d for girls and boys, respectively. Maximum accrual occurred between ages 14 and 16 among boys (236–296 mg/d) and between ages 12 and 14 among girls (164–235 mg/d), which is in line with a study on Danish children and adolescents (71). Peak bone mass is generally attained during late adolescence (82–84). In the study by Magarey et al. (83), 94% of peak bone mass was attained in girls and 86% in boys at 17 years of age.

Adaptation to the increased demand for calcium is very efficient during puberty (72, 85), and this efficient absorption was one reason for setting the RI for this age group at 900 mg/d in NNR 2004. The SR by Winzenberg et al. (20, 21) showed that a higher calcium intake in the form of supplements was associated with some improvement in bone health indicators, but the long-term effects on future risk for fractures are uncertain. Because calcium absorption appears to be more efficient up to age 24 than in later life (86, 87) the RI of 900 mg/d in NNR 2012 should cover the entire age group of 10–20 years.

Potential interaction of high calcium intakes with iron absorption and iron status was considered in NNR 2004 when setting the RI for adolescents. However, available data do not support a major role for calcium in long-term iron status (88, 89).

Adults

The results from two classical balance studies among Norwegian men (1) and Peruvian men (90) show that humans can adapt to very low calcium intake levels. In the study by Malm (1), calcium balance was monitored in men aged 20–79 years fed controlled diets with two different calcium levels. The diet was based on the Norwegian standard for an "ideal" diet and consisted of common Norwegian foods. The calculated macronutrient composition was protein 14 E%, fat 28 E%, and carbohydrates 58 E%. Thirty-nine men were monitored for several months (mean 7 months) with a mean calcium intake of 940 mg/d (sd 38 mg/d). All except one were in positive balance. The intake was gradually reduced to a mean of 460 mg/d (sd 58 mg/d) in 26 men monitored for several months (mean 7 months). All except three adapted to this lower level of intake. It should be noted that 20 of the men went through a transient period of more or less marked negative balance before they again reached balance. This indicates that adaptation in most individuals is a slow process. In the study by Hegsted (90), 10 male prisoners aged 30–56 years adapted to a low habitual calcium intake and were in balance at intakes of 300–400 mg/d. However, the latter study has limited relevance for the current dietary circumstances in the Nordic countries.

Long-term balance studies in women similar to those in men have not been performed, and it is not clear if women after menopause are at or near balance at the same low levels of calcium intake as in men. Some balance studies indicate that this is not the case (91). However, most of these balance studies have been of short duration and it is not clear if the individuals were adapted to the actual intakes. The bone loss in early menopause due to lack of oestrogen is not appreciably altered by calcium supplementation. However, supplementation studies are difficult to interpret because they alter the rate of bone remodelling in the short term. If they are not of long enough duration (about 4 years), any lasting effect on bone density cannot be evaluated. Most of the supplementation studies included in the NNR SR (19) have been of shorter duration.

The US IoM based their RDAs on intakes of calcium that promote bone maintenance and maintain calcium balance (77). The RDA was set to 1,000 mg/d for the age group 19–50 years based on short-term (minimum 18 days) controlled metabolic ward studies (92). A possible additional limitation is the low vitamin D content of the experimental diets (mean 2.9 µg/8.4 MJ). For the age group 51–70 years, the RDA was set to 1,000 mg/d for men and 1,200 mg/d for women. The higher RDA for

women was based on data from intervention studies suggesting a positive effect on BMD and reduced risk of fractures (36). However, the report states that the meta-analysis by Tang et al. (36) "is compromised by the inability to study a true dose-response relationship; many studies were grouped at the 1,200 mg/d level of intake and could not be used to reveal the effects at lower levels of intake". Data on total calcium intake were missing for several of the included studies. For adults older than 70 years, the RDA was set to 1,200 mg/d for both men and women.

The RI for calcium in NNR 2004 of 800 mg/d was based on long-term balance studies (1) in combination with epidemiological and clinical studies (10, 93–96). Evidence from subsequent supplementation studies or epidemiological studies does not indicate that a higher calcium intake would confer additional health benefits (19).

The NNR 2004 did not set an AR for adults. The results from the balance study by Malm (1) indicate that a mean intake of about 500 mg/d maintained long-term balance in men. In NNR 2004 the lower intake level (LI) was set to 400 mg/d, which is also maintained in NNR 2012.

There are some observations that supplementation with calcium alone in doses > 1,000 mg/d above the usual intake might increase the risk for cardiovascular events and fractures, although results are controversial. The NNR SR concluded that there is *limited-suggestive* evidence that higher calcium intakes are associated with a decreased risk of colorectal cancer. The WCRF/ACIR concluded that calcium probably protects against colorectal cancer. Higher calcium intakes have also been associated with increased risk of prostate cancer, but the evidence is *limited-suggestive*. No association with total cancer was found. The interpretation of these findings is complicated by large variations in habitual calcium intakes in the study populations, the use of calcium-containing supplements, and differences in dietary assessment methods (19, 32, 97).

The evidence that increasing calcium intake in the form of supplements alone reduces fracture incidence is *inconclusive*. Combined supplementation with calcium (500–1,600 mg/d) and vitamin D (10–20 µg/d) has, on the other hand, been shown to reduce the risk of fractures in elderly women living in institutions (19).

The RI of 800 mg/d from NNR 2004 is maintained in NNR 2012 because no strong evidence to change it has emerged. An intake of 500 mg/d is used as the AR.

Pregnancy and lactation

Adaptation is very efficient during pregnancy, and this might be connected to the increased serum levels of 1,25-dihydroxyvitamin D during pregnancy (98–101). Studies among women with low (about 400 mg/d) or high (700–900 mg/d) intakes have shown that both groups increase calcium absorption during pregnancy and that retention corresponds to the amount of calcium deposited in the foetus (98, 99). Supplementation with extra calcium in addition to that in the diet was not shown to influence the retention among women with high calcium intakes (1,300–1,400 mg/d) (102).

The NNR SR concluded that there is *suggestive* evidence that calcium supplementation during pregnancy reduces the risk of developing hypertension and *probable* evidence for an effect on birth weight. However, the effect seems to be dependent on baseline calcium intake, and because total intake was not given the relevance for setting DRVs is limited. The SR did not identify any studies that investigated calcium intake and bone health in pregnancy. In one RCT, calcium supplementation of 1,500 mg/d during pregnancy in women with dietary intakes below 600 mg/d did not impact foetal somatic or skeletal growth or neonatal characteristics and anthropometric measurements at delivery compared to placebo (24). A prospective study showed no significant association between maternal calcium intake in the third trimester and bone mass in their offspring at 16 years of age, although mean calcium intake was high at 1,670 mg/d (25).

In NNR 2004, the recommended calcium intake during pregnancy was set to 900 mg/d because many young women might become pregnant before termination of skeletal growth. This recommendation is maintained in NNR 2012 because no new data supporting a change have emerged (19).

Calcium absorption during lactation does not appear to increase above normal (101, 103, 104). The extra calcium needed for milk production appears to be provided by increased bone resorption combined with renal conservation of calcium (103, 105, 106). These adaptive changes are not influenced by calcium intake. The bone loss resulting from calcium mobilisation is regained when ovarian function is resumed and menstruation reappears.

Based on available data, the NNR 2004 concluded that there was no need for additional calcium intake above that of pregnant women (107), and the RI was set to 900 mg/d. This recommendation is maintained in NNR 2012 because no strong evidence to change it has emerged (19).

Reasoning behind the recommendation

The recommendations for calcium are maintained in NNR 2012 because no strong scientific evidence to change them has emerged.

Upper intake levels and toxicity

The NNR SR did not identify any dose-response data that could be used to evaluate the safety limits of an upper intake level (19). The SR included clinical outcomes, such as all-cause mortality, cancer, and cardiovascular events. Calcium/dairy intake was not associated with an increased risk of total mortality. In cohort studies, all-cause mortality was lowest in subjects in the highest calcium intake category (60, 63, 68). Results for cancer showed either no relation or a protective effect for high calcium intake categories. Prostate cancer was an exception with inconsistent results. Observational studies, however, suggested an increased risk of prostate cancer among men with high daily calcium intakes of above 2,000 mg (45, 108).

The European Food Safety Authority (EFSA) re-evaluated the previous Tolerable Upper Intake Level (UL) for calcium of 2,500 mg/d for adults including pregnant and lactating women (109). Additional placebo-controlled human intervention studies in adults showed that total daily calcium intakes of 2,500 mg from both diet and supplements are tolerated without adverse effects. Health outcomes evaluated were risk of nephrolithiasis, cardiovascular disease, and prostate cancer. Due to lack of data, ULs for infants, children, and adolescents were derived from the UL for adults.

The US IoM used the risk of kidney stone formation to set the UL to 2,500 mg/d and 2,000 mg/d among adults 18–50 years and older than 50 years, respectively (77). The report stated that limited new information was available since the previous report from 1997 (110). For younger age groups, ULs were derived from those of adults after accounting for needs for growth and development.

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29 Phosphorus

Phosphorus mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	600	600	470	540	700
Average requirement	AR	450	450			
Lower intake level	LI	300	300			
Upper intake level	UL	3,000	3,000			

Introduction

Phosphorus plays an essential role in many biological processes. Phosphorus-containing compounds have important roles in bone mineralization, cell structure, cellular metabolism, regulation of subcellular processes, and maintenance of acid-base homeostasis. In biological systems, phosphorus is present as phosphate (1).

The total amount of phosphorus in the body is 800–1200 g, 85% of which is in the skeleton and the rest evenly distributed in all tissues. Phosphate is the most abundant anion in the human body and comprises about 1% of the total body mass. It is predominantly an intracellular anion, and in the skeleton phosphate is generally complexed with calcium in the form of hydroxyapatite. In soft tissue and cell membranes, phosphorus exists mainly as phosphate esters and to a lesser extent as phosphoproteins and free phosphate ions. In the extracellular fluid, about one-tenth of the phosphorus content is bound to proteins, one-third is complexed to sodium, calcium, and magnesium, and the remainder is present as inorganic phosphate (1, 2). Serum phosphate concentration varies with age, with the highest concentration in infants. The concentrations decline towards adulthood, and the normal range in adults is 0.8–1.5 mmol/L (1).

Dietary sources and intake

Meat, milk, grain products, and legumes are high in phosphorus and contribute the largest amounts to the total dietary phosphorus intake in an average diet in the Nordic countries. The bioavailability of phosphorus differs among food sources. Some forms of dietary phosphorus are less bioavailable, especially the phosphorus in the phytic acid found in the outer layer of cereal grains. The actual bioavailability depends on the way these grain products are processed and the amount of residual phytate. Little is known about phosphorus bioavailability from different food sources, but inorganic phosphate salts such as additives used in food processing are readily hydrolysed in the gastrointestinal tract and absorbed (3–5).

Diets in the Nordic countries contain 1.560–1.940 mg/10MJ. The intake from food additives is largely unknown, but it is likely to be of significant importance.

Physiology and metabolism

The understanding of phosphorus homeostasis has increased dramatically in the past 5–10 years with the discovery of two new compounds, Klotho and fibroblast growth factor 23 (FGF23). The FGF23-Klotho system regulates body phosphorus content together with parathyroid hormone (PTH). After ingestion of phosphorus, both PTH and FGF23 are released, the former from the parathyroid glands and the latter from bone, probably from osteocytes (1).

Dietary phosphate is absorbed by the epithelium of the duodenum and jejunum in the small intestine via both passive diffusion, which depends on the amount of phosphorus in the intestine, and an active sodium-dependent process that is regulated by calcitriol (1,25-dihydroxyvitamin D_3. Calcitriol in turn is regulated by serum phosphate such that a decrease in phosphate concentration leads to an increase in the synthesis of calcitriol. Phosphate absorption is thought to depend on the function of sodium-dependent phosphate transporters. The most highly expressed phosphate transporter in the small intestine is NaPiIIb, and the activity of NaPiIIb is regulated by calcitriol (1).

Net absorption from a mixed diet has been reported to vary between 55% and 70% in adults and between 65% and 90% in infants and children. There is no evidence for a dose-response relationship (3).

The kidney is the major organ involved in the regulation of short-term phosphate homeostasis. PTH, FGF-23, and dietary phosphate are considered to be the major regulators of NaPiIIa, which is the main sodium-dependent phosphate transporter in the kidney. Brush border membrane expression of NaPiIIa is reduced within minutes in response to PTH and within 2 h in response to altered dietary phosphate load (1, 6). There is little phosphate reabsorption in the proximal straight tubule in the presence of PTH. An increase in PTH enhances the urinary excretion of phosphorus by removing the sodium phosphate co-transporter from the apical membrane of the proximal tubule, whereas FGF23 and its cofactor, Klotho, shut down the synthesis of the sodium phosphate co-transporter. FGF23 and Klotho also decrease the synthesis of calcitriol and this leads to a decrease in intestinal phosphate absorption. As a result of these events, more phosphorus is excreted in the urine and less phosphorus is absorbed from the intestine and the serum phosphorus level is reduced (1, 7). Other factors that can affect the renal handling of phosphate include bicarbonate concentrations, sodium reabsorption rates, and the effects of other hormones such as growth hormone and insulin (8).

Chronic phosphorus insufficiency results in impaired bone mineralization, rickets, and osteomalacia. In addition to these skeletal defects, the clinical consequences of phosphorus insufficiency include problems with the nervous system, muscle tissue, and kidney function. Low dietary phosphorus intake is rare, and intestinal absorption of phosphorus is very efficient. Renal regulation of phosphorus excretion is the most important step in phosphorus homeostasis and this is also a very efficient process. Although vitamin D deficiency or resistance decreases phosphorus absorption, hypophosphataemia due to low intestinal absorption is rare and only becomes apparent when phosphorus deprivation has continued for a long time, such as in the case of diarrhoea (9).

Requirement and recommended intake

The exact requirement for phosphorus is not known, but 400 mg daily is considered adequate for adults to maintain a plasma concentration of 0.8 mmol/L.

The EU Scientific Committee for Food suggested that phosphorus intakes should correspond on a molar basis with those of calcium and, therefore, proposed an average requirement (AR) of 400 mg/d and a population reference intake of 550 mg/d (10).

The US Food and Nutrition Board (FNB) has set the Estimated Average Requirement (EAR) for phosphorous at 580 mg/d for both men and women aged 19–70 years using serum inorganic phosphorus level as the criterion (11). The RDA (Recommended Dietary Allowance) is 700 mg/d for both genders after applying a coefficient of variation of 10%. For adolescents 9–18 years of age, the RDA is 1,250 mg phosphorus per day based on both dietary data and estimated additional needs during growth (11).

In NNR 2004, the recommended intake (RI) for phosphorus was 600 mg per day for both men and women. There are no substantial new data since then to indicate that these values should be changed. This intake level adheres to the view that an equimolar relationship between calcium and phosphorus is used as a basic principle for recommendations (1 mmol calcium = 40 mg, 1 mmol phosphorus = 30.9 mg). The RI values for children are also maintained and are based on the same considerations.

Reasoning behind the recommendation

The recommendations for phosphorus are maintained in NNR 2012 because no strong scientific evidence to change them has emerged.

Upper intake level and toxicity

Excessive phosphorus is toxic to the body by causing kidney and bone damage, vascular calcification, and premature ageing (12). The harmful effects of phosphorus are well documented in patients with chronic kidney disease (CKD) in which excess phosphorus results in vascular disease and bone loss. Over the last 5–10 years, new effects of increased serum phosphorus concentrations and high phosphorus intake on the vascular system and the skeleton have been observed in healthy populations with no kidney disease. Excessive dietary phosphorus intake might be one cause of mildly elevated serum phosphorus concentrations in persons with relatively normal kidney functions (7).

The potential adverse effects of phosphorus intakes at the high end of the range of habitual intakes on bone metabolism have been investigated and debated in recent decades (5, 13). A high-phosphorus diet produces mild hyperparathyroidism and reduces calcitriol concentrations. Moreover, it has been demonstrated in experimental settings in animals and humans that high-phosphorus diets increase bone resorption and decrease bone formation – at least in combination with low calcium diets. Some

cross-sectional studies have indicated that phosphorus intake, especially as food-additive phosphorus, is associated with higher PTH concentrations and could be deleterious to bone health (9, 14). However, results from a meta-analysis of 12 RCTs on phosphate supplementation with study periods ranging from 1 to 56 days showed that supplemental dietary phosphate was associated with decreased calcium in the urine and increased calcium retention (15).

The use of food additives containing phosphorus in the food industry is widespread. It has been estimated that phosphorus added during processing can represent an average daily intake of 500 mg/d in the US. This value ranges from 300 mg/d to 1,000 mg/d depending on individual food preferences (1). There are no corresponding estimates in the Nordic countries.

There is also a discussion as to whether data on phosphorus in food composition databases might underestimate the contribution from phosphate additives. This is not a problem specific for phosphorus, and the ability to accurately capture dietary intakes is related to the food coverage in the database and the proportion of values based on chemical analysis as well as to the dietary assessment method used.

Hyperphosphataemia and abnormal mineral metabolism have been recognized as risk factors in the development of vascular calcification in patients with CKD and are associated with increased mortality in both pre-dialysis and dialysis patients (16, 17). In the general population, phosphorus concentrations in the upper quartile of the normal range are also associated with increased cardiovascular and all-cause mortality (18, 19).

Some studies have shown that the risk of end-stage renal disease and mortality increases with increasing serum phosphorus within the normal range (20). Whether this is related to dietary intake of phosphorus is unclear. No significant association between dietary phosphorus intake and mortality was seen in subjects with moderate CKD during a mean follow-up of 6.5 years in the US NHANES III study (21). Dietary intake, however, was assessed with only one 24-h recall. Results from another prospective study among patients with cardiovascular disease with normal or moderate CKD showed decreased risk of cardiovascular events with increasing levels of urinary phosphorus excretion after a median of 7.4 years follow-up (22). There was no significant association with all-cause mortality.

Cardiovascular calcification is not only the result of precipitation of calcium and phosphate. Recent studies have documented that high phosphate is one factor that triggers the differentiation of vascular smooth muscle cells into osteoblast-like cells (18). Even transient increases of

serum phosphate concentrations, e.g. post-prandial hyperphosphataemia, can promote endothelial dysfunction (23, 24).

The US FNB set a Tolerable Upper Intake level (UL) of 4,000 mg/d in 1997 (11). A subsequent evaluation by the European Food Safety Agency (EFSA) was published in 2006. The EFSA concluded that there was not enough scientific evidence (in 2005) to establish a UL but stated that normal, healthy persons can tolerate intakes up to at least 3,000 mg/d (3).

In NNR 2004, the UL was set to 4,000 mg/d based on the evaluation by the US FNB (11). In NNR 2012, a provisional UL of 3,000 mg/d is used based on the EFSA evaluation. Given the recent observations of possible adverse health effects, a re-evaluation of the UL should be considered.

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30 Magnesium

Magnesium mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	280	350	120	200	280
Average requirement	AR	–	–			
Lower intake level	LI	–	–			
Upper intake level	UL	–	–			

Introduction

Magnesium is a divalent ion and is involved in a range of biochemical reactions and cellular functions. The metabolism and requirements for magnesium are still poorly understood.

Dietary sources and intake

Magnesium is found in abundance in green, leafy vegetables, legumes, and whole grain cereals. Magnesium concentrations are especially high in dark chocolate, nuts, and coffee. "Hard" water contains more magnesium than "soft" water and can contribute to total magnesium intake. The average dietary intake ranges from 354–479 mg/d (see the chapter on Dietary intake in Nordic countries).

Physiology and metabolism

The content of magnesium in the body is regulated by absorption and excretion. At normal dietary intakes, 20–60% is absorbed and this percentage is inversely proportional to the amount of magnesium ingested (1, 2). It is uncertain to what degree the composition of the diet influences absorption (3). Plasma concentrations are probably regulated via the kidneys and are kept within a narrow range of 0.75–0.95 mmol/L. When magnesium intake is low, kidney excretion is reduced.

A large number of biochemical and physiological processes are regulated by magnesium. Magnesium is necessary for energy-dependent membrane transport, gene regulation, sustained electrical potential in nerves and cell membranes, and for transmission of neuromuscular impulses.

The total body content of magnesium in an adult is estimated to be 20–28 g with 40–45% being intracellular in muscles and soft tissue, 1% being extracellular, and the remainder being found in the skeleton. Although humans do not have a true storage organ for magnesium, approximately one-third of skeletal magnesium is in equilibrium with plasma magnesium levels and functions as a buffer to maintain extracellular magnesium concentrations.

Magnesium depletion is very unusual in the absence of dietary restriction or some disorder causing magnesium loss from the body. Magnesium depletion is usually secondary to another disease process or to a therapeutic agent. The physiological manifestations of severe magnesium depletion include hypokalaemia and hypercalcaemia, neuromuscular hyperexcitability, electrocardiographic abnormalities, and cardiac arrhythmias. Adverse heart rhythm changes have been observed after 78 days of magnesium depletion with a daily magnesium intake of 101 mg (4).

Therapeutic use of magnesium in heart arrhythmia conditions (5–7) and to reduce the risk of eclampsia in women with pre-eclampsia (8–12) has received wide scientific attention in recent years. The neuroprotective role for antenatal magnesium sulphate therapy given to women at risk of preterm birth has also been established (13). However, no studies have been conducted to show a preventive potential of high- versus low-magnesium diets in relation to reducing the risk of these conditions in the general population.

Requirement and recommended intake

Magnesium research has been hampered by the lack of good biomarkers of magnesium status in the body (14). At present, useful data that could contribute to the development of evidence-based dietary recommendations is limited, especially for specific vulnerable population groups such as infants, children and adolescents, pregnant women, and the elderly (14). Epidemiological studies have reported a relationship between low magnesium intake and increased risk of cardiovascular disease, hypertension, stroke, colorectal tumour risk, obesity, and type 2 diabetes (15–25). However, at present the results are difficult to interpret because it is not

possible to tell whether the observed associations are primarily attributable to magnesium intake itself or to other constituents of magnesium-rich food. High quality randomised controlled trials in this area are scarce (14).

Adults. In the absence of functional indicators of magnesium status, the only basis we have for evaluating requirements are balance studies. Because absorption of magnesium varies with the dietary intake, it seems possible to adapt to a low intake through more effective absorption. The U.S. Food and Nutrition Board (26) set an Estimated Average Requirement (EAR) for magnesium of 255 mg/d for women and 330 mg/d for men aged 19–30 years. The RDA (Recommended Dietary Allowance) is 310 and 400 mg/d for women and men, respectively. For adults aged 31–70 years the RDA for women is set at 320 mg/d and for men at 420 mg/d in this age group.

Data from 27 balance studies where pooled by Hunt and Johnson in 2006 (27) at the U.S. Department of Agriculture, and they suggested that the previously estimated EAR by the U.S. Food and Nutrition Board might have been too high. Neutral magnesium balance was predicted at a magnesium intake of 165 mg/d, and neither age nor sex affected the relation between magnesium intake and output (27). Data were reported for adults only.

The EU Scientific Committee for Food (28) considered 150–500 mg/d to be an acceptable range of magnesium intake based on observed intakes.

In the NNR 2004 (29) the recommended intakes (RI) were 350 mg/d and 280 mg/d for men and women (including pregnant and lactating women), respectively. There are no substantial new data since then indicating that these values should be changed (14, 27, 30).

Infants and children. The magnesium content in human breast milk is 23–47 mg/L (30), and this concentration is relatively constant during the first 12 months of lactation (31). For children, the RI values from 2004 are maintained (29).

Upper intake levels and toxicity

Excessive magnesium intake (0.5–5 g/d) gives diarrhoea, but otherwise no negative symptoms are observed when kidney function is normal.

The U.S. Food and Nutrition Board (26) has set a Tolerable Upper Intake level (UL) of 350 mg/d from supplements. This level is based on

the lowest observed adverse effect levels. The EU Scientific Committee for Food (28) has derived a maximum daily intake of 250 mg based on similar data. The UL does not include magnesium normally present in foods and beverages.

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31 Sodium as salt

Population goal	Adults and children > 10 y	Children 2–9 y
Sodium	2.4 g/d	0.5 g/MJ
Salt	6 g/d	3–4 g/d

Introduction

Salt is nutritionally equivalent to sodium chloride (NaCl) and is used as a food ingredient or condiment. Sodium is also found in unprocessed foods but usually in very low concentrations. One gram of salt corresponds to about 0.4 g sodium, and 1 g sodium is equivalent to 2.5 g salt. One millimole of sodium corresponds to 23 mg and is equivalent to about 58 mg sodium chloride.

Dietary sources and intake

The main sources of sodium in the diet are processed foods such as bread, cheese, spreads, meat and fish products (1). The contribution of sodium from added salt in cooking and at the table varies but on average this intake constitutes approximately 10% to 20% of the total salt intake (1, 2). Data on the total dietary intake of sodium in Nordic populations are scarce. According to national food balance sheets, the daily amount of salt available for consumption in the Nordic countries is estimated to be 10 g to 12 g per person. Estimations of the sodium intake from national dietary surveys among adults generally show somewhat lower values. Average dietary sodium contents calculated from national dietary surveys among adults were 3.9 g/d (9.8 g salt) in men and 2.9 g/d in women (7.3 g salt) in Denmark, 3.7 g in men (9.3 g salt) and 2.7 g in women (6.8 g salt) in Finland, 3.8 g in men (9.1 g salt) and 2.6 g in women (6.5 g salt) in Iceland, and 3.6 g (9.0 g salt) in men and 2.7 g (6.9 g salt) in women in Sweden (1–6).

The contribution from discretionary salt intake – such as that from extra salt added to meals, etc. – is generally not included in these estimates. Data from Finnish population studies suggest that sodium intake assessed from dietary records and 24 h and 48 h dietary recalls are valid and give similar estimates of the mean level of sodium intake as determinations of 24 h urinary sodium (1). Results from 24 h urine collections in different population groups show wide variations ranging from about 7 g to 12 g of salt per day (7–10).

Physiology and metabolism

The sodium ion is essential for a number of metabolic processes in the cell and is involved in the regulation of the acid-base balance, the osmotic pressure in the extracellular fluid volume (ECV), blood volume, nerve function, and the transport of glucose and certain amino acids (11).

The body pool of sodium in an adult is approximately 100 g. About half is found in the ECV and 10% is found in the cells. The rest is mainly bound in the skeleton, of which half is exchangeable and thereby functions as a store for the body fluids.

The absorption of sodium is effective and generally amounts to more than 90% of the dietary intake. The excretion of sodium mainly occurs through the kidneys where it is effectively regulated depending on sodium and fluid intake. Losses through the skin in the Nordic climate are generally not more than 1 mmol/d (12). Small amounts of sodium (0.1–8 mmol) are also lost daily in the faeces (13). During profound sweating or in massive diarrhoea or vomiting, the extrarenal loss might become clinically significant. Healthy kidneys can retain almost all of the sodium in the body because the tubule cells reabsorb up to 99.5% of the sodium. Healthy kidneys can also excrete large amounts of sodium. This requires a sufficient water supply, however, because the urine can only be concentrated to a limited degree. The daily excretion through the kidneys and skin is normally 100–200 mmol.

Requirement

Dietary sodium deficiency does not normally occur in the Nordic countries. Acute deficiency, however, can develop in connection with heavy sweating in combination with large fluid intakes devoid of sodium or in connection with prolonged vomiting and diarrhoea without a compensatory salt

supply. Clinical symptoms include muscle seizures, loss of appetite, and circulation disturbances. Severe deficiency can result in coma and death.

Among adults, sodium balance can be maintained at intakes as low as 10 mmol (230 mg) per day, which corresponds to about 0.6 g of salt. An intake of 25 mmol (575 mg) per day, corresponding to about 1.5 g salt, is set as the estimated lower intake level and accounts for variations in physical activity and climate (11).

Salt and blood pressure

From a public health perspective, the role of sodium as dietary salt in the regulation of blood pressure has received the most interest. The relationship between salt and blood pressure has been studied since Kempner's classic observations during the 1930s and 1940s (14). He treated diabetics and hypertensive patients with a salt-restricted rice and fruit diet containing less than 2 grams of salt per day and found that blood pressure was drastically reduced among most of these patients.

Cross-sectional population studies

Population studies have shown that hypertension is rare in populations with a very low salt intake (< 2 g/d) and that blood pressure does not normally rise with age in these populations (15, 16). In areas with very high salt intakes (30–35 g/d), severe hypertension has been reported among 30%–35% of the population (15). In the large, multi-centre Intersalt study (16), the relationship between 24 h sodium and potassium excretion and blood pressure was investigated. The study included 10,000 men and women aged 20–59 years from 52 centres around the world. The median sodium excretion varied from 0.2 mmol/d to 242 mmol/d between centres. In four centres with very low sodium excretion, blood pressure was low and no age-related increase in blood pressure was observed. In the other 48 centres, sodium excretion was related to the increase in blood pressure with age but not to median blood pressure or prevalence of high blood pressure. Potassium excretion was found to be inversely related to blood pressure on an individual basis, while the sodium to potassium ratio showed a pattern similar to that of sodium. Increased body mass index and heavy alcohol intake were strongly related to increased blood pressure.

Law et al. (17) analysed published data on blood pressure and sodium intake from 24 different communities (47,000 subjects) throughout the world, including those of the Intersalt study. Allowance was made for

differences in blood pressure between economically developed and underdeveloped communities to minimise overestimation of the association through confounding with other determinants of blood pressure. The authors found that blood pressure was higher on average in the developed communities, but the association with sodium intake was similar in both types of community. A difference in sodium intake of 100 mmol/24 h was associated with an average difference in systolic blood pressure that ranged from 5 mmHg at 15 to 19 years of age to 10 mmHg at 60 to 69 years of age. The differences in diastolic blood pressure were about half as great. The authors concluded that the association of blood pressure with sodium intake is substantially larger than is generally appreciated and increases with age and initial blood pressure. Data from within-population studies also generally support such an association (17, 18).

In the EPIC-Norfolk (the European Prospective Investigation into Cancer in Norfolk) study with 23,104 community-living adults aged 45 years to 79 years, the mean systolic and diastolic blood pressure increased as the ratio of urinary sodium to creatinine increased and differences of 7.2/3.0 mmHg for systolic/diastolic blood pressure between the top and bottom quintiles were observed (19). This trend was independent of age, body mass index, smoking, and the ratio of urinary potassium to creatinine and was consistent by sex and history of hypertension.

Clinical trials

Several meta-analyses of clinical trials of dietary salt reduction have been published (17, 19–22), and these differ in scope and inclusion criteria. Law et al. (17) analysed 68 crossover and 10 randomised controlled trials of salt reduction among normotensives and hypertensives that included studies published up to 1989. They found that the blood pressure lowering effect of salt restriction was related to the duration of the study and that less of an effect was seen in trials lasting less than 4 weeks. The authors concluded that in people aged 50 to 59 years, a reduction in daily sodium intake of 50 mmol (approximately 3 g of salt) would, after a few weeks, lower systolic blood pressure by an average of 5 mmHg and by 7 mmHg in those with high blood pressure (170 mmHg). The diastolic blood pressure would be lowered by about half as much.

Midgley et al. (20) analysed 56 trials published between 1966 and 1994. These studies had randomised the allocation of subjects into a control group or to various dietary sodium intervention groups, had monitored sodium excretion, and had both systolic and diastolic blood

pressure as outcome measures. All papers in the analysis were selected by blinded review of the methods sections. Several of these studies, including some published before 1990, were not included in the analysis by Law et al. (17). The mean reduction in daily urinary sodium excretion was 95 mmol/d (range 71–119 mmol/d) in 28 trials with 1,131 hypertensive subjects, and 125 mmol/d (range 95–156 mmol/d) in 28 trials with 2,374 normotensive subjects. In hypertensive subjects, a reduced urinary sodium excretion of 95 mmol/d was associated with a reduction in systolic blood pressure by 5.9 mmHg (95% CI: 4.1–7.8 mmHg) and in diastolic blood pressure by 3.8 mmHg (95% CI: 2.9–4.8 mmHg). In normotensive subjects, the corresponding changes for a reduced urinary sodium excretion of 125 mmol/d were a reduction of 1.6 mmHg (95% CI: 0.9–2.4 mmHg) for systolic and 0.5 mmHg (non-significant; 95% CI: 0.1–1.2 mmHg) for diastolic blood pressure. A weakness of the analysis of trials on normotensives was the short duration of the trials (on average 14 days), although the authors state that there was a tendency for a greater blood pressure reduction in trials with a shorter duration (< 2 weeks). This is in contrast with the findings of Law et al. (17, 18) and could be due to problems of compliance in some of the more long-term studies. Trials on normotensive subjects involved mainly young subjects, while the trials on hypertensives mainly involved middle-aged or older subjects. The decreases in blood pressure were larger in trials on older hypertensive individuals than in trials on younger patients, but no data were given for normotensives.

Graudal et al. (21) published another meta-analysis including 58 randomised trials on dietary sodium restriction among hypertensives and 56 trials among normotensives published between 1966 and 1997. In the 58 trials of hypertensive persons (the exact criteria for hypertension was not stated), a reduced urinary mean sodium excretion of 118 mmol/24 h was associated with a significant reduction in systolic blood pressure of 3.9 mmHg and a reduction in diastolic blood pressure of 1.2 mmHg. In the 56 trials of normotensive persons, a reduced mean sodium excretion of 160 mmol/24 h was associated with a significant average reduction in the systolic blood pressure of 1.2 mmHg, but only a non-significant reduction in the diastolic blood pressure of 0.26 mmHg was observed. In this study, the trials on normotensives also had a short duration with a mean of only 8 days and included younger subjects (mean age 27 years) with a mean systolic blood pressure of 120 mmHg. This limits the relevance of the results for public health action. The mean duration of trials of hypertensives

was 28 days and the mean age of the subjects was 49 years, which was comparable to the analysis by Midgley et al. (20).

The meta-analysis by Cutler et al. (22) included 23 trials published up to mid-1994. The lower number of trials included was due to stricter inclusion criteria. The combined weighted data showed that a decrease in sodium excretion of 100 mmol/24 h (5.8 g salt) was associated with a reduction in systolic blood pressure of 4.8 mmHg in hypertensives and 2.3 mmHg in normotensives. The corresponding figures for diastolic blood pressure were 2.5 mmHg and 1.4 mmHg, respectively.

The meta-analysis by Geleijnse et al. (23) only included randomised controlled trials with a duration greater than 2 weeks, and 40 trials published between 1966 and 1991 were included. A median reduction in sodium excretion of 77 mmol/24 h (4.5 g salt) was associated with a 2.5 mmHg reduction in systolic blood pressure and a reduction of 2.0 mmHg in diastolic blood pressure. Reductions were more pronounced in hypertensives, and the same tendency was seen in older subjects. A subsequent meta-analysis including trials with a duration of 4 weeks or more with a similar reduction in sodium excretion (74–78 mmol/24 h) found a 5.0 mmHg reduction in systolic blood pressure and a 2.7 mmHg reduction in diastolic blood pressure among hypertensives. Corresponding figures for subjects with normal blood pressure were 2.0 mmHg and 1.0 mmHg, respectively (24, 25). A dose-response relationship was observed with a systolic/diastolic blood pressure reduction of 7.2/3.8 mmHg among hypertensives and a reduction of 3.6/1.7 mmHg among normotensives per 100 mmol/24 h (5.8 g salt) reduction in sodium excretion.

Only a few studies have examined the long-term effects on blood pressure of sodium restriction. Jula et al. (26) studied the effects on blood pressure and serum lipids of a non-pharmacological treatment based mainly on sodium restriction in a 12 month controlled randomized study with 91 middle-aged untreated and mildly hypertensive men and women. The estimated daily sodium intakes, calculated from 24 h urine samples, decreased in men from 227 mmol to a mean level of 105 mmol and in women from 129 mmol to 63 mmol. After 12 months of non-pharmacological treatment, the mean weight in men was 1.9 kg lower and in women 0.3 kg higher compared to the mean weight at baseline. In the treatment group, energy derived from fat decreased in men by 4% and in women by 3% reflecting decreased intake of saturated and monounsaturated fats. The net blood pressure decrease (the difference in changes between the treatment and control group) during the 12 months was 8.2 mmHg for systolic and

5.8 mmHg for diastolic blood pressure in men and 9.5 mmHg for systolic and 5.6 mmHg for diastolic blood pressure in women. All changes were significant. In the treatment group, LDL-cholesterol also decreased by 6.8% in men and by 12.1% in women.

In the DASH trials (Dietary Intervention to Stop Hypertension), the effects of various controlled diets on the blood pressure of adult Americans with normal or moderately elevated blood pressure were studied (27, 28). The study by Sacks et al. (28) assessed the influence of sodium intake on blood pressure in 412 subjects who were randomly assigned to follow either a control diet typical of the sodium intake in the US or to follow the DASH diet. In both groups, a second randomization was done and the subjects followed their assigned diets at three sodium levels for 30 days in random order in a crossover design. The subjects were selected among adults 22 years or older who were not taking antihypertensive medication and who had a systolic blood pressure ranging from 120 mmHg to 160 mmHg and a diastolic blood pressure ranging from 80 mmHg to 95 mmHg. The control diet had a fat composition corresponding to the usual American diet (36 E% total fat, 14 E% saturated fat) but a low content of fruits, vegetables, and dairy products. The DASH diet was rich in fruits, vegetables, and low-fat dairy products but low in edible fats, snacks, and sweets and had a low content of total fat (25 E%), saturated fat (7 E%), and cholesterol. The content of calcium, potassium, and magnesium in the control diet was lower than in the average US diet but was higher in the DASH diet. The intake of dietary fibre was similar in both groups. Within the assigned diets, sodium levels were adjusted to provide a daily intake of 150 mmol (high, about 9 g salt), 100 mmol (intermediate, about 6 g salt), and 50 mmol (low, about 3 g salt) for 30 consecutive days each, in random order. The estimated sodium intakes, calculated from 24 h urine samples, indicated a sodium intake of 141–144 mmol (about 8 g salt) during the high sodium phase and an intake of 64–67 mmol (about 4 g salt) during the low sodium phase and an intake of 106–107 mmol (about 6 g salt) during the intermediate sodium phase. Reducing the sodium intake from the high to the intermediate level significantly reduced the systolic blood pressure by 2.1 mmHg during the control diet and by 1.3 mmHg during the DASH diet. A further reduction from the intermediate to the low level caused additional reductions of 4.6 mmHg while on the control diet and 1.7 mmHg while on the DASH diet. A regression analysis of these data showed that a reduction in the sodium intake of 100 mmol per day would lead to a reduction in the systolic blood pressure of about 3 mmHg in the

DASH group and of about 7 mmHg in the control group. Corresponding values for diastolic blood pressure were 1.5–2 mmHg and about 3 mmHg, respectively. The effects of sodium were observed in normotensive and hypertensive subjects, subjects of different ethnicities, and in both women and men, and the effects were not dependent on weight (28, 29).

An aspect that was only partly addressed in the meta-analyses was the relationship between the sodium intake and the age-related change in blood pressure. Data from the Intersalt study strongly indicated a relationship between the median daily urinary sodium excretion and the difference in blood pressure with age (30). In within-population analyses, an individual 24 h urinary sodium excretion increase of 100 mmol was associated with a 3–6 mmHg higher systolic and 0–3 mmHg higher diastolic blood pressure. Associations were larger at 40–59 years of age than at younger ages. In cross-population analyses, a median 24 h sodium excretion greater than 100 mmol was associated with 5–7 mmHg higher median systolic and 2–4 mmHg higher median diastolic blood pressure. At age 55, the estimated mean increases in systolic and diastolic blood pressure were 10–11 mmHg and 6 mmHg, respectively, compared to the values at age 25. This indicates a strong age-related effect of high sodium intakes on blood pressure. In the DASH trial, the blood pressure reduction was higher in older (> 45 years) than in younger subjects, e.g. a 100 mmol reduction in sodium excretion was associated with a 6 mmHg lower systolic blood pressure among older non-black subjects (29).

The DASH trials clearly showed an effect of sodium restriction ranging from 2–5 g/d on blood pressure that was independent of other dietary and lifestyle factors. An important finding was that the blood pressure reduction was larger in the control group than in the DASH group. This implies that the benefits of sodium restriction are more pronounced among persons consuming a diet that is less than optimal in terms of fat, fruit, and vegetable intake (which is similar to the current dietary patterns in the Nordic countries) than among those already consuming a diet in line with the general nutrition recommendations. A limitation of the study was the relatively short duration (30 days) and the fact that the study excluded subjects with low blood pressure (systolic blood pressure < 120 mm Hg) and high blood pressure (systolic blood pressure > 160 mm Hg). However, the blood pressure lowering effect of dietary salt reduction on hypertensives is well documented, and the proportion of the adult population with systolic blood pressure below 120 mm Hg is small, especially among the middle-aged and older.

Observational population studies and population-based intervention studies

In Finland, salt intake decreased by 40% from the 1970s to 2002 along with a decrease in the intake of saturated fats and an increased intake of fruits and vegetables (10, 31). The dietary changes were associated with a 10–20 mmHg and 6–10 mmHg decrease in population systolic and diastolic blood pressure, respectively, and with a 70% decrease in stroke and coronary heart disease mortality (32–34). In a Portuguese population-based intervention study, sodium intake was reduced by dietary advice (35). The mean dietary intake of salt decreased by approximately 40% (from approximately 20 g/d to 11.5 g/d) as estimated by food consumption data, but estimations based on urinary sodium to creatinine ratios indicated a lower reduction of approximately 25% (5 g salt) after one year and 9% (2 g salt) after 2 years. After 2 years of intervention, the systolic and diastolic blood pressure had both decreased by approximately 5 mmHg. The systolic blood pressure rose in the control community, and after 2 years there was a 13/6 mmHg difference in systolic/diastolic blood pressure between the intervention and control communities.

Salt intake and blood pressure among children

The blood pressure of children living in industrialized countries rises with age, and this increase is more rapid in children of hypertensive parents than in children of normotensive parents (36–39). In the Finnish STRIP study (39), systolic blood pressure of children living in southwestern Finland increased with age along with sodium intake and by the age of 10 years their systolic blood pressure exceeded that of adults in populations consuming low-sodium diets. The mean daily sodium intake was 1,500 mg at the age of 13 months and 3,000 mg at the age of 15 years. Similar levels of salt intake by children have been reported in other countries (40, 41). Childhood blood pressure tracks with adult blood pressure (42, 43) and predicts early atherosclerosis in adolescence (44) and adulthood (44, 45).

A randomised trial among 476 Dutch newborn infants studied the effect of a low-sodium (average 120 mg/d) or a normal-sodium (average 330 mg/d) diet on blood pressure during the first 6 months of life (46). The sodium intake in the low-sodium group was approximately the same as the intake of breastfed infants, whereas the intake in the normal group was similar to the sodium intake of infants fed commercial infant formula. At the end of the trial, systolic blood pressure in the low-sodium group was 2.1 mmHg lower than in the control group. The authors also measured

blood pressure in 167 children from the original cohort (35% of the original study participants) after 15 years of follow-up. The adjusted systolic blood pressure at follow-up was 3.6 mmHg lower and the diastolic pressure was 2.2 mmHg lower in adolescents who as infants had been assigned to the low-sodium group compared with those assigned to the control group. One meta-analysis of controlled trials has been carried out to assess the effect of reducing salt intake on blood pressure in children and adolescents (47). Ten trials with 966 participants were included. Among adolescents (the mean ages for the participants in the individual trials ranged from 8 to 16 years), a reduction in salt intake by 42% corresponded to a reduction in systolic blood pressure of 1.2 mmHg (95% CI: 0.6–1.8 mmHg) and a reduction in diastolic blood pressure of 1.3 mmHg (95% CI: 0.7–1.9 mmHg) after a median duration of 4 weeks. In the three trials with infants, sodium excretion was reduced by 54% and systolic blood pressure was decreased by 2.5 mmHg (95% CI: 0.9–4.0 mmHg) after a median duration of 20 weeks.

Other dietary factors and blood pressure

A number of dietary factors, including alcohol, potassium, calcium, magnesium, and fatty acid composition, as well as levels of physical activity have been associated with blood pressure (see respective chapters).

Salt and morbidity and mortality

Cardiovascular disease (CVD)

A number of prospective cohort studies have investigated the association between dietary salt intake and the risk of stroke and other cardiovascular events. A systematic review and meta-analysis of prospective studies published between 1996 and 2008 assessed the relation between habitual salt intake and stroke or total cardiovascular events (48). The analysis included 19 independent cohorts with a total of 177,025 participants and over 11,000 vascular events. Follow-up varied between 3.5 years and 19 years. A higher salt intake of approximately 5 g per day was associated with a 23% higher incidence of stroke and a 14% higher incidence of total cardiovascular events. Study populations included both men and women, and salt intake was estimated using various dietary assessment methods and/or 24 h urine samples. Most of the included studies showed an increased risk of stroke and CVD. One of the included studies reported an increased risk of myocardial infarction in association with a lower sodium intake among male hypertensive subjects who had been treated with

blood pressure reducing drugs (49). The trend for women was the opposite, although not significant. The sodium intake was measured using a single 24 h urine sample that was collected 5 days after the subjects had been asked to avoid consumption of foods with a high salt content. One can, therefore, question whether the assessment provided a representative measure of the subjects' usual sodium intake. The results could also have been biased due to confounders, such as alcohol, not being accounted for.

In another study, Alderman et al. (50) reported a significant negative correlation between sodium intakes estimated by 24 h recalls and all-cause mortality and CVD mortality in a follow-up of the first National Health and Nutrition Examination Survey (NHANES I) study in the US. Based on these results, the authors concluded that sodium restriction might lead to negative health effects and that advice to reduce sodium intake in the general population is not justified. A critical examination of the data (51), however, favoured the opposite interpretation because the authors also found a positive correlation between the sodium content of the diet expressed as mg/kcal and mortality. A major weakness of the NHANES I data was the low energy intake. When the study population was classified according to sodium density (mg Na/kcal), the energy intakes were more comparable among the quartiles indicating that underreporting was more evenly distributed. The energy-adjusted sodium intakes are, therefore, more reliable, and in the absence of 24 h urine data only these data can be used with some confidence in the analysis of a possible relationship between sodium intake and mortality. The result of this analysis, which the authors briefly mention, is that there is a weak, but significant, positive association between the sodium content of the diet and both all-cause mortality and CVD mortality.

In another study from the NHANES I cohort (included in the above-mentioned meta-analysis (48), a 100 mmol higher sodium intake among overweight persons was associated with a 32% increase in stroke incidence, an 89% increase in stroke mortality, a 44% increase in coronary heart disease mortality, a 61% increase in CVD mortality, and a 39% increase in mortality from all causes (52). Dietary sodium intake was, however, not significantly associated with CVD risk in non-overweight persons. The limitations of the study are the same as for the earlier mentioned study by Alderman et al. (50) on the same population.

Subsequent prospective studies have shown J-shaped (53), positive (54, 55), or inverse associations between sodium intake or excretion and CVD (56). The study by Cook covers a prospective follow-up of 2,275 adults

with prehypertension aged 30 to 54 years not assigned to active sodium restriction in two intervention trials (TOPH I and II). The association between urinary sodium and potassium (the mean of three to seven 24 h urine collections) and CVD events (n=193) during 10 to 15 years of post-trial follow-up showed a non-significant trend for an increased CVD risk across sex-specific quartiles of urinary sodium excretion, but a significant trend for an increased risk across quartiles of the sodium to potassium excretion ratio was evident (RR = 1.00, 0.84, 1.18, and 1.50 for each quartile, respectively; p = 0.04 for trend). The study by O'Donnell (53) included two cohorts with 28,880 patients at high risk of CVD aged ≥ 55 years followed for a mean of 56 months. Compared with a baseline sodium excretion of 4 g/d to 5.99 g/d, sodium excretion of greater than 7 g/d was associated with an increased risk of all cardiovascular events, and a sodium excretion of less than 3 g/d was associated with increased risk of cardiovascular mortality and hospitalization for congestive heart failure. The 24 h urinary sodium excretion was estimated from morning urines, which adds some uncertainty to the risk estimates in this study.

The multi-centre study by Stolarz-Skrzypek (56) included 3,681 participants without CVD, of which 2,096 were normotensive. During a median of 7.9 years, 84 CVD deaths occurred. Risk of CVD death decreased with increasing baseline 24 h sodium excretion tertiles of 107 mmol/d, 168 mmol/d, and 260 mmol/d. The study by Yang investigated all-cause, cardiovascular, and ischemic heart disease (IHD) mortality in a nationally representative sample of 12,267 US adults from the third NHANES. After a mean follow-up of 14.8 years, a total of 2,270 deaths, including 825 CVD and 443 IHD deaths, had occurred. A 1,000 mg/d higher sodium intake was associated with a 20% increased risk for all-cause mortality. A higher sodium-potassium ratio was also associated with an increased risk of all-cause mortality and CVD mortality when comparing the highest and lowest quartiles. The findings did not differ by sex, ethnicity, body mass index, hypertension status, or physical activity. Dietary sodium intake was measured by a single 24 h recall that was calibrated with data from a subgroup with two valid recalls.

A Cochrane Review included seven randomized controlled trials with a follow-up of at least 6 months that included a total of 6,250 participants and 665 deaths (57). Results from meta-analyses performed separately for normotensive and hypertensive subjects did not find any benefits of reduced dietary salt reduction for the prevention of CVD. One of the included trials included subjects suffering from severe heart failure (58). The

participants were severely salt and water depleted due to being medicated with large doses of diuretics and being put on fluid restriction of 1,000 mL per day. A re-analysis of these studies combined the data for hypertensives and normotensives and excluded the study performed with subjects suffering from severe heart failure (59). This new analysis showed that a decrease in salt intake of 2–2.3 g per day decreased cardiovascular events by 20% ($p < 0.05$) and all-cause mortality non-significantly by 5%–7%.

A previous review of controlled studies, published from 1984 to 1995, in which the sodium intake was restricted did not reveal any evidence of adverse effects of moderate sodium restriction (60). The analysis included 20 randomised intervention studies with at least 6 months follow-up using urinary excretion data.

The review by Perry (61) concluded that available studies suggest that sodium intake is independently related to left ventricular hypertrophy, a condition that is associated with increased risk of coronary mortality. Long-term sodium restriction decreases left ventricular hypertrophy in hypertensive subjects (62, 63).

Cancer

The WCRF/AICR concluded that there is probable evidence that total intake of salt and sodium is associated with stomach cancer (64). A meta-analysis of seven prospective cohort studies found an increased risk with dietary intakes categorised as "high" or "moderately high" compared to "low" intakes (65). The meta-analysis included 10 cohorts, 268,718 participants, and 1,474 events with a follow-up of at least 4 years. The categorisation of intakes was based on reported tertiles or middle and extreme quintiles.

Other outcomes

Several studies have indicated a positive relationship between sodium excretion and calcium excretion and that sodium intake might play a role in the aetiology of osteoporosis and kidney stones (66).

Recommended intake

According to epidemiological studies, hypertension is practically non-existent in populations with low salt intake, and a lower sodium intake will attenuate the usual age-related increase in blood pressure. Data from individual trials and meta-analyses of previous trials show that reduction of sodium decreases blood pressure and that the effect is greater among

hypertensive subjects. The magnitude of the blood pressure decrease upon sodium restriction also depends on the dietary composition. The effect seems to be more pronounced when the diet is less optimal with respect to energy-providing nutrients, dietary fibre, potassium, and calcium as well as with respect to other dietary constituents such as those provided by fruits and vegetables.

Observational studies suggest that population blood pressures and cardiovascular morbidity and mortality have declined together with decreased salt intake. Blood pressure is a strong independent risk factor for CVD, and a lower sodium intake is associated with decreased risk of CVD morbidity and mortality. It has been estimated that the cardiovascular benefits of reduced salt intake are on par with the benefits of population-wide reductions in tobacco use and would be highly cost-effective (67).

Adults

There is a progressive dose-response relationship between sodium intake and blood pressure. Any recommendations on the sodium intake have to be compatible with the overall dietary recommendations, and also account for public health considerations, rather than on a precise estimate of an optimal intake. Based on an overall evaluation of the available data, a limitation of sodium intake to about 2.4 g/d – corresponding to about 6 g salt (NaCl) – is feasible at the population level.

Children

Blood pressure rises with age beginning in early childhood and systolic blood pressure may, with increasing sodium intake, already by the age of 10 years exceed that of adults in populations consuming low-sodium diets. Blood pressure measured in childhood tracks with the level measured in adulthood and predicts early atherosclerosis in adulthood. The available data suggest that a reduction in sodium intake at a young age is associated with lower blood pressure in later life. Following a lifelong salt-reduced diet beginning in early childhood is recommended. It is also prudent to limit sodium intake in childhood in order to avoid preference for a diet with a high salt content.

The recommended sodium intake for children up to 10 years age is set to 0.2 g per MJ (0.5 g NaCl/MJ), which is based on the energy-adjusted recommended levels for adult women.

Pregnancy and lactation

Pregnancy and lactation are associated with a small increase in the physiological requirements for sodium by about 0.07 g or 3 mmol per day (pregnancy) and 0.12 g or 5.2 mmol per day (full lactation). These amounts are small and can apparently be handled by the body's homeostatic system. There is a lack of evidence to suggest that sodium requirements during pregnancy and lactation differ significantly from that of non-pregnant women.

International expert reports

As early as 1982, a WHO report on prevention of CVD (68) recommended that salt intake should not exceed 5 g/d. This recommendation was based on various clinical and epidemiological data. Since then, several international and national expert bodies including the WHO (69), the US Food and Nutrition Board (70), the American Heart Association (71, 72), and a British Expert Panel (73) have published recommendations to limit salt intake to 6 g/d among adults. The British Expert Panel also set recommendations for children and adolescents. A joint report from three German institutes recommends that salt intake in the German population should be reduced to between 3.5 g/d and a maximum of 6 g/d (74). The importance of population-wide sodium reduction as a means to prevent CVD and stroke has been pointed out by the American Heart Association (75) and the British National Institute for Health and Clinical Excellence (76).

Reasoning behind the recommendation

There is a progressive dose-response relationship between sodium intake and blood pressure. Results from both prospective cohort studies and randomised controlled trials generally show that sodium intake is positively associated with an increased risk of stroke and cardiovascular events and mortality among the general adult population. A precise lower threshold for intakes associated with health benefits is difficult to assess, but intakes of 4 g/d to 6 g/d for adults have been recommended internationally. Based on an overall evaluation of the available data, a limitation of the sodium intake to about 2.4 g/d – corresponding to 6 g salt (NaCl) – is feasible at the population level in the Nordic countries. Thus, the recommendation in NNR 2004 is maintained.

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32 Potassium

Potassium g/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y girls/boys
Recommended intake	RI	3.1	3.5	1.8	2.0	2.9/3.3
Lower intake level	LI	1.6	1.6			
Upper intake level	UL	– [a]	– [a]			

[a] Not established.

Introduction

Most of the potassium in the body (98%) is found in the cells, and potassium is quantitatively the most important intracellular cation. Extracellular potassium, which constitutes the remaining 2%, is important for regulating the membrane potential of the cells and is necessary, therefore, for nerve and muscle function, blood pressure regulation, etc. Potassium also participates in the acid-base balance. 1 mmol potassium is equivalent to 39 mg.

Dietary sources and intake

Important potassium sources in the Nordic diets are potatoes, fruits and berries, vegetables, and milk and dairy products. The average dietary intake ranges from 3.6 g/10 MJ to 4.8 g/10 MJ (see chapter on intake of vitamins and minerals in the Nordic countries).

Physiology and metabolism

The absorption of potassium is efficient and about 90% of the dietary potassium is normally absorbed from the gut. The potassium balance is primarily regulated by renal excretion in urine. A small amount can be lost in sweat.

Potassium deficiency can develop as a consequence of increasing losses from the gastrointestinal tract and kidneys, such as that which occurs during prolonged diarrhoea or vomiting, and in connection with the use of laxatives or diuretics. Potassium deficiency due to low dietary intake alone is very uncommon due to the widespread occurrence of potassium in foods. Treatment with diuretics without potassium compensation or potassium-sparing diuretics can, however, lead to deficiency. Hyperaldosteronism, hereditary defects in renal salt transporters such as Bartter's syndrome and Gitelman's syndrome, and excessive consumption of liquorice increase sodium retention and potassium excretion and can lead to hypokalaemia. Symptoms of potassium deficiency are associated with disturbed cell membrane function and include muscle weakness and disturbances in heart function that can lead to arrhythmia and heart seizure. Mental disturbances such as depression and confusion can also develop.

About 800 mg/d (20 mmol) of potassium is lost via the gastrointestinal tract, urinary excretion, and sweat, and an intake of 1.6 g/d (40 mmol) is needed to avoid low plasma levels and loss of total-body potassium in adults (1). The potassium intake can affect sodium balance, and low potassium intakes of 10–30 mmol/d can induce sodium retention and an increase in blood pressure in both normotensive and hypertensive subjects (2–4).

Potassium and blood pressure

In the Intersalt study, a 30–45 mmol increase in urinary potassium excretion was associated with a 2–3 mm Hg lower systolic blood pressure (5). An inverse relationship between blood pressure and potassium excretion and the K/Na ratio in urine was also observed (6). A number of studies of both normotensive and hypertensive subjects indicate that an increased potassium intake in the form of supplements can lower blood pressure and increase urinary sodium excretion (7–12). However, a clear dose-response effect was not observed, and not all studies showed a beneficial effect (9). The lack of a clear dose-response could be due to factors such as differences in the duration of the studies, initial blood pressure, sodium intake, habitual diet, race, and age.

Two meta-analyses of randomised trials with potassium supplementation showed a significant reduction in blood pressure (7, 8). In the study by Whelton and co-workers (8), 33 studies conducted between 1981 and 1995 with a mean duration of five weeks (range of 4 days to 3 years) were included. The average net increase in potassium excretion from baseline

was 54 mmol/d. Potassium supplementation was associated with a mean decrease in systolic blood pressure of 4.4 mm Hg (95% CI: -2.2 to -6.6) and a mean decrease in diastolic blood pressure of 2.5 mm Hg (95% CI: -0.1 to -4.9) among hypertensive individuals. Corresponding figures for normotensive subjects were decreases of 1.8 mm Hg (95% CI: -0.6 to -2.9) and 1.0 mm Hg (95% CI: 0.0 to -2.1), respectively, but the changes were not significantly different between hypertensives and normotensives. The blood pressure lowering effect of potassium supplementation was greater in trials with a higher urinary sodium excretion indicating the close interrelationship between sodium and potassium in this respect. Using urinary excretion data for potassium, the average intake of potassium in the supplemented groups was estimated at 4.5–5 g/d. In a subsequent meta-regression analysis including 27 randomised controlled trials with potassium supplementation with a duration of more than 2 weeks (mean 6 weeks), an increased median potassium excretion of 44 mmol/d was associated with a 2.4 mm Hg (95% CI: -1.08 to -3.75) decrease in systolic blood pressure and a 1.6 mm Hg (95% CI: -0.50 to -2.65) decrease in diastolic blood pressure (7). Reductions were larger among hypertensives than among normotensives.

A review and meta-analysis included six RCT studies published between 1986 and 1991 with a duration of at least 8 weeks that included participants over 18 years of age with elevated blood pressure and with no changes in medication during the follow-up (9). The intervention arms included increased potassium intake from foods (one study) and from supplements as potassium chloride (four studies), potassium citrate, or potassium bicarbonate (one study). A meta-analysis of five eligible studies including 483 participants showed overall non-significant reductions in systolic and diastolic blood pressures. However, studies with doses less than 100 mmol were associated with significant decreases in both systolic and diastolic blood pressure. The authors concluded that the small number of participants in two high quality trials, the short duration of follow-up, and the unexplained heterogeneity between the trials made the evidence for an effect on blood pressure inconclusive (9). Another meta-analysis of 10 RCTs in hypertensives (556 patients) with high salt intake found that supplementation with potassium reduced both systolic and diastolic blood pressure by 9.5 mmHg and 6.4 mmHg, respectively (13). High salt intake was defined as >170 mmol/d (9.9 g NaCl) or "high salt intake" and follow-up was 8–16 weeks. Potassium dose was not stated.

Two subsequent RCTs among normotensives have found significant

reductions in systolic and diastolic blood pressure of 5–8 mmHg and 4–6 mmHg, respectively, after four to six weeks supplementation with potassium salts (23–30 mmol/d, 900–1,200 mg) (11, 14). No significant effects were, however, seen in two other RCTs (15, 16). In the study by Berry et al (15), potassium intake was increased by increased intake of fruit and vegetables (20–40 mmol/d, 780–1,560 mg) or potassium citrate (40 mmol/d) during six weeks. In the study by Matthesen et al. (16) subjects received daily supplements of potassium chloride of 100 mmol/d (3.9) during between four weeks. A RCT in 144 patients with mild to moderate essential hypertension but otherwise healthy showed that supplementation with potassium aspartate (30 mmol/d) significantly reduced both office and 24-h blood pressure compared to placebo (17).

Most of the RCTs have used potassium chloride supplements. Some studies have investigated the effect of other potassium salts, such as citrate, but the results are conflicting with respect to any differential effects on blood pressure (14, 15, 17–19).

Potassium and cardiovascular disease

An inverse association between potassium intake and the risk of stroke has been shown in most cohort studies. The association between dietary potassium intake and incidence of cardiovascular disease (CVD) was assessed in a systematic review and meta-regression analysis of 11 prospective cohort studies published from 1966 through 2009 including 15 cohorts with 247,510 men and women with a follow-up of 5–19 years (20). Potassium intake was assessed by 24-h dietary recall in two studies, a food frequency questionnaire in six studies, and 24-h urinary excretion in three studies. In a pooled analysis, a 1.64-g (42 mmol) per day increase in potassium intake was associated with a 21% lower risk of stroke (RR: 0.79; 95% CI: 0.68 to 0.90). There was also a trend toward lower risk of CHD and total CVD. The results of the meta-analysis are supported by subsequent studies (21), and an interaction between potassium and sodium intake has been shown in some studies (21, 22).

In an intervention trial, the effect of using potassium-enriched salt on cardiovascular mortality was investigated (22a). Five kitchens at a veteran's retirement home in Taiwan were randomized into two groups, and the 1,981 veterans assigned to those kitchens were given either potassium-enriched salt (n = 768) or regular salt (n = 1,213) for approximately 31 months. One hundred three CVD-related deaths were observed during the

follow-up. A 17% lower urinary sodium-to-creatinine ratio and a 76% higher urinary potassium-to-creatinine ratio in the experimental group were associated with a significant reduction in CVD mortality (HR: 0.59; 95% CI: 0.37 to 0.95).

In controlled intervention studies using diets designed to meet recommended levels of fat, fat quality, and dietary fibre similar to those in NNR 2004 (23), the dietary potassium intakes (estimated from urinary potassium excretion) in these diets have all been around 3–4 g/d (24–26). In these studies, blood pressure reductions were observed both with and without changes in sodium intake.

Requirement and recommended intake

The recommended intake of potassium in NNR 2004 (23) was based mainly on data on the effect of potassium on blood pressure (5–12, 24–27). Several clinical trials and cohort surveys published since that time support the finding that a diet rich in potassium alone, or in combination with calcium and magnesium, might have a favourable effect on blood pressure and might reduce the risk of stroke and other cardiovascular endpoints (20). The reference values in NNR 2012 are kept unchanged compared to NNR 2004 (23) because there are no new data to justify any major changes.

The recommended intakes are set at 3.5 g/d (90 mmol) for men and 3.1 g/d (80 mmol) for women. The figure for women also includes pregnant and lactating women. It should be pointed out that potassium intakes somewhat over and above these values might have further beneficial effects. The reference values for children and adolescents are extrapolated from adult values based on needs for growth and adjusted for body weight. The lower intake level (LI) is estimated to be 1.6 g/d (40 mmol) for adults.

Reasoning behind the recommendation

The recommended intake of potassium in NNR 2004 was based mainly on data on the effect of potassium on blood pressure. Data from clinical trials and cohort studies published since that time support the finding that a diet rich in potassium alone, or in combination with calcium and magnesium, might have a favourable effect on blood pressure and might reduce the risk of stroke and other cardiovascular endpoints. The reference values are kept unchanged compared to NNR 2004 because there are no new scientific data to justify any major changes.

Upper intake levels and toxicity

Potassium chloride has been associated with acute poisoning in humans. Case reports have described heart failure, cyanosis, and cardiac arrest after ingestion of high doses of potassium chloride tablets. Gastrointestinal effects have also been described after chronic ingestion of potassium chloride in case studies and supplementation studies. These effects include abdominal pain, nausea and vomiting, diarrhoea, and ulceration of the oesophagus, stomach, duodenum, and ileum. The occurrence and severity of the effects depend on a number of factors of which formulation of the preparation, dose, and gut transit time seem to be the most important. Slow release, wax-coated potassium chloride tablets appear to induce more lesions than microencapsulated tablets (28).

Dietary potassium has not been associated with any negative effects in healthy subjects. Prolonged high potassium intakes from diet and potassium-containing salt substitutes might, however, cause hyperkalaemia and affect heart function in subjects with renal insufficiency or impaired kidney function (28, 29). The available data are insufficient to set an upper level for dietary potassium. A British expert group proposed an intake of 3.7 g/d from supplements as an upper guidance level for adults. Supplemental intakes up to this level are generally not associated with overt adverse effects, but certain preparations might induce mild lesions of the gastrointestinal mucosa. It seems prudent to include potassium from potassium-containing mineral salt in this figure.

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33 Iron

Iron mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	15 / 9[1]	9	8	9	11
Average requirement	AR	10 / 6[1]	7			
Lower intake level	LI	5[1]	7			
Upper intake level	UL	60	60			

[1] post menopause.

Introduction

Iron deficiency anaemia (IDA) is the most common micronutrient deficiency across the globe (1), and many population groups have high iron requirements but insufficient iron intake or absorption to meet their needs. The relative iron requirement is greatest in infants and young children (aged 6–24 months) and adolescents (aged 12–16 years) because of the rapid growth rates in these age groups. During childbearing years, women also have increased needs for iron because of iron losses due to menstrual bleeding and the transfer of iron to the foetus during pregnancy. Iron overload can also occur, and people with hereditary haemochromatosis are those most likely to be affected. The prevalence of this condition is much higher than previously assumed, and up to 7 per 1000 Caucasians of Northern European descent are homozygous for the C282Y mutation in the HFE gene as recently reported by Thorstensen et al (2).

Dietary sources and intake

Recent dietary surveys in the Nordic countries show that iron intake among adult men and women ranges from 11 to 14 mg/d on average with a considerably lower intake among women than men. The average intake in Iceland is 9.4 mg/d among women and 12.5 mg/d among men between

the ages of 18 and 80 years old, but the intake of women of childbearing age is 10.2 mg/d (3) and the intake of 6-year-olds was recently shown to be 11.1 mg/d (4). In Finland, the figures for adults are 13.2 mg/d for men and 10.0 mg/d for women after the fortification of wheat flour was ceased (5). The figures for Swedish adolescents are 14 mg/d for boys and 9 mg/d for girls compared to 12.3 mg/d and 10.4 mg/d for adult men and women, respectively (6). The majority of iron in the Nordic diet comes from cereal products, some of which, for example breakfast cereals, are iron-fortified. However, the bioavailability of that iron seems to be low and today fortification of cereals in Finland, Sweden, and Denmark has ceased. Lower proportions of iron have traditionally come from iron-rich foods such as a variety of meats and lean meat.

To ensure a higher absorption of iron from the diet, people with high iron needs, such as adolescent girls and women of childbearing age, can increase the bioavailability of iron by several means. For these vulnerable groups, foods with factors that enhance iron absorption, such as vitamin C, should be included in meals containing iron. Examples of such foods are fresh vegetables or vegetable salad, fresh fruits and berries, and fruit juice. Meat, fish, and poultry contain a factor (MPF-factor) that also enhances iron absorption from food. In addition, these groups of people should avoid foods that inhibit iron absorption. A significant inhibitor of iron absorption is the calcium found in cow's milk and other dairy products, and these foods should be consumed in moderation. However, cow's milk is an important source of several nutrients and should not be eliminated from the diet simply due to its effect on iron absorption. The influence of enhancing and inhibiting factors on iron absorption is most noticeable in single-meal studies, and studies on whole diets over longer time periods have shown varying effects, and sometimes no effect, on iron absorption.

Physiology and metabolism

Iron is essential to virtually all living organisms. The most important biological characteristic of iron is its ability to alternate between two oxidation states – ferrous iron (Fe^{2+}) and ferric iron (Fe^{3+}) – that can donate or accept one electron, respectively. Due to the poor solubility of ferric iron at physiological pH and the ability of ferrous iron to reduce oxygen intermediates to harmful free radicals, all organisms have developed binding molecules (chelators) to transport and store iron and to control its reactivity (7, 8).

Iron has many vital functions in the body, the most significant of which

is to form the oxygen-binding part of haemoglobin (Hb) that transports oxygen from the lungs to the tissues. Iron is also found in myoglobin, the oxygen-binding protein in muscle fibre. Iron is an important component of many enzymes that transfer oxygen and electrons in a variety of metabolic pathways in the liver, brain, and endocrine organs. For example, iron is necessary for the function of cytochromes that are part of a series of enzymes that couples energy to ATP formation during oxidative phosphorylation.

The human body can store iron as ferritin and haemosiderin that are storage proteins in the liver, spleen, and bone marrow. Minute amounts of ferritin are also found in plasma in an iron-free form, and the serum ferritin level (s-ferritin) is considered to reflect the size of the body's iron stores.

Absorption and bioavailability

Iron homeostasis is maintained through absorption. Compared to many nutrients, however, iron is poorly absorbed by the human body and iron metabolism in the human body does not have an associated excretory pathway. As an aid to maintaining iron homeostasis, the body produces absorption regulators. An example of such a regulator is the small peptide hepcidin that is encoded by the HAMP-17 gene and is predominantly expressed in the liver (9). Absorption in the intestine depends on the iron status of the body, the amount and type of iron in the diet, and the composition of the meal (10).

Iron in foods exists as either haem iron or non-haem iron. Haem iron constitutes about 10% of the total iron in the Nordic diet and is mainly found in meat where it accounts for about half of the total iron content. Iron in grains and other plant-derived foods is in the form of non-haem iron. Haem iron is generally more efficiently absorbed than non-haem iron and it is not subjected to the same regulatory mechanisms. Absorption is increased in subjects with iron deficiency compared with normal subjects, and this demonstrates that absorption depends on the body's iron stores (11). About 25% of the total amount of haem iron is usually absorbed from food and is in general not affected by other food components, although reduced bioavailability of haem iron due to interaction with calcium has been reported (12). The absorption of non-haem iron depends on the composition of meals. Absorption of non-haem iron is enhanced by ascorbic acid with the most pronounced effects at moderate intakes of up to 100 mg/d of ascorbic acid (13, 14), but a less pronounced effect is seen in complete diets compared to single meals (15). It is still unclear to what extent organic acids other than ascorbic acid promote absorption. Iron absorption is also

enhanced by the MFP-factor found in meat, fish, and poultry (16). A possible explanation for enhanced absorption because of muscle protein in e.g. meat is that partially digested peptides, cysteine and histidine residues from muscle proteins, bind iron and form complexes that are soluble and available for absorption. The enhancing effect of muscle tissue on iron absorption is mainly protein related but this indicates that other factors might also play a role in enhancing iron absorption (17).

The absorption of non-haem iron is inhibited by phytates and their metabolites, iron-binding polyphenols such as tannins, and calcium (12, 18–20). Manganese in larger amounts than can be obtained from food can compete with iron for absorption in the intestines (21).

Copper and zinc are divalent metals, and it has been suggested that a high iron intake can influence intestinal absorption of these two minerals and potentially lead to deficiencies. Copper is believed to use the same transporter protein as iron, divalent metal transporter 1, but zinc is believed to use specific zinc transporter proteins (22). A recent study in mice reported the modulation of iron absorption through hypoxia/HIF-2 that is independent of hepcidin and duodenal iron levels but is reflective of overall body copper status (23). In a systematic review (SR) undertaken for the Nordic Nutrition Recommendations, no conclusive evidence could be found with regard to the effect of iron supplementation on zinc and copper absorption (24). Intervention studies by Domellöf and co-workers (25) and Harvey and co-workers (26) gave supplemental iron to breastfed infants or pregnant women and found no significant effects on zinc or copper levels. Troost et al investigated the effects of a single dose of 100 or 400 mg iron versus placebo in 55-year-old ileostomy subjects and found lower zinc absorption but no difference in copper absorption after iron administration (27).

The effects of enhancing and inhibiting factors on absorption can be seen in studies on different diets. Fruits and vegetables rich in vitamin C and meat can counteract the effect of inhibiting factors (28). Tea and coffee to a lesser extent, drunk with a meal reduce the absorption of non-haem iron because of the iron-binding polyphenols that they contain. Even cocoa diminishes absorption for the same reason, but it also contains considerable amount of phytates. A SR concluded that there was suggestive evidence that tea drinking might have a negative impact on iron nutrition in individuals with marginal iron stores (24). There is no reason to advice against tea in conjunction with meals for the general population, but in subpopulations at increased risk of IDA it could be considered advisable

to drink tea only between meals. The SR concluded that tea drinking has only a marginal impact on iron status in the Nordic countries because tea drinking is not very widespread and most people in these countries have adequate iron stores.

Phytic acid is mainly found in unprocessed fibre-rich products. Part of the phytic acid is degraded during the leavening of bread. Low pH, which can be obtained, for example, with a lasting sourdough leavening or if acetic acid is added to the dough, increases the probability of phytic acid breakdown and iron absorption increases (10, 19). Calcium, however, reduces the breakdown of phytates during dough fermentation and baking (12). Calcium also has a direct inhibiting effect on both haem and non-haem iron absorption indicating a mucosal rather than luminal effect (12). Measurements from single meals showed that 40 mg calcium did not reduce iron absorption, but one glass of milk (165 mg calcium) caused a 50% reduction in iron absorption. There was a dose-dependent effect up to a consumption of 300 mg calcium in the meal, and higher quantities of calcium did not cause any further reduction in the absorption of iron. Other experiments that evaluated iron absorption from the diet showed that iron absorption was reduced by about 40% when milk was drunk with an iron-rich meal compared to when water was drunk with such a meal (29, 30). Supplemental calcium has also been shown to reduce iron absorption substantially when taken with meals (31).

The influence of enhancing and inhibiting factors on iron absorption appears to be most apparent in single meal studies, and studies of whole diets show varying results. Two-week studies comparing iron absorption from a whole diet containing either enhancing or inhibiting factors of absorption found about two times higher iron absorption from the diet with the enhancing factors (32). Algorithms for calculating the absorption of iron have also been developed for adults (33, 34). The algorithm of Hallberg and Hulten (34) predicts the effects of dietary factors known to influence iron status based on their content in consumed foods with consideration taken of the interactions between individual factors such as phytate, polyphenols, ascorbic acid, meat, fish and seafood, calcium, eggs, soy protein, and alcohol (34).

Hunt and Roughead found no effect of enhancing and inhibiting components in iron-replete men over time and concluded that their subjects homeostatically adapted to a diet of high or low iron bioavailability to maintain body iron stores (35). Another study on subjects with normal iron stores showed long-term calcium supplementation with meals had no effect on iron status, but short-term supplementation decreased iron

absorption (36). A study on complete diets for 5-day periods reported no effect from calcium intake or the intake of animal foods and vitamin C on the absorption of non-haem iron in 14 subjects with normal iron status (37). Cook and Reddy found that the facilitating effect of vitamin C on iron absorption from a complete diet was far less pronounced than that seen in single meals (15).

Despite the varying results from studies on whole diets, subjects with poor iron status seem to benefit from a diet rich in factors enhancing iron absorption.

Iron deficiency and iron deficiency anaemia

Development

When iron supply is inadequate, the development of iron deficiency (ID) proceeds continuously from normal iron status to iron deficiency anaemia (IDA), a serious health concern. Initially body iron stores diminish, which is reflected in a decreasing concentration of s-ferritin. When iron can no longer be obtained from stores, iron deficiency in tissues develops and this leads to increasing levels of transferrin and transferrin receptors (TfR). This in turn leads to reduced transferrin saturation and a higher concentration of erythrocyte protoporphyrin, which is often assayed as an increasing serum level of zinc protoporphyrin (ZPP) because zinc is incorporated into the protoporphyrin molecule in the absence of iron (38). Finally the Hb level starts to decrease, and if the negative iron balance is not corrected anaemia develops. Anaemia is defined as a level of Hb two standard deviations below the mean of the population. Iron status variables in iron-replete individuals and those with IDA overlap (39, 40). Indications of the effect of iron deficiency on the formation of red blood cells, e.g. reduced mean cell (corpuscular) volume (MCV), can be seen before stores are completely emptied (41–43).

Effects of iron deficiency

ID can lead to various symptoms. Serious consequences of ID are anaemia (IDA), reduced work capacity, and impaired cell-mediated immunological defence. Altered temperature regulation has also been noted in connection with ID (44). Of particular concern is the suggestion that severe IDA seems to affect children's mental development and cognitive functions. These effects might even be irreversible depending on the age of the child, the severity and duration of the deficiency, and the child's socioeconomic environment (38, 45–49). ID without anaemia has also been shown to be associated with lower scores in cognitive tests (50, 51). In summary, ID

and IDA are associated with poor physical, cognitive, and behavioural performance, impaired neurodevelopment and growth inhibition in children, hypertension, and reduced immune function (50–54).

Assessment and indicators of iron status

Several indicators are used for the detection of ID, but s-ferritin is considered to be the best single indicator of iron status and is also the most widely used (55). S-ferritin levels are a good indication of the size of the iron stores in the absence of infection and inflammation, and the WHO recommends 12 mg/L as the cut-off for children below the age of 5 years and 15 mg/L for males and females 5 years and older (56). These cut-offs are based on global criteria that also include various races and countries, including developing countries. Lower s-ferritin values have been used as cut-off values for ID in infants and young children, e.g.10 mg/L in the Euro-Growth study (57), and this reference value was also used for US children up to 5 years of age in a nationwide study (58). Scientists from different countries have used values <12 mg/L as the cut-off for s-ferritin in adolescence (58–64). Other indicators of iron status are s-transferrin levels (total iron binding capacity, TIBC), transferrin saturation (s-iron/TIBC), and s-TfR levels (serum transferrin receptor). Transferrin saturation is less useful for detecting ID due to diurnal variations in s-iron, and s-TfR is considered among most sensitive indicator of functional iron depletion (65). The level of transferrin saturation is, however, very useful as a screening variable for hereditary haemochromatosis (56). In recent years, s-Tfr/s-ferritin has also been used as an indicator of iron status in scientific studies (59, 60). Free erythrocyte protoporphyrin (or ZPP) and MCV become abnormal relatively late in the development of ID (65) so alone they would be relatively insensitive indicators of iron deficiency and are not often used in studies on iron status.

Anaemia is defined as a reduced concentration of Hb. According to the WHO, Hb <110g/L should be used to diagnose anaemia in infants and children from 6 months up to 5 years of age and 115 g/L in children up to 11 years of age (56). Higher values are recommended for children aged 12–14 years and in adult women (120 g/L) and men (130 g/L), but during pregnancy the cut-off is lowered to 110 g/L. However, reference values for Hb (and also for other iron status variables) are still not sufficiently validated in infants and young children. In clinical practice as well as in research, the commonly used cut-off levels to identify ID and IDA in infants (Hb <110 g/L and s-ferritin <10–12 mg/L) are, in fact, extrapolated from

older age groups and there are indications that they might not be appropriate (66). Emond et al suggested a cut-off of 97 g/L for Hb in 8-month-old infants (67). Others have used cut-offs of 105 g/L (68, 69) and 100 g/L (66, 70) in similarly aged infants.

IDA is defined as Hb concentrations below a given cut-off in addition to abnormal iron status indicators. The number of iron status indicators used for diagnosis, as well as their cut-offs used for indicating iron deficiency, varies (Table 34.1.). Sometimes only s-ferritin is used, but some studies have used the approach that the individual is diagnosed with IDA when two out of three iron status indicators are below (or above) a given cut-off together with a concentration of Hb below the cut-off.

Table 34.1. Cut-off values for different iron status indicators

Indicator	Units	Adults		Children and adolescents	Infants aged 4/6/9 months[c]
		Males	Females		
Haemoglobin (Hb)	g/L	<130 [a]	<120 [a]	<105 [b]<110 [a]	<105/105/100 <105 [d]
Serum ferritin	mg/L	<15 [a]	<15 [a]	<12 [a, i, j]	<20/9/5
Mean cell volume (MCV)	fL [k]	<80 [c, e, f]	<80 [e, f]	<74 [g]	<73/71/71
Serum transferrin receptors (TfR)	mg/L	>8.5 [f, h]	>8.5 [f, h]	>8.5 [f, h]	>11/11/11
Free erythrocyte protoporphyrin	mg/dL erythrocyte	>70 [e]	>70 [e]	>80 [e]	
Transferrin saturation	%	<16 [e]	<16 [e]	<12 [e]	
Total iron binding capacity (TIBC)	mg/dL	>400 [e, f]	>400 [e, f]		
Zinc protoporphyrin (ZPP)	mmol/mol				>75/75/90

a WHO (56).
b Thorsdottir et al (75).
c Domellof et al (66).
d Michaelsen et al for 9-month-olds (68).
e Expert Scientific Working Group (55).
f The US recommendations (14).
g Gill et al (149).
h Baynes (65).
i Samuelson et al (59).
j Samuelson et al (60).
k fL, is 10^{-15} L.

Prevalence of iron deficiency and iron deficiency anaemia

Globally, it is estimated that about 25% of pre-school children have IDA (71). In studies from Norway, Sweden, and Iceland published in the years 2004, 2008, and 2011, the prevalence of ID and anaemia was relatively low, and ID (s-ferritin <12 mg/L) in 12-month-olds was 10%, 18%, and 6%, respectively (72–74). In a Norwegian study published in 2004, 13% of two-year-olds had s-ferritin <12 mg/L (72), but at the age of two years iron status generally improves. Poorer iron status at one and two years of age has been related to faster growth from birth (75, 76), but other reasons, such as nutrient imbalance, cannot be excluded (72). Iron status in young children seems to have improved since the 1990s, and a report on iron status in the 1990s in the Nordic countries can be found in chapter 34 in NNR 2004 (77). In a Danish study, 5% of 9-month-old infants had anaemia (defined as Hb <105 g/L) and 20% had Hb <110 g/L, but no cases of IDA were found (68). In the 1990s, the prevalence of Finnish children aged 3–4 years with Hb <110 g/L was 4% (78). The prevalence of ID among adolescents and adults varies from study to study in the Nordic countries (77). In Norway, ID was found in 5%–18% and 6%–30% of 13- to 15-year-old Norwegian boys and girls, respectively (79). In a Swedish longitudinal study from 15 to 21 years of age, s-ferritin concentrations <12 mg/L were found in 2%–3% of males and in 18%–26% of females (60). Studies have found ID in 10%–22% of Nordic women of childbearing age and IDA in 0%–17% of pregnant Nordic women (77, 80).

Only a few studies have been conducted on iron status in elderly populations in the Nordic countries, and very few of these are recent studies. The prevalence of low Hb among the elderly (>65 years) has been found to be 0%–5%. ID is relatively uncommon in 70-year-olds, and even more uncommon in healthy 80- and 85-year-olds, but high iron stores (s-ferritin >300 mg/L) have been observed in 8.7% of elderly men and 3.7% of elderly women (77, 81).

Requirement and recommended intakes

In the recent SR on the health effects of iron intake, it was concluded that there is no reason to alter the NNRs on iron intake from those in NNR 2004. The SR suggested that advice on iron supplements should be given to pregnant women and to parents of low birth weight infants (24).

The recommended daily intakes of iron for adult men, post-menopausal

women, and children are based on the amounts needed to cover basic losses and growth for approximately 95% of the individuals in each age group. The lower intake level (LI) of iron for adults is the same in NNR 5 as in NNR 2004. That level was also suggested by UK's Scientific Advisory Committee on Nutrition (SACN) 2010, which generally defined lower intake levels as two standard deviations below the average requirement (AR) (82).

Women's requirements for iron during childbearing years are not normally distributed, which makes decision-making on recommended intakes more difficult. The recommendation in NNR 5 is an intake that meets the iron needs of approximately 90% of menstruating teenage girls and women and is similar to what was recommended in NNR 2004.

Iron stores of vegetarians are lower than non-vegetarians, but the incidence of IDA has been shown to be similar (83, 84). However, vegetarians and athletes, especially female athletes, are two groups that might deserve special attention with respect to their iron needs.

Children and adolescents

Children and adolescents need iron to cover basic losses and for growth. Full-term infants have iron stores sufficient to cover their needs during the first 4–6 months of life. The concentration of iron in human milk is low and is similar to that in cow's milk (0.3–0.4 mg/L), but this low level is to some extent counteracted by the high bioavailability of iron in human milk (14). An infant's blood Hb concentration falls rapidly after birth, and iron is transferred from Hb to iron stores, which also helps to ensure that the full-term, normal birth weight, healthy, breastfed infant is virtually self-sufficient with regard to iron during the first 4–6 months of life. A recent randomized controlled trial found lower s-ferritin concentrations in 6-month-olds who had been exclusively breastfed for 6 months than those given small amounts of complementary food from 4 months of age. However, none of the infants had clinically low values that were significantly below the reference values (85). Healthy, full-term infants in a developed country who were either exclusively breastfed or given infant formula with only 1.6[3] mg iron/L did not develop ID during the first 6 months of life (86, 87). Infants, therefore, seem to have no need for extra iron from birth to 6 months even though their body weight doubles during this time.

All formula-fed infants theoretically have higher iron requirements due

3 Infants who are not breastfed during the first 6 months should be fed an iron-fortified infant formula. Infant formulas that are not fortified with iron should not be used.

to the lower bioavailability of iron from formula compared to breast milk. Even though an iron concentration of about 1.5 mg/L in infant formula would be sufficient, much higher levels of fortification have traditionally been used. In Europe, infant formulas are usually iron fortified to a level of 4–8 mg/L (88). The growth and development of the central nervous system (CNS) is rapid during early childhood and iron is critical for this process. Several case-control studies in children have shown a consistent association between IDA in early childhood and long-lasting poor cognitive and behavioural performance, and an association between early ID and later developmental scores has also been observed in the Nordic setting (50, 51). Meta-analysis including preventive trials in high-risk groups, mostly in low-income countries, and therapeutic trials in children with diagnosed IDA show limited but suggestive evidence that preventive iron supplementation of infants might improve psychomotor development (89). There is no evidence, however, for preventive iron supplementation before 6 months of life and beneficial effects on cognition or psychomotor development in healthy, breastfed infants of normal birth weight in low-risk populations such as the Nordic countries.

Based on the above evidence, no recommendation is given for the first 6 months[1]. In addition, there is evidence to suggest that during the first 6 months infants might not down-regulate their absorption of iron as efficiently as children and adults so excessive iron intake should be avoided in this age group. The recent SR, however, suggested that low birth weight infants (<2,500 g) should be given supplemental iron at a dosage of 1–2 $mg \cdot kg^{-1} \cdot d^{-1}$ from week 6 to at least 6 months of age (24). This is supported by a meta-analysis from 1992 (90), a randomized trial testing different amounts of supplemental iron to marginally low birth weight infants (91), and the WHO recommendation that iron supplements should be given to all low birth weight infants (92). Studies have shown that infants with higher growth rates are at greater risk of iron deficiency that is thought to be due to more rapidly depleted iron stores from birth that coincides with greater weight gain (93). It is well known that birth weight can influence iron endowment at birth (94). Low birth weight infants often have low iron stores at birth and they tend to grow faster, and this can increase the risk of developing ID and IDA. Infants who are born weighing between 2,000 g and 2,500 g represent 3%–5% of all infants in affluent countries (91). It has been previously reported that delayed umbilical cord clamping after birth can have a beneficial effect on the infant's iron status even up to 6 months of age (95, 96).

After the first 6 months of life, the requirement for exogenous iron is high and the infant now becomes dependent on iron-rich complementary foods (97). High intake of cow's milk (>300–500 mL/d) might be associated with ID (24, 75), and it seems prudent, therefore, to avoid such high intakes of cow's milk in infants and toddlers. This is supported by the reduced prevalence of ID at 12 months in infants after new recommendations suggesting the avoidance of cow's milk before 12 months of age and instead using iron-fortified formula (74). The basic iron requirements are similar from 7 months to 5 years of age, and the Nordic iron recommendation is 8 mg/d for children in this age range. This amount of iron, mainly provided by iron-fortified phytate-rich cereals, protects against ID late in infancy and also improves iron status in toddlers (76, 78, 98). A higher recommendation would require a diet unrealistically dense in iron for that age group and much denser than for older children and adults. For children 6–9 years old, the iron recommendation is 9 mg/d.

Table 34.2. shows the iron needs of adolescents and adults calculated from daily needs and losses using Nordic body weight values. The need for iron is relatively high in adolescence because it is a period of rapid growth. For 10- to 13-year-old boys, an iron intake of 9 mg/d meets the requirements of 95% of the population given a 15% absorption rate, and for 14- to 17-year-old boys about 12 mg/d is needed to meet their requirements (Table 34.2.). For boys aged 10–17 years, the Nordic recommendation of iron is 11 mg/d.

In addition to their requirement for growth and basal losses, adolescent girls need iron to cover losses during menstruation. Table 34.2. shows the total iron need for menstruating girls and women estimated by the sum of basal losses, the need for growth in adolescent girls, and menstrual losses. The iron need of 95% of 10- to 13-year-old pre-menarchal girls is 9 mg/d (Table 34.2.). The variation in menstrual losses is shown and used to estimate the 50th (median), 90th, and 95th percentiles of total iron need, with both basal losses and need for growth kept constant (Table 34.2.). The median daily iron requirement of adolescent girls is 10 mg, but 19 mg/d is required to satisfy the need of 95% of adolescent girls when assuming that the absorption rate is 15% (Table 34.2.). The iron need of about 90% of post-menarchal girls aged 10–17 years is satisfied by 14 mg/d (Table 34.2.). The 90th percentile of need represents the recommended intake and is justified by the fact that those in the top 5th percentile of iron need probably have a higher absorption rate than 15%. However, there will always be some small proportion of girls and women

with higher iron needs that must be satisfied with iron supplements. The recommended intake is 15 mg/d for 14- to 17-year-old girls and 11 mg/d for 10- to 13-year-old girls.

Women of childbearing age

The daily iron requirement is high among women during childbearing years because of blood loss during menstruation. This loss is highly variable between women, for example, it is diminished by contraceptive pills while contraceptive sponges enhance menstrual blood loss (99). The daily iron amount required to meet the need of 50% and 95% of adult women is 9 mg/d and 19 mg/d, respectively, given a 15% absorption rate (see Table 34.2.). The iron need for about 90% of women is satisfied by 15 mg/d. By the same criteria discussed for menstruating girls, the 90th percentile is chosen to represent the recommended intake because the top 5th percentile probably has a higher absorption rate than 15%. The recommended iron intake is 15 mg/d for women of childbearing age.

Table 34.2. Iron needs of adolescents and adults calculated from daily needs and losses

Age (years)	Weight (kg)	Need for growth (mg/d)	Basal losses (mg/d)[1]		Menstrual losses (mg/d)[2]		Total iron need (mg/d)			Necessary intake of iron from foods to cover 50%, 90%, and 95% of the iron need of groups on a diet for which iron absorption is assumed to be 15% (mg/d)		
	mean		median	median	90%	95%	median	90%	95%	50%	90%	95%
Boys												
10–13	37.5[5]	0.55	0.53				1.08		1.35	7		9
14–17	57[5]	0.60	0.80				1.40		1.75	9		12
Men												
18+	76[6]		1.05				1.05		1.37	7		9
Girls												
10–13[8]	38.5[5]	0.55	0.54				1.09		1.36	7		9
10–13	38.5[5]	0.55	0.54	0.46[3]	1.05	1.69[4]	1.55	2.14[7]	2.78[7]	10	14	19
14–17	53.5[5]	0.30	0.75	0.46[3]	1.05	1.69[4]	1.51	2.1[7]	2.74[7]	10	14	18
Women 18+	62[6]		0.87	0.48[3]	1.35	1.90	1.35[2]	2.22[7]	2.77[7]	9	15	19
Women after menopause	62[6]		0.87				0.87		1.13	6		8

1 Basal losses are estimated to be 0.014 mg·kg^{-1}·d^{-1} (105).
2 Evaluated from the amount of menstrual blood in ml/28 days (99, 105). For girls, the median and 90% intakes are based on reference (78) and the 95% intake on reference (11, 12). Menstrual losses for girls are assumed to be the same in both age groups. Haemoglobin concentration is calculated as 135g/L and it is assumed that 1 g of haemoglobin contains 3.34 mg iron. Menstrual iron loss (mg) = [blood loss (mL)/28 days × 135 g Hb/L × 3.34 mg iron/g Hb)/ (1000 mL/L)].
3 Calculated with a median blood loss of 28.4 mL for adolescent girls and 30 mL for adult women every 28 days (99, 105).
4 Calculated from the equation in the US recommendations derived from a fitted log normal distribution with a Monte Carlo simulation [ln (blood loss) = 3.3183 + 0.6662(SD)] (14).
5 Children weights 1973–1977 (77).
6 Mean weight of men and women aged 15–80 years (6).
7 Sum of basal losses, need for growth, and 90th and 95th percentiles of menstrual losses, respectively. It is assumed that there is no distribution in values for basal losses and need for growth.
8 Not menstruating.

The calculated estimates in Table 34.2. assume that blood losses in menstruation are the same as in the 1960s, although it is known that oral contraceptive use today is higher, which might mean less blood loss and, therefore, lower requirements (100). However, a recent study by Hunt et al showed slightly higher daily total iron excretion by menstruating and postmenopausal women (101) than the NNR estimates, and this would mean higher requirements. The levels in that study were average losses, not medians as shown in Table 34.2., and this might partly explain the difference (101). Also, data on body weight, e.g. growth of children and adolescents, indicate that the average weight of the different age groups

of the population is slightly higher than used in Table 34.2. (102), but the reference weights chosen are based on Nordic healthy weights before the current obesity epidemic. Even if these factors were to be taken into consideration, they would not change the estimates for necessary intake from foods as shown in Table 34.2.

As discussed earlier in this chapter under 'Absorption and bioavailability', the composition of meals can affect the absorption of iron, especially in iron-deficient individuals. It is difficult to put together a menu that contains enough iron to meet the needs of almost all women if the recommendations of the proportions of energy-giving nutrients and fibre are to be maintained and iron-fortified products are not used. It can, therefore, be important for some women to improve the bioavailability of the iron consumed by evaluating meal compositions. Two small studies looking at iron status markers in women with low iron stores support the recommendation of 15 mg/d. One studied iron intake between 11.5 and 13.9 mg/d over 8 weeks that maintained iron status independently of a fish or a meat diet (103). Supplementation with approximately 15 mg iron in a fruit-based meal every day appeared sufficient to substantially improve iron status over 16 weeks (104).

Pregnancy and lactation

Maternal iron need during pregnancy increases slowly as the pregnancy progresses because of growth and maintenance of the foetus and uterus, the increase in red blood cell count, and the expected iron losses when giving birth. According to Hallberg, the total iron requirement is 1,040 mg during pregnancy, of which 840 mg goes to the foetus or is lost while giving birth (105). During the first trimester of pregnancy, iron intake must cover basal losses. Iron demand increases during the second trimester and is greatest during the third trimester. Even though iron absorption increases during the last two thirds of pregnancy, for some women the amount of iron in food is not enough to satisfy the greatly increased iron demand that takes place during pregnancy. The US recommendation during pregnancy is 27 mg/d (24). Studies by Milman et al (106), Makrides et al (107), and Sandstad et al (108), and supported by other studies, provide probable evidence that supplementing with 40 mg iron/d from week 18–20 of gestation, without any knowledge of s-ferritin values, will achieve prevention of ID in more than 90% and IDA in more than 95% of women at delivery and at 6–8 weeks postpartum (24). Supplementation with 40 mg iron/d from week 18–20 of gestation might be adviced. The

supplementation could either be given as a general prophylaxis of 40 mg iron/d to all pregnant women or as an individual prophylaxis of 60 mg iron/d or 40 mg iron/d depending on whether s-ferritin is below 30 mg/L or between 30 mg/L and 70 mg/L measured early in pregnancy or before 15 weeks of gestation. Both regimens would prevent ID and IDA at delivery and at 6–8 weeks postpartum in more than 90% and 95% of cases. There is, however, no evidence that maternal iron supplementation has any effect on the offspring in the Nordic countries (24).

During the first months of lactation, menstruation has often not yet resumed and, therefore, the need for iron during lactation might be less than usual (109). This is the basis for the lower US recommendations for lactating women compared to other women of the same age (14). The median iron needs are assumed to be the sum of basal losses and iron secretion in human milk with no menstrual losses. However, women may have low iron stores postpartum and many women in the Nordic countries breastfeed their infants for quite a long time – greater than six months – and menstrual losses can start within the partial breastfeeding period. Therefore, 15 mg/d is recommended for lactating women, which is the same as for women of childbearing age who are not pregnant.

Post-menopausal women and adult men

Older women and adult men have to replenish basal losses of iron. Minimum iron intake has not changed since the NNR 1989 and varies from 5 mg/d to 7 mg/d depending on body size. As shown in Table 34.2., the median need is 6 mg/d for post-menopausal women and 7 mg/d for adult men and the requirements of the 95th percentile are met by a dietary intake of 8 mg/d or 9 mg/d, respectively. The recommended intake of iron is 9 mg/d for both post-menopausal women and adult men.

Upper intake levels and toxicity

Under physiological conditions, iron status is almost exclusively regulated by adaptation of intestinal iron absorption to demand and this process is well described for both deficiency and supply via food. Several studies indicate that this regulation operates up to the level of an additional 10–15 mg iron/d (11, 14, 40, 110, 111). However, Fleming and co-workers found that an additional iron intake of >30 mg iron per day was associated with an increased risk of high iron stores that are defined as plasma-ferritin >300 mg/L or >200 mg/L in elderly men and women,

respectively (112). Thus, the homeostatic regulation of iron absorption in elderly people seems able to prevent iron overload at a total iron intake of 17.5–25 mg/d (10 mg/d habitual dietary intake + 7.5–15 mg/d), but not at a total intake of 40 mg/d (10 mg/d habitual dietary intake + 30 mg/d). Theoretical calculations of prolonged intake of pharmaceutical iron and s-ferritin levels showed that ingestion of an extra 60 mg iron/d over 5 years or more would risk building up excessive iron stores in a fertile non-pregnant woman with a body weight of 63 kg (113). Long-term effects of high iron (12 mg/L) infant formula from 6 to12 months of age in healthy, non-anaemic infants were found in a follow-up at 10 years of age as lower scores for visual-motor integration (114). This negative effect seemed to be limited to those infants who were initially iron-replete but suggests possible adverse effects of excessive iron intake during late infancy. NNR 5 set the upper limit (UL) for iron for non-pregnant adults at 60 mg/d. It is not possible to set an UL for infants, but infant formulas should not provide more than 8 mg/L (88).

Acute effects of iron overload

Ingestion of an acute overdose of pharmaceutical iron preparations causes mucosal erosion in the stomach and intestine. Young children are especially at risk (115). Due to damage to the intestinal mucosa, non-controlled iron absorption can be high and cause acute systemic symptoms such as shock due to vascular dilatation, capillary leakage, and heart failure. Iron can also damage organs such as the liver, pancreas, kidney, CNS, and red blood cells (115).

Nausea, vomiting, heartburn, and epigastric discomfort, along with constipation and occasionally diarrhoea, are common side effects of oral therapeutic doses of iron (116–118). The mechanisms are mucosal irritation, alteration of gastrointestinal motility, and the rapid transfer of iron into the circulation. The occurrence of side effects of therapeutic iron is dependent on the dose and the luminal iron concentration. The lower dose level associated with such acute effects seems to be 50–60 mg iron/d (116, 117).

Chronic effects of iron overload

Because iron absorption is homeostatically regulated, at least in adults, the risk of iron overload from dietary iron is mainly limited to individuals with hereditary (primary) haemochromatosis, a relatively common disorder in the Nordic countries with a reported frequency of homozygosity for

the C282Y mutation ranging from 0.20% to 0.75% (2, 119). In primary haemochromatosis, iron absorption is increased 2 to 3 times in homozygotes due to a genetic defect in the HFE gene. Three mutations have been described, and for the two most common, C282Y and H63D, the frequencies of homozygotes are about 0.4% and 2%, respectively, in Scandinavia (2, 119, 120). Individuals who are heterozygous for the C282Y mutation do not appear to respond abnormally to dietary iron and, therefore, do not need to change their diet to prevent accumulation of iron in the body (121). Homozygosity for the C282Y mutation is most often associated with clinical signs of haemochromatosis and risk of developing serious symptoms even at the iron levels normally present in the diet. These symptoms include hepatomegaly, hepatic fibrosis, and hepatoma in addition to joint inflammation, diabetes mellitus, cardiomyopathy, and cardiac failure. The treatment is phlebotomy. If untreated, the risk of symptoms is five times higher in men than in women due to a constantly higher loss of iron among women via menstrual bleeding. The penetrance of the C282Y mutation, which is the most frequent one leading to haemochromatosis, has been estimated to be between 1% and 25% depending on the study design and the endpoints used (122).

Studies have found moderate and slight liver fibrosis in several cases with hepatic iron concentrations of 51 mmol/g to 240 mmol/g dry weight (123, 124). Hepatic fibrosis and iron concentration have also been correlated to s-ferritin levels. In the study by Bell et al, a dose response curve for severity of fibrosis and s-ferritin was found, and s-ferritin was mostly above 1000 mg/L in those with liver fibrosis (124). The median s-ferritin concentration for the mildest form of fibrosis was 858 mg/L with values as low as 520 mg/L. Åsberg et al found a clear correlation between hepatic iron and s-ferritin with quite a wide distribution (123). To keep hepatic iron below 400 mmol/g of dry weight, the limit for s-ferritin would be about 250 mg/L. In this study, 4 of 12 patients with moderate liver fibrosis had s-ferritin concentrations below 1000 mg/L and ranged from 311 mg/L to 629 mg/L.

Earlier reports have described secondary haemochromatosis caused by high intake of iron, e.g. as part of a habitual intake of iron-contaminated beer or as pharmaceutical iron, over a period of several years. Iron doses thought to stimulate secondary haemochromatosis might exceed 150 mg/d (77).

Iron and risk of cardiovascular disease

In the NNR 2004 a possible relationship between iron overload and cardiovascular disease was discussed, but no stable or causal relationship between iron and risk of cardiovascular disease had been established (77). In the recent SR (24), an association between both hypertension and cardiovascular disease was explored. The evidence for a relationship between haem iron intake and cardiovascular disease was determined to be suggestive based on the SACN report of 2010 that evaluated iron and cardiovascular disease and iron and health (82). This relationship between iron overload and cardiovascular disease has also been shown in the Iowa women's health study cohort in women using more than 10 g of alcohol per day and even more clearly in women using more than 30 g of alcohol per day (125). Some studies have indicated a protective effect of iron intake against high blood pressure, but no conclusions (24) could be drawn about associations between high iron intake and lower blood pressure either as intake during pregnancy *vs.* blood pressure in the offspring (126, 127) or as intake *vs.* blood pressure in adults (128, 129).

Iron and risk of cancer

According to a recent meta-analysis, individuals carrying the C282Y haemochromatosis mutation have an increased risk of hepatocellular carcinoma (130). Regarding extra-hepatic malignancies in the general population, there were studies cited in NNR 4 indicating an increased risk of colon cancer and other cancers related to high iron stores (77). However, a causal relationship between iron and extra-hepatic cancer could not be established. Several new studies have examined the possible relationship between dietary iron intake and various forms of cancer (131–140). However, no convincing evidence that dietary iron intake is associated with increased risk of colon cancer, lung cancer, breast cancer, oesophageal cancer, or other cancers could be found (24).

Iron and risk of diabetes

Based on the SR undertaken for NNR 5, there is probable evidence for an association between haem iron intake and type 2 diabetes (T2D) as well as gestational diabetes mellitus (GDM). Three recent large epidemiological studies have examined the association between iron intake and T2D (141–143). The studies reported similar figures for the lowest and the highest quintile of haem iron intake and they arrived at the exact same relative risk for T2D (RR = 1.28). No effect or an inverse effect on the risk

of T2D was seen for non-haem iron and for total iron intake. Two case studies looking mainly at the association between markers of iron stores and risk of T2D (144, 145) also found that cases with T2D had the highest intake of haem iron.

High intake of haem iron before or during pregnancy seems to increase the risk of developing GDM (146, 147). The studies on the association between haem iron intake and T2D and GDM adjusted their data for many confounders, but the facts that haem iron intake is closely related to the intake of red or processed meat and that subjects with high haem iron intake had significantly less healthy behaviour in terms of diet, physical activity, smoking, and BMI (142), as well as an absence of an effect of total iron intake, suggest that there are other dietary or lifestyle factors rather than iron that increase the risk of T2D. Haem iron intake might be an indirect marker of T2D development, but a meta-analysis found that the intake of both unprocessed and processed red meat was positively associated with T2D risk after adjustment for age, BMI, and lifestyle such as smoking (148). The association between haem iron and T2D could, therefore, be related to the increased risk of T2D that is associated with the intake of red meat.

There is probable evidence for the association of haem iron intake with the risk of T2D and GDM even though these associations might not be causal. Because there is no evidence that total iron intake is associated with increased risk of T2D, this does not have any implication for recommended daily intakes of iron.

There is no conclusive evidence for an association between iron intake and type1 diabetes (24).

Reasoning behind the recommendation

Requirements and recommendations for iron were based on calculations including the body's estimated basal loss of iron (taking body size into account), the requirements for growth of a child, an adolescent and fetus and maternal growth in pregnancy, and the estimated menstrual losses of a woman in fertile age. Varying absorption of different groups depending on possible iron status was taken into account. The recommendations of iron in NNR 2012 are maintained unchanged from NNR 2004 since no strong scientific evidence to change has emerged.

Upper level of iron intake

Epidemiological data on the association between iron and the risk of cardiovascular disease, cancer, or diabetes do not permit the establishment of any dose-response relationships with dietary iron. Consequently, a quantitative UL for iron intake cannot be set on this basis, nor is it possible to directly derive a limit based on liver fibrosis or increased hepatic iron and s-ferritin concentrations. However, it seems clear that an s-ferritin level above 300 mg/L, which is often referred to as "biochemical iron overload" when caused by increased iron stores, is associated with an increased risk of slight liver fibrosis. Based on homeostatic control of iron absorption and the risk of biochemical iron overload, the UL might occur at intake levels between 10 mg/d and 30 mg/d of additional iron over and above typical dietary intakes. A regular intake of 60 mg/d in a fertile woman has been calculated to lead to biochemical iron overload, and a quantitative UL for iron intake in addition to habitual dietary iron is set to 10 mg non-haem iron per day in order to avoid such overload. Based on the above evidence, the UL for total iron intake is 60 mg/d.

Although it is not possible to establish a cause-effect relationship between iron and diseases, it seems prudent at least in sub-populations such as adult males, post-menopausal women, and heterozygotes for haemochromatosis to avoid an intake of iron above the current recommendation, which already provides for the highest need.

Studies indicate possible adverse effects of high iron intake during late infancy. Infant formulas, therefore, should not provide more than 8 mg/L of iron.

Maintaining an iron intake below the UL would also protect against the local intestinal toxicity that is a side effect of therapeutic iron. The lower dose level of iron associated with such acute side effects seems to be in the range of 50–60 mg/d.

The UL and intake advice do not apply to individuals receiving iron prophylaxis and pharmaceutical iron preparations under medical supervision, such as pregnant women (for whom a supplement should be considered in the amount of 40 mg/d from week 18–20 of gestation) and low birth weight infants.

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34 Zinc

Zinc mg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y girls/boys
Recommended intake	RI	7	9	6	7	8/11
Average requirement	AR	5	6			
Lower intake level	LI	4	5			
Upper intake level	UL	–	–			

Introduction

The biochemical role of zinc (Zn^{2+}) is as an essential part of more than 300 enzymes involved in synthesis, metabolism, and turnover of proteins, carbohydrates, lipids, nucleic acids, and some of the vitamins such as vitamin A. Well known zinc-containing enzymes include superoxide dismutase, alkaline phosphatase, and alcohol dehydrogenase. Zinc is essential for normal function of the immune system and normal DNA synthesis and cell division and protects proteins and lipids from oxidative damage. Dietary intake of zinc has also been related to maintenance of normal bone density, cognitive function, fertility and reproduction, metabolism of fatty acids, acid-base metabolism, vitamin A metabolism, and vision (1, 2).

Dietary sources and intake

Good sources of zinc are meat, milk and milk products, and whole-grain cereals. The intake of zinc in the Nordic countries is approximately 12–14 mg/10 MJ (see the chapter on Intake of Vitamins and minerals in Nordic countries).

Physiology and metabolism

Absorption of zinc is dependent on the dose and occurs mainly in the upper part of the small intestine. Absorbed zinc is transported in the blood, mostly bound to albumin. The majority of body zinc – estimated to be between 2 g and 4 g in adults – is located within cells. Approximately two thirds of the body's zinc is located in muscle tissue and one third is found in bone tissue. Plasma zinc only represents 0.1% of total body zinc.

High concentrations of zinc are found in parts of the eye and in prostate liquid. Zinc is excreted through the kidneys, skin, and gastrointestinal tract. Strong homeostatic mechanisms keep the zinc content of tissues and fluids constant over a wide range of intakes through changes in excretion and absorption. The molecular mechanisms involved in this regulation, however, are not fully understood.

Well-defined clinical zinc deficiency has only been reported in a limited number of cases that are related to incomplete total parenteral nutrition, malabsorption, and the use of drugs. Estimates based on evaluation of zinc intakes and diet composition in different parts of the world suggest that the populations of many countries in Asia and Africa are at high risk for developing zinc deficiency and that the risk is low in European countries and North America (1). The clinical manifestations of severe zinc deficiency are growth retardation, delayed sexual maturation, skin lesions adjacent to the body orifices, hair loss, and behavioural disturbances (3). These clinical signs have almost exclusively been observed in subjects with an inborn error in zinc transport (acrodermatitis enteropathica) and in adolescents subsisting on diets with a presumably very low availability of zinc. The consequences of moderate and mild zinc deficiency are still unclear.

In a meta-analysis of randomized controlled trials by Brown and coworkers (4) covering the years 1966–2001, zinc supplementation was associated with increases in both height and weight. The responses were greater in children with low initial weight-for-age z-scores. However, results from a more recent meta-analysis did not show any improvements in linear growth in intervention studies including zinc supplementation only (5). Studies published after those included in the study by Brown et al. accounted for the difference, possibly reflecting improvements in zinc status in many parts of the world (5). Further, zinc has successfully been used as a pharmacological agent to treat chronic diarrhoea in countries where zinc deficiency is prevalent (6). Zinc plays a role in the synthesis and action of insulin and seems to stimulate insulin action and insulin

receptor tyrosine kinase activity, but the role of zinc supplementation in the prevention of type 2 diabetes mellitus remains unclear (7). Further studies are also needed to assess potential benefits and risks of maternal zinc supplementation on pregnancy and lactation outcomes (8).

Requirement and recommended intake

Adults

The only biomarker recommended by WHO/UNICEF/IAEA/IZiNCG (9) to assess the zinc status of populations (not individuals) is measurement of serum or plasma zinc concentration. Serum zinc concentrations fall sharply when dietary zinc intakes are less than ~ 2 to 3 mg/d, but rise slightly but continuously when intakes are greater, reaching plateau when intakes reach ~ 25 to 30 mg/d (10), However, because the plasma zinc concentration is also influenced by factors unrelated to zinc status, such as food intake, infection, and tissue anabolism or catabolism the measurement cannot be used for estimating zinc requirements. In addition, the activities of the zinc-dependent enzymes explored so far have not proven sensitive enough to identify optimal or desired levels of zinc intake. In populations in which signs of zinc deficiency have been observed, reliable food intake data are usually not available. Consequently, zinc requirements have to be estimated by the factorial method, i.e. estimates of the daily losses of zinc and the corresponding amount of zinc to be ingested to replace these losses. Additional zinc is needed during periods of tissue growth. The use of the factorial method to estimate zinc requirements is complicated by a strong homeostatic regulation of body zinc – primarily through changes in endogenous zinc excretion – and by the pronounced impact of diet composition on zinc absorption and potentially also on the excretion of zinc. At zinc intakes close to zero, total endogenous zinc losses through urine, faeces, and skin are on the order of 0.5–0.6 mg/d (8, 11), and a daily intake of 10–15 mg of zinc results in losses of >4 mg/d. During the first few days on low zinc intakes, before adaptive mechanisms have become fully operational, zinc losses are approximately 1.0 mg/d and 1.4 mg/d for women and men, respectively (8, 11).

The dietary requirement is dependent of the efficiency of absorption. Fractional zinc absorption is dependent on zinc content; when intakes are increased, fractional absorption decreases. However, the relationship is not linear and the amount of zinc absorbed increases when zinc intake increases. Superimposed on the relationship between intake and fractional

absorption is the effect of enhancing and inhibiting components in the diet (12). At low intakes of zinc in diets with no inhibitors, the fractional absorption can be >50% (13), but at more common intakes 15–40% is absorbed depending on the composition of the diet. Phytic acid, which is present in cereals and leguminous plants, inhibits zinc absorption, and animal protein counteracts this inhibition (14, 15). From a cereal-based meal with a high content of phytic acid, 10–15% of the zinc is absorbed, but 20–40% can be absorbed from meals based on animal protein sources depending on the zinc content. In some foods, the negative effect of phytic acid is partly counteracted by a high zinc content.

A number of single-meal studies using radioisotope techniques have been undertaken to identify the dietary factors affecting absorption and their relative impact. Relatively few studies have measured zinc uptake from total diets with realistic compositions, and the techniques used in these studies are based on the use of stable zinc isotopes that are typically added in amounts that account for 20% or more of the total zinc content.

The U.S. Food and Nutrition Board (16) set the recommended daily allowance (RDA) was set to 11 mg/d for men and 8 mg/d for women. Although the absolute numbers are similar to those of other expert reports and the approach used is the same factorial method, they have introduced a somewhat different concept in the calculations. The data used are almost exclusively derived from total diet studies using semi-synthetic basic diets or blended low zinc foods with added zinc and stable zinc isotopes for the absorption estimates. The FNB used a three-step approach to estimate the average requirement of zinc. First, the losses of zinc via routes other than the intestine are estimated. These losses are regarded as constant over the range of intake that encompasses zinc requirements. For men, the estimates for losses via kidneys and sweat, integumental losses, and losses in semen are estimated to be 0.63, 0.54, and 0.1 mg/d, respectively. For women, menstrual zinc losses are estimated to be 0.1 mg/d and losses via kidneys and skin are estimated to be 0.44 mg/d and 0.46 mg/d, respectively. Thus, total losses via these routes are 1.27 mg/d and 1.0 mg/d for men and women, respectively. The second step, and the new concept, is the use of the relationship between the quantity of zinc absorbed and the excretion of endogenous zinc via the intestine. In the stable isotope/balance studies used for this calculation, the data suggest a linear relationship between absorbed zinc and intestinal (endogenous) excreted zinc. The constant losses via other routes are added and the point where the absorbed zinc is equal to the sum of the endogenous intestinal excretion and the

other losses is taken as the minimum requirement for absorbed zinc (i.e. the physiological requirement), which is 3.84 mg/d for men and 3.3 mg/d for women. The same studies are then used to calculate the amount of zinc that has to be ingested to give this amount of absorbed zinc. These calculations give an EAR of zinc of 9.4 mg/d and 6.8 mg/d for men and women, respectively. In the third step, a coefficient of variation of 10% is used as an estimate of the inter-individual variations and the RDA is set to 11 mg/d and 8 mg/d. Thus, the major differences in the U.S. estimates compared to other reports are a much higher estimate of the physiological requirement, the use of estimates of the endogenous intestinal losses, a higher estimate of the fractional absorption, and a smaller figure for the inter-individual variations.

In NNR 2004 (17), the following estimates were made. For the estimate of the endogenous losses and routes other than the intestine, the Food and Nutrition Board figures (16) have been used although it should be noted that the majority of the studies quoted in that report were performed at a time when reference urine samples were not available for quality control purposes. Losses via kidneys, skin, and semen or menses are thus set at 1.27 mg/d for men and 1.0 mg/d for women. Endogenous intestinal losses are estimated to be 1.4 mg/d for both genders based on the observed losses at low intakes (1–5 mg/d). Thus, 2.67 mg/d and 2.4 mg/d for men and women, respectively, have to be absorbed in order to replace these losses. At these levels of intake, absorption from a mixed animal and vegetable protein diet more realistic for Nordic conditions is assumed to be 40%. The average dietary requirement of zinc is, therefore, 6.4 mg and 5.7 mg for men and women, respectively. Using an inter-individual variation in requirement of 15%, the recommended intakes were set to 9 mg/d for men and 7 mg/d for women. This recommended intake probably has a high safety margin because the ability of the body to adapt to lower intakes appears to be substantial.

In NNR 2012, the RIs from 2004 are kept unchanged, since no new scientific data that justify a change has emerged.

Lower intake level

Balance studies with a combination of a semi-synthetic formula based on egg white and low zinc foods have shown that an intake of 4.4 mg/d or 4.6 mg/d for 35 days or 10 weeks do not give any indications of an impaired zinc status or the need for adaptation based on plasma levels and zinc excretion in urine (18, 19). The latter study also showed no changes

in exchangeable zinc pool mass during the low intake diet. These data are used as the basis for the lower limit of zinc intake.

Children

Data on endogenous losses of zinc at different intakes are almost completely lacking for children. In relation to body weight, children appear to have larger losses of zinc than adults. The need of zinc for growth is a daily intake of approximately 175 mg/kg during the first month and then a daily intake of approximately 30 mg/kg for the next 9–12 months (20). For growing children, the need for zinc is based on basal losses of 0.1 mg/kg and a zinc content in new tissue of 30 mg/kg. For adolescents, growth is assumed to result in an average zinc content in new tissue of 23 mg/kg due to an increase in fat tissue with a lower zinc content than that in younger children. The physiological requirements for rapidly growing adolescents can, therefore, be increased by 0.3–0.4 mg/d. Applying the same principles as for adults, the recommended daily zinc intake varies from 2 mg in the youngest age group to 12 mg for adolescent boys. In NNR 2012, the RIs from 2004 are kept unchanged.

Pregnancy and lactation

The total need for zinc during pregnancy for the foetus, placenta, and other tissues is approximately 100 mg (21). This additional need for zinc in pregnancy can be met by an increase in zinc intake or by adjustment in zinc homeostasis. There is no evidence that pregnant women increase their intake of zinc, so homeostatic adjustments in zinc utilization must be the primary mechanism for meeting the additional zinc demands for reproduction (21). It is assumed that an increased efficiency of zinc absorption or other metabolic changes occur during pregnancy and these changes ensure that the requirement for zinc can be met with an unchanged intake. However, studies in this area are inconclusive and there are some that show increased absorption during pregnancy (22) and other studies that have found no significant increase in fractional absorption (23). The results from the latter study might reflect inadequate power of the study design. The U.S. recommendations from 2001 for zinc intake in pregnancy (16) are based on this reference. In NNR 2012, the RIs are based on an increase in the physiological requirement by 0.7 mg/d with adjustment for absorption. With adjustment for absorption, the additional dietary intake is set to 2 mg/d.

Ortega and co-workers (24) showed lower zinc concentration in the breast milk of women consuming less than 7.5 mg/d of zinc during the

third trimester. Zinc content in breast milk is approximately 2.5 mg/L in the first month of lactation and thereafter falls to approximately 0.7 mg/L after 4 months (20). Theoretically this means that the zinc requirement of lactating women is double that of non-lactating women. A fractional increase in zinc absorption of up to 70–80% has been shown for lactating women compared with non-lactating postpartum or never-pregnant women (23, 25). Release of zinc from bone tissue could also be an explanation why zinc concentrations in breast milk are relatively independent of the mother's zinc intake and do not seem to result in zinc deficiency of the mother even after a long period of lactation. An elevated intake corresponding to the zinc content in breast milk is recommended for women lactating for a long time, i.e. a physiological need of 1.7 mg/d. With adjustment for absorption, the additional dietary intake is set to 4 mg/d.

Reasoning behind the recommendation

The recommended daily intake in NNR 2004 (17) was based on estimated zinc requirements by the factorial method, i.e. estimates of the daily losses of zinc and the corresponding amount of zinc to be ingested to replace these losses. Additional zinc is needed during periods of tissue growth. In NNR 2012 the reference values are kept unchanged compared to NNR 2004 because there are no new scientific data to justify any major changes.

Upper intake levels and toxicity

The risk of excessive intake of zinc from food alone is very low. Symptoms of acute toxicity from excessive intake occur at intakes of gram quantities of zinc and are related to consumption of dietary supplements. Reduced activity of copper-containing enzymes has been observed with zinc intakes of 50 mg/d, and with slightly higher daily intakes of ≥150 mg more pronounced signs of impaired copper metabolism have been observed along with negative changes in immune defence and blood lipids (26–28). More recent studies in which strictly controlled intakes of copper and zinc were given showed that at zinc intakes of 50 mg/d no adverse effects on a wide range of relevant indicators of copper status could be observed (29–32). Based on these data, the EU Scientific Committee on Food set an uncertainty factor of 2 and arrived at an upper level of 25 mg zinc per day for adults and for children and adolescents the upper levels are extrapolated on a surface area basis (33). In recent years, zinc has been provided in

therapeutic trials (75–150 mg/d) for a few weeks up to few months. Zinc lozenges administered within 24 hours of onset of symptoms have been shown to reduce the duration and severity of the common cold in otherwise healthy people (34). However, there is a potential for zinc lozenges to produce side effects and further studies are needed to determine possible risks associated with long-term use of therapeutic doses of zinc for prevention of the common cold (34).

In NNR, no ULs intake limits are set for zinc.

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35 Iodine

Iodine µg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	150	150	90	150	120
Average requirement	AR	100	100			
Lower intake level	LI	70	70			
Upper intake level	UL	600	600			

Introduction

Iodine deficiency is considered to be one of the most common nutritional disorders in the world and the most common cause of goitre (1, 2). In Sweden and Finland, goitre in adults and cretinism in children due to iodine deficiency was common during the first decades of the 1900s. The introduction of iodine fortification of salt resulted in a sharp decrease in the prevalence of these ailments (3). In 2000, mandatory iodisation of table salt and bread salt was introduced in Denmark as a response to studies showing low iodine status and goitre in certain population groups (4, 5). In 2004–2005, urinary iodine excretion had increased significantly in all age groups compared with the excretion levels before mandatory iodine fortification (6). However, salt iodisation has not been required to reduce goitre in all of the Nordic countries. Before 1950, there was endemic iodine deficiency in Norway with goitre prevalence as high as 80% in certain inland areas (7). Iodine fortification of cow fodder resulted in a relatively high concentration of iodine in milk and dairy products, and high levels of consumption of these products led to eradication of endemic goitre (8). Iceland has long been known for its high iodine status that is believed to be due to high levels of fish consumption (9).

Dietary sources and intake

In plants, iodine occurs predominantly in inorganic forms and the iodine content varies with the iodine content in the environment. The iodine content in sea-plants is higher than in plants grown on land. The iodine content of milk and milk products varies considerably depending on the concentration of iodine in the animal fodder and the use of iodine-containing disinfectants in connection with milking. The iodine content is generally higher in winter milk than in summer milk (10). The iodine in drinking water varies considerably between regions and can be a significant iodine source in some locations (3, 11). Fish, especially marine fish and shellfish, generally have high iodine contents. Eggs can also be an important iodine source depending on the iodine concentration in the chicken feed.

Iodised table salt is available in Denmark, Sweden, Finland, and Norway and contributes to iodine intake. The concentration of iodine present in iodised salt varies from 5 µg/g to 50 µg/g, and Denmark also fortifies the salt used in bread (5, 6, 12). Iodised salt is not commonly used in Iceland (13), and in Norway the iodisation of cow fodder has been more important for iodine intake than iodised table salt (10, 14).

The dietary intake of iodine is difficult to assess in dietary surveys because data for iodised table salt and drinking water are commonly lacking. An overview of studies on iodine intake and excretion in the Nordic countries published from the year 2000 to 2010 is given in the NNR systematic review (SR) (15) that covered studies on health effects of dietary iodine intake.

Physiology and metabolism

Iodine is essential for a number of animal and plant species. Only vertebrates, however, have developed a thyroid gland for the synthesis, storage, and secretion of the iodine-containing hormones thyroxine (T4) and its biologically active form triiodothyronine (T3) (16). The utilisation of iodine in the thyroid gland occurs via active uptake of iodide (the iodide concentration is approximately 30 times higher in the gland than in plasma), incorporation of iodine in thyroglobulin and iodine tyrosine, and secretion of the iodine thyronines triiodothyronine and thyroxine. The thyroid-stimulating hormone (TSH) from the pituitary gland regulates the formation of the thyroid hormones.

The thyroid hormones regulate cellular metabolism. The mechanism of

action is not completely known, but protein synthesis of enzymes necessary for increased metabolic activity increases in response to these hormones. The thyroid hormones also increase the size and number of mitochondria – a sign of increased ATP-production.

Dietary iodine is generally efficiently absorbed as iodide, although some sources of iodine, such as seaweed and protein-bound iodine, are absorbed less efficiently (17, 18). For a mixed diet that provides about 200 µg/d of iodine, about 90% of the iodine is excreted in the urine (18). Faecal losses vary, but are in general only 10–20 µg/d. Small amounts are also lost through the skin. Iodine absorption and utilisation can be affected by goitrogens, mainly sulphur-containing glucosides (glucosinolates). These are dietary constituents that can inhibit the uptake of iodine into the thyroid gland (e.g. thiocyanates) or interact with hormone production (e.g. goitrins) (17). These compounds occur in *Brassica* species such as cabbage, Brussels sprouts, turnips, and rapeseeds. The levels of glucosinolates in the modern Nordic diet are generally too low to have an impact on iodine status.

The iodine concentration in breast milk varies with the iodine intake from the diet (19). Reported levels in breast milk from Danish mothers before the introduction of salt iodisation were about 30 µg/L (20). No data is available on the iodine content of breast milk from Danish mothers after the introduction of iodised salt. Older data from Finland reported average levels of 25 µg/L in breast milk from goitrous areas compared to 53 µg/L in non-goitrous areas (19). In Sweden, breast milk samples have been reported to contain 50–90 µg/L iodine (19). Smoking is associated with lower iodine concentrations in breast milk, possibly due to impaired iodine uptake in the mammary gland (21).

The recommended indicator for measuring iodine status is the median urinary iodine concentration (UIC) in the population. Other potential indicators of iodine status and thyroid function include the thyroid volume (TV) and the concentrations of TSH, T3, T4, and serum thyroglobulin (22–25). Iodine intake is regarded as sufficient when the median UIC in the population is 100–199 µg/L (19). Iodine sufficiency during pregnancy is defined as a median UIC of 150–249 µg/L (24).

Iodine deficiency presents primarily as non-toxic goitre, i.e. an enlarged thyroid gland with normal production of thyroid hormones. Non-toxic goitre can gradually progress to toxic goitre with an increased secretion of hormones and a subsequent increase in metabolism (thyrotoxicosis). In cases of hyperthyroidism, the thyroid gland can be enlarged (toxic goitre) either in a diffuse form (Basedow's or Graves' disease) or with focal

changes (nodular goitre). In more severe cases of iodine deficiency, cretinism – which is characterised by impaired growth, mental disturbances, and disturbances in speech and acuity (deaf mutism) – can occur in infants and children, and hypothyroidism (myxoedema) can occur in adults (2, 22, 26). Although more studies are needed, mild iodine deficiency has been suggested to be associated with developmental impairment in children (15).

Requirement and recommended intake

Adults and children

The recommendations in NNR 2004 (23) for adults and children remain unchanged because there is no new data supporting changes (15). The iodine requirement to prevent goitre (increased thyroid gland size) is estimated to be 50–75 µg/d or a daily intake of approximately 1 µg/kg bodyweight (27, 28). The average requirement (AR) is estimated to be 100 µg/d for both adult women and men, and at this intake the iodine concentration in the thyroid gland reaches a plateau. The daily iodine turnover in subjects with normal thyroid function is at a similar level (29). The recommended intake is set to 150 µg/d for adults and adolescents and this includes a safety margin for any goitrogenic substances in foods. The lower limit of intake for adults is estimated at 70 µg/d.

The recommended intakes for infants and children are based on data on goitre prevalence and urinary iodine excretion in European children (30) and on extrapolations from adults based on energy and growth requirements. In iodine-sufficient populations, breast milk will cover the needs of an infant during the first months of life. For children 2–5 years old, 90 µg/d is recommended and 50–70 µg/d is estimated to be sufficient for infants and children younger than 2 years old (31).

Pregnancy and lactation

During pregnancy and lactation, an extra daily supply is needed to cover the needs of the foetus, to maintain maternal thyroid gland function, and to provide sufficient iodine in the breast milk. In NNR 2004, an extra 25 µg/d was recommended during pregnancy and an extra 50 µg/d was recommended during lactation to provide sufficient iodine in the breast milk (23).

Results from the Norwegian Mother and Child Cohort Study showed that women who used iodine-containing supplements had higher levels of urinary iodine excretion than those who did not use such supplements

and that inclusion of milk and seafood in the diet is important to secure optimal iodine nutrition (32, 33). Results from a subsample analysis in this study (n = 119) indicate that iodine intake of at least 150 µg/d would be required to get the median UIC up to the optimal range of 150–249 µg/L for pregnant and lactating women defined by the WHO (34). Because pregnant women in the Nordic countries are generally well nourished and have easy access to milk, seafood, and dietary supplements, and because there is no new data supporting changes (15), the recommendations from NNR 2004 are kept unchanged. However, there is need for better surveillance and more data on the level of iodine intake that ensures normal thyroid function in both maternal and new-born in the Nordic countries (15). Studies from Norway and Iceland show that pregnant women who do not consume, or have low intake of, dairy and/or seafood and who do not obtain iodine from supplements are at great risk of having an inadequate iodine intake (13, 34).

Reasoning behind the recommendation

The recommended daily intake for adults in NNR 2004 was based on the iodine requirement to prevent goitre and maintain normal thyroid function. The recommended intakes for infants and children were based on data on goitre prevalence and urinary iodine excretion in European children (30) and extrapolations from adults based on energy and growth requirements. The recommended daily intake for pregnant and lactating women in 2004 was based on the extra daily supply needed to cover the needs of the foetus and to provide sufficient iodine in breast milk. Iodine deficiency is known to affect thyroid function of the mother and the neonate as well as the mental development of the child (24). The reference values are kept unchanged compared to NNR 2004 (23) because there are no new scientific data to justify any major changes (15).

Upper intake levels and toxicity

An iodine intake in excess of 2 mg/d can, in rare cases, cause sensitivity reactions such as rhinitis, nasal congestion, swollen salivary glands, headache, and acne-like skin changes (35). High iodine intakes can also cause disturbances in thyroid function. Symptoms include inflammation in the thyroid gland (auto-immune thyroiditis), goitre, and hypo- or hyperthyroidism (35). High iodine intakes from drugs, certain types of seaweed, or

supplements in amounts corresponding to up to 10 mg iodine per day have resulted in increased incidence of iodine goitre along with hyperthyroidism or myxoedema in certain cases (35–39). Very high iodine excretion (up to 1,700 µg per 24 h) has been reported in subjects consuming seaweed preparations (40).

There is a substantial inter-individual variation with respect to the dose of iodine that can cause adverse effects. This complicates the assessment of an upper safe limit of intake. Persons with normal thyroid function can, in general, tolerate prolonged consumption of iodine up to 1 mg/d (35). The Scientific Committee for Food has proposed 600 µg/d of iodine as the safe upper level (UL) for adults (41). The UL is based on elevations in TSH levels after iodine intake and an enhanced response in TSH levels to thyrotropin releasing hormone (TRH) stimulation. These effects are of a biochemical nature and are not associated with any clinically adverse effects. The UL includes an uncertainty factor and is also considered acceptable for pregnant and lactating women. In children, a median UIC ≥500 µg/L was found to be associated with increasing thyroid volume in children 6–12 years old but a UIC of 300–500 µg/L was not (42). The authors of that study, however, did not rule out the possibility of adverse effects of a UIC in the range of 300–500 µg/L that were not detected in the study (42).

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36 Selenium

Selenium µg/d		Women	Men	Children		
				2–5 y	6–9 y	10–13 y
Recommended intake	RI	50	60	25	30	40
Average requirement	AR	30	35			
Lower intake level	LI	20	20			
Upper intake level	UL	300	300			

Introduction

Selenium is found in all tissues, mainly as selenomethionine, an analogue to the sulfur-containing methionine, and as selenocysteine in various selenoproteins. Selenium primarily functions as a co-factor in antioxidant activities and thyroid hormone metabolism. Severe selenium deficiency can cause cardiomyopathy, and excessive selenium intake causes toxic symptoms. Organic and inorganic selenium compounds have different metabolism and different bioavailability.

Dietary sources and intake

Foods contain a number of selenium compounds. In animal foods, there are specific selenoproteins containing selenocysteine. Foods of both animal and plant origin contain selenomethionine and possibly some selenocysteine incorporated into proteins. The inorganic forms selenite and selenate are used in dietary supplements, but they are not normally found in food.

Assessment of selenium intake from food composition databases is difficult because the selenium content varies according to the selenium concentration of the soil where crops are grown or the animals graze. Fish and other seafood, eggs, and offal are relatively rich in selenium. Cereal products and vegetables grown in the Nordic countries, with the exception of Finland after 1984, have low selenium content, whereas wheat imported

from North America has high selenium content. In general, foods from seleniferous areas of Venezuela contain much more selenium than the same foods from Scandinavia or New Zealand where the selenium levels are low (1). The selenium concentration in meat and milk depends on the amount of organic selenium in animal feeds. Fodder is generally enriched with selenite, which has a limited effect on the selenium concentration of meat and milk. In Finland, selenate has been added to agricultural fertilizers since 1984 (2). Plants convert inorganic selenate to selenomethionine. It has been assumed that selenium is not essential for plants, but evidence from Finland suggests that low levels of selenium are beneficial for plant growth through several mechanisms (3). Supplementation with fertilizers has increased both human and animal intake of organic selenium in Finland. The most important sources of selenium in the diet of Finns today are meat (which provides 40% of the selenium consumed), dairy products and eggs (25%), and cereal products (20%) (2). In Norway and Iceland, the intake of selenium has been influenced by high-selenium wheat imported from North America. In Norway, an increased use of domestically grown wheat during the last 20 years has reduced the average selenium intake of the population as measured by a reduction in blood selenium concentrations (4). In Sweden selenium has been added to animal feed since the late 1980s, thereby increasing the intake from meat and dairy products. Fish and seafood are also important dietary sources. Some animal studies have shown poor bioavailability of selenium from fish, but there were differences in bioavailability between various fish species. In humans, selenium has been shown to be readily available from Baltic herring and rainbow trout (5, 6). Other human studies have suggested reduced bioavailability of selenium from fish compared with other selenium-containing foods (7, 8). The reason for the observed differences in bioavailability is probably due to the variety of selenium species in fish, which might vary in bioavailability. Selenium reduces the availability of mercury in fish (9).

The selenium content of meat depends on the animal feed used and whether it is supplemented with inorganic or organic selenium. In muscle meat, 50%–60% of the total selenium content might be in the form of selenomethionine, and about 20%–30% of the selenium in beef and up to 50% in poultry might be selenocysteine (10).

Dairy products contain selenium mainly as selenocysteine and selenite. Supplementation could result in a wider spectrum of selenium species. Plant foods cultivated in the Nordic countries without selenium-containing fertilizers generally have low selenium concentrations. The selenium con-

centrations in meat and milk from animals fed organically grown feeds might therefore be lower than meat and milk from animals conventionally fed. The selenium intake of people who regularly consume organically grown products might thus be lower. This also applies to vegetarians and vegans because plant foods might contain very little selenium.

Approximately 80% of selenium is absorbed from food. Selenomethionine is actively transported, but knowledge to what extent other organic selenium compounds from plants are absorbed and metabolised by the body is incomplete.

According to recent dietary surveys, mean selenium intake (per 10 MJ) in the Nordic countries is 57 µg in Sweden, 47 µg in Denmark, 63 µg in Norway, 86 µg in Finland, and around 85 µg in Iceland (2, 11–16). Mean serum selenium concentrations in adults from studies during the last two decades range from 70–100 µg/L in Denmark, Norway (17, 18) and 100–120 µg/L in Finland (2, 19). Results for Swedish adolescents are comparable (20).

Physiology and metabolism

Water-soluble selenium compounds and dietary selenium (mainly organic selenium in forms such as selenomethionine and selenocysteine) are effectively absorbed, and selenates and organic selenium are absorbed somewhat better than selenites. Selenium compounds are converted to selenides before they are incorporated into specific selenoproteins. Selenomethionine is incorporated as selenide into a number of unspecific proteins. Inorganic selenium salts are retained less effectively because a major proportion is excreted in the urine. At high intakes, detoxified excretory products such as dimethyl selenide and trimethyl selenonium ions are formed. The former is exhaled via the lungs, and the latter is excreted in the urine. Dietary selenium affects the selenium concentrations in serum or plasma and red blood cells, which are useful biomarkers for all species of selenium intake in deplete individuals. Only organic selenium forms show a dose-response correlation in selenium-replete individuals (7, 21). The selenium concentration in the toenails has been recommended as the best indicator of the long-term intake of organic selenium.

Men and women tend to have similar serum selenium concentrations despite different intakes. Part of the selenium in tissues is found in functional selenoproteins. The human selenoproteome has been reported to consist of 25 selenoproteins. These include the following glutathione per-

oxidases (GSHPx): cellular (cGSHPx), extracellular (eGSHPx), phospholipid hydroperoxide (phGSHPx), and gastrointestinal (giGSHPx). Together with other metalloenzymes, these peroxidases protect tissues against oxidative damage. It is believed that the essentiality of selenium is based on the effect of GSHPx and other selenoproteins. The iodothyronine deiodinases (types I, II, and III) that produce triiodothyronine and related metabolites from thyroxine are selenoproteins. Selenium also affects the activity of the selenoprotein thioredoxin reductases, which have a number of physiological functions (22). Selenoprotein P (SePP) is synthesised mainly in the liver and is present in plasma. It has a double function as a selenium transport protein and as an antioxidative protective enzyme, and it might protect endothelial cells and low-density lipoproteins against lipid peroxidation (10, 21, 23). Other selenoproteins with unknown functions are selenoprotein W and prostatic epithelial selenoprotein (24).

Requirement and recommended intake

Three syndromes are associated with selenium deficiency. The first is a type of cardiomyopathy that particularly affects children and young women and is associated with a low intake of selenium (< 20 µg/d). This syndrome, known as Keshan disease, has occurred in people from certain parts of China (25). A similar cardiomyopathy has been observed in some isolated cases during parenteral nutrition without selenium supplementation. Keshan disease likely has a dual aetiology that involves both a nutritional deficiency of selenium as well as an infection with an enterovirus (coxsackievirus) (26). The second syndrome is an osteoarthropathy that affects children in the low-selenium areas of China. It is characterized by metaphyseal involvement with swollen joints and shortened fingers and toes and is presumably caused by selenium deficiency in combination with other pathogenic factors. In the third syndrome, the combination of low iodine and selenium intake can lead to myxoedema with development of cretinism, which has been described in the endemic goitre area of central Africa (27).

In two Finnish studies from the 1970s, low serum selenium levels (< 45 µg/L) were associated with an increased risk of cardiovascular death (13a). In Denmark, men with serum selenium concentrations below about 75 µg/L were reported to have an increased risk of myocardial infarction (28).

In a recent Cochrane meta-analysis to determine the effectiveness of selenium supplementation for the primary prevention of cardiovascular

disease (CVD) and to examine the potential adverse effect of selenium on type 2 diabetes, twelve randomised controlled trials (RCTs) met the inclusion criteria and included a total of 19,715 randomised participants (29). The two largest trials (SELECT and NPC), which were conducted in the USA, reported clinical events. There were no statistically significant effects of selenium supplementation on all-cause mortality, CVD mortality, non-fatal CVD events, or all CVD events (fatal and non-fatal). There was a small increased risk of type 2 diabetes with selenium supplementation, but this was not statistically significant. Other adverse effects reported in the SELECT trial that increased with selenium supplementation included alopecia and dermatitis grade 1 to 2. The meta-analysis concluded that the trial evidence available to date does not support the use of selenium supplements in the primary prevention of CVD. However, the baseline selenium levels in the supplemented groups were substantially higher than the threshold value (45 µg/L) reported in the earlier Finnish studies.

The cancer-preventing potential of selenium has been investigated in several large studies. A meta-analysis investigating the preventive effect of selenium supplements on cancer reported by RCTs was published in 2011 (30). Eight articles on nine RCTs were included in the analysis, and the total number of participants was 152,538, with 32,110 participants in antioxidant supplement groups and 120,428 participants in placebo groups. In a random effects meta-analysis of all nine RCTs, selenium supplementation alone was found to have an overall preventive effect on cancer incidence. Among subgroup meta-analyses, the preventive effect of selenium supplementation alone on cancer was observed in populations with a low baseline serum selenium level (< 125.6 µg/L) (RR = 0.64; 95% CI = 0.53–0.78; I^2 = 45.5%; n = 7) and in populations with a high risk for cancer (RR = 0.68; 95% CI=0.58–0.80; I^2 = 41.5%; n = 8). The meta-analysis indicated that there is possible evidence to support the use of selenium supplements alone for cancer prevention in people who have a low baseline level of serum selenium or a high risk for cancer.

The daily losses of selenium are determined by dietary intake and tissue stores and provide only limited information about requirements. The daily requirement of selenium is assumed to depend on body size. Selenium intakes of 30–40 µg/d are needed to achieve maximal GSHPx activity in serum. Intakes of 80 µg/d and 120 µg/d are needed for maximal GSHPx activity in red blood cells and platelets, respectively (31). It is not apparent, however, that maximal GSHPx activity in all tissues is necessary for optimal health.

In a 40-week supplementation study in Chinese subjects with a mean body weight of 48 kg, the plasma GSHPx activity was optimised with selenium supplements of 35 µg/d, and the SePP concentration was optimised with 49 µg/d of selenium (32). In a study of subjects with an estimated baseline selenium intake of 55 µg/d in the UK, it was found that the SePP concentration was optimised with a daily supplemenmt of 50 µg yeast selenium (33). Smaller doses were not studied, and the effects were not analysed separately for men and women. Unfortunately, only a few centres in the world are able to measure SePP. Many studies still rely on serum or plasma selenium as an endpoint for examining the response to changes in selenium intake or cross-sectional analyses to explore the association between habitual intake and selenium levels. Ballihaut et al. (34, 35) described the technical difficulties of measuring SePP. The effect of varying selenium intakes on the activity of newly discovered selenoproteins has not been studied in humans.

Information on selenium requirements for children and pregnant and lactating women is incomplete. During continued lactation, the selenium concentration of the mother's milk is reduced over time when selenium intake is less than 45–60 µg/d, but remains unchanged at intakes of 80–100 µg/d.

The selenium recommendations in different countries have been based on a Chinese study that showed maximal stimulation of plasma GSHPx activity in serum by selenium supplementation of 30 µg/d in people whose basal intake was 11 µg/d (36). In the NNR 2004, the recommendation was based on the mean + 2SD of this study and adjusted for the difference in mean body weight. The recommended intake was set to 50 µg/d for men and 40 µg/d for women.

It now appears more reasonable to base the recommendation on the optimisation of the plasma SePP concentration (32, 33), although the usefulness of this measure has been discussed for selenium-replete populations (37). In a 40-week placebo-controlled double-blind study of selenium repletion in 98 healthy Chinese subjects who had a daily dietary selenium intake of 14 µg, fourteen subjects each were assigned randomly to daily dose groups of 0 µg, 21 µg, 35 µg, 55 µg, 79 µg, 102 µg, and 125 µg of selenium as L-selenomethionine. Plasma glutathione peroxidase (GSHPX) activity, SePP1, and selenium were measured. The SePP1 concentration was optimized with the 35 µg supplement at 40 weeks, which indicated that 49 µg/d of total dietary selenium could optimize SePP concentration. GSHPX activity was optimized by the 21 µg supplement (total ingestion

of 35 µg/d). The plasma selenium concentration showed no tendency to become optimized (32).

Translating the results of the Chinese intervention study to Nordic conditions and correcting for average body size, the recommended intake in the Nordic countries should be 60 µg/d for men and 50 µg/d for women. The recommendation of the EU Scientific Committee on Food (SCF) and the US Institute of Medicine is 55 µg/d for both men and women (38, 39).

The EU SCF recommendation is 55 µg/d and 70 µg/d for pregnant and lactating women, respectively, and the recent US recommendation is 60 µg/d and 70 µg/d, respectively. The NNR 2004 recommendation was 55 µg/d for both pregnant and lactating women. Based on the considerations above, the NNR 2012 recommendation for pregnant and lactating women is increased to 60 µg/d.

The lower intake level for adults is unchanged from NNR 1996 at 20 µg/d.

The recommended intakes for children and adolescents are derived from the values for adults.

Reasoning behind the recommendation

Saturation of plasma SePP activity is now considered a better measure of adequate selenium status than the earlier used plasma GSHPx. Optimisation of SePP requires a higher intake of selenium than optimisation of GSHPx. In a recent study with Chinese participants, 50 µg/d of selenium optimised SePP (32). Correcting for body size, this would support a recommended dietary selenium intake of 50 µg/d for women and 60 µg/d for men in Western populations. The recommendation for pregnant and lactating women is increased to 60 µg/d, which accounts for the increased needs for tissue growth and lactation.

Upper intake levels and toxicity

Selenium toxicity is rare in humans but well known in animals. Acute toxicity has been observed after consumption of a large (250 mg) single dose or after multiple doses of ~30 mg. The symptoms include nausea, vomiting, and garlic-like breath odour. Other symptoms of toxicity are nail and hair deformities and, in severe cases, peripheral nerve damage and liver damage. Because of the risk of toxicity, high doses of selenium are not recommended. A no observed adverse effect level (NOAEL) for clini-

cal signs of selenium toxicity and a threshold of 850 µg/d for inhibited prothrombin synthesis were found in Chinese studies. The EU SCF derived an upper level of 300 µg/d using a factor of three to allow for uncertainties in different studies (40).

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37 Copper

Copper mg/d		Adults	Children		
			2–5 y	6–9 y	10–13 y
Recommended intake	RI	0.9	0.4	0.5	0.7
Average requirement	AR	0.7			
Lower intake level	LI	0.4			
Upper intake level	UL	5.0*			

* SCF 2003 (1).

Introduction

Copper has two oxidation states and is involved in oxidation and reduction reactions inside cells. Copper functions as a component of a number of enzymes involved in energy metabolism, the formation of connective tissues, and defence against free radicals.

Dietary sources and intake

Copper is widely distributed in food. The highest levels of copper are found in liver and other offal, while milk and milk products have a low copper content. Most grain products, meats, chocolate products, dried fruits, mushrooms, tomatoes, bananas, and potatoes contain intermediate amounts. The intake of copper in the Nordic countries varies between 1.0 mg/d and 2.0 mg/d (1).

Physiology and metabolism

Copper absorption occurs primarily in the small intestine. At normal dietary intakes (1–5 mg/d) absorption varies between 35% and 70% and is mainly regulated by the amount of copper in the diet, i.e. the percentage absorption decreases with increasing intakes. In the enterocytes of the small

intestine, copper is either bound to a copper chaperone or is chelated by metallothionein, which is a protein that is induced by zinc and sequesters copper in the mucosal cells and prevents its transfer into the circulation (2) At high zinc intakes (>50 mg/d), therefore, copper absorption is inhibited. The copper chaperones deliver the copper to copper transporting proteins for final absorption into the circulation. At high levels of dietary copper, passive diffusion also plays a role in the absorption of copper (3). After absorption from the gut, copper binds to albumin, transcuprein, low molecular weight copper histidine complexes, or a combination of these and is transported to the liver. Once absorbed into the liver, it has been suggested that copper is stored intracellularly by binding to either metallothionein or reduced glutathione. Release of copper from reduced glutathione or metallothionein makes copper available for other purposes and it is transported once again by chaperones. For example, the copper chaperone CCS1 traffics copper to superoxide dismutase (SOD) (4). Most of the copper in the plasma is transported as caeruloplasmin, which is produced in the liver. Homeostasis of copper is regulated to some extent by absorption, but also through excretion via bile, which can account for approximately 0.5 mg/d to 1.5 mg/d. Urinary excretion of copper is low.

The total body content of copper of an adult is approximately 50 mg to 120 mg, and 40% is found in muscle tissue, 15% in the liver, 10% in the brain, and approximately 6% in the plasma and erythrocytes. New-born infants have a larger amount of copper in the liver than adults, and this might act as a store of copper during the first couple months of growth. Copper deficiency in humans is rare, but it has been found in a number of circumstances. Copper deficiency has been observed in premature infants fed milk formula, in term infants recovering from malnutrition associated with chronic diarrhoea who have been fed cow's milk (5), and in patients with prolonged total parenteral nutrition without additional copper. Symptoms of copper deficiency in children are low concentrations of white blood cells, anaemia, and hair and skin depigmentation (6). Heart and skeletal abnormalities have also been observed. Most of the symptoms can be related to deficiencies in copper-containing enzymes.

There is substantial evidence from animal studies to suggest that diets low in copper reduce the activity of many of the copper-dependent metalloenzymes. The activity of some of these metalloenzymes has also been shown to decrease during human copper depletion (7, 8). There is also evidence that immune and cardiac dysfunction can occur during experimental copper deficiency and the development of such signs of deficiency

has been demonstrated in infants (7, 9). Furthermore, it has recently been demonstrated that low copper intake (<0.6 mg/d compared to a usual intake of >1.5 mg/d) might be associated with increased risk of colorectal cancer because low dietary copper increases faecal free radical production, faecal water alkaline phosphatase activity, and cytotoxicity in otherwise healthy males (10).

Serum copper and caeruloplasmin concentrations are currently used as biochemical indices of copper status and can be used to detect severe copper deficiency. The decline in serum copper and caeruloplasmin concentrations observed when healthy young men were fed a diet containing 0.38 mg/d of copper for 42 days was reversed by copper supplementation (11). In a number of other studies with higher levels of copper intake (0.66 mg/d and above) serum copper and caeruloplasmin concentrations did not decline significantly (12, 13), suggesting that this was a sufficient level of intake.

The dietary copper intake at which the serum caeruloplasmin concentration no longer increases in response to increased dietary copper might be considered the copper requirement for caeruloplasmin synthesis. Other suggested indices of copper status include SOD activity, platelet copper concentration, and cytochrome C oxidase activity because all of these have been shown to decline at low copper intakes. However, none of these indicators have been found suitable for detection of marginal copper deficiency or marginal copper toxicity (14). Instead, animal studies have suggested that copper chaperone CCS1 might be a potential biomarker for marginal copper deficiency and toxicity (14–16).

Requirement and recommended intake

Adults

The precise requirement for copper is not known. Indications of deficient copper status, using SOD activity as a marker of copper status, have been reported with intakes of 0.7 to 1 mg/d (17–19). However, other studies in young men have not found indications of changes in copper status based on SOD activity, caeruloplasmin production, or plasma copper concentrations at intakes of 0.79 mg/d for 42 days (12). In a subsequent study in young men, an intake of 0.66 mg/d for 24 days followed by an intake of 0.38 mg/d for 42 days resulted in decreasing indicators of copper status over time (11, 20). Although the levels did not fall into the deficient range, a steady state was not completely reached. Other studies have shown that intakes below 0.7 mg/d are associated with increases in biomarkers related to disease

such as faecal free radical production, faecal water alkaline phosphatase activity, and cytotoxicity (10) or deceased immune function (21). There are, therefore, limited data to establish an average copper requirement for adults, but the available data suggest that an intake of approximately 0.7–0.8 mg/d will maintain adequate copper status based on plasma copper concentrations, caeruloplasmin production, and SOD activity. The U.S. Food and Nutrition Board has based its recommended copper intake for adults on a number of indicators including plasma and platelet copper concentration, serum caeruloplasmin concentration, and erythrocyte SOD activity in controlled depletion-repletion studies (22). Data on obligatory copper losses were also used in these estimates. Based on these indicators, the average requirement was estimated to be 0.7 mg/d for adults. With a coefficient of variation of 15%, the recommended daily allowance of copper (RDA) was calculated to be 0.9 mg/d, and this recommendation has also been adopted in NNR 2012.

Children

The copper content of human breast milk is highest during early lactation and then declines over the course of lactation. The mean copper content of human breast milk during the first 6 months of lactation is approximately 0.25 mg/L (22), and there are no indications of inadequate copper status in breast-fed infants. For infants 6 to 11 months old, the requirements are based on extrapolation from adults with allowance for growth. The copper requirements for children older than one year have been calculated from estimates of adult requirements with allowance for growth (22).

Pregnancy and lactation

The requirement for extra copper during pregnancy is relatively low – approximately 0.15 mg/d in the last trimester – and this is probably met by adaptation through increased fractional absorption. The copper content of human breast milk is approximately 0.25 mg/L. With a milk production of approximately 750 mL/d and an estimated copper absorption of 50%, an extra 0.3 mg/d of copper during lactation is recommended.

Reasoning behind the recommendation

The recommendations from NNR 2004 are kept in NNR 2012 due to a lack of new data. Recommendations for children, pregnant and lactating women are also kept unchanged.

Upper intake levels and toxicity

Intake of high doses of copper leads to acute toxicity, which includes symptoms of gastric pain, nausea, vomiting, and diarrhoea, and storage of food in non-galvanised copper containers is associated with an increased risk of childhood sclerosis (26). In areas with soft water, copper can leach from copper tubes and result in high copper concentrations (more than 100 mg/L) in drinking water, and gastro-intestinal disorders have been seen with intakes of copper-contaminated water containing 3.7 mg/L (27). Infants are probably the most sensitive group, and case studies have indicated an association between high copper intake from water and symptoms of copper toxicity. Recent controlled and population-based studies found weak evidence for copper toxicity from drinking water at concentrations up to 2 mg/L (28), but it is considered prudent to recommend letting tap water run before it is used for consumption by infants, especially when used for formula.

The EU Scientific Committee on Food (SCF) has proposed that an upper limit of 5 mg/d is safe for adults (29). This is based on the absence of negative effects on liver function during copper supplementation and includes an uncertainty factor to allow for potential variability within the normal population. In addition, the SCF noted that the UL upper limit (UL) is not applicable during pregnancy and lactation due to inadequate data. The U.S. Institute of Medicine set an UL for copper of 10 mg/d largely based on the same data but used an uncertainty factor of 1.0 (22).

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38 Chromium

No recommendation given due to lack of sufficient evidence

Introduction

In ionic form, chromium exists in many valence states. Trivalent chromium (III) is the most stable form and is the principal form of chromium found in foods and dietary supplements. It is ubiquitous in nature and occurs in the air, water, soil, and biological materials. Hexavalent chromium (VI) forms chromates and dichromates that are strong oxidizers and can traverse biological membranes. Hexavalent chromium compounds occur only rarely in the environment and are almost always man-made. They are toxic, mutagenic, and environmental contaminants.

Dietary sources and intake

Analysis of chromium in foods requires special sampling procedures to avoid chromium contamination from the environment (air, stainless steel, etc.). Older analytical data on chromium contents in foods, produced before about 1980, should, therefore, be used with care. Fish, whole grain products, nuts, pulses, spices, and processed meats are good sources, but most other foods have at least low concentrations of chromium (<10 µg/100g). Foods high in simple sugars, such as soft drinks and table sugar, are not only low in chromium content but also promote chromium loss (1). Studies analysing chromium intake in the diet of the Nordic countries are scarce, but estimated intakes are in the range of 20–160 µg/d (2). Many food supplements contain chromium in doses ranging from 50–100 µg per serving unit.

Physiology and metabolism

Only 0.4–2.5% of the dietary intake of trivalent chromium is absorbed by the body (3). The element is mainly excreted via urine, and only small amounts are eliminated in sweat and bile. Organic chromium compounds are absorbed more efficiently but are rapidly excreted via bile. Simultaneous ascorbate administration increases chromium uptake both in humans and animals, and chromium absorption is also higher in both zinc- and iron-deficient animals.

The exact biological function of chromium has not yet been determined, but experimental chromium deficiency in animals results in reduced glucose tolerance in spite of normal insulin levels. Other deficiency signs in animals include impaired growth, elevated levels of serum cholesterol and triglycerides, increased incidence of aortic plaques, corneal lesions, and decreased fertility and sperm count.

Chromium is considered to be a cofactor for insulin, possibly through an influence on membrane receptors. A low molecular weight chromium-binding substance is believed to be involved in the process (4). It has also been suggested that chromium influences carbohydrate, lipid, and protein metabolism via its effect on insulin action.

Three cases have been reported of possible chromium deficiency in humans after long-term parenteral nutrition (5–7). The symptoms observed were impaired glucose tolerance and glucose utilization, weight loss, neuropathy, elevated concentrations of plasma fatty acids, depressed respiratory quotient, and abnormalities in nitrogen metabolism. The symptoms improved after chromium supplementation (200 µg/d). However, the reported concentrations of chromium in the blood and urine were above those considered normal even before the supplementation was initiated. As with foodstuffs, analytical data on chromium concentrations in biological specimens, produced before about 1980, should be regarded with caution because possible contamination in sampling and processing may have led to spuriously high levels of chromium (3). The lack of reliable biomarkers for chromium status combined with the absence of clear-cut chromium deficiency conditions are the main reasons for the current uncertainties about the biological significance of chromium as an essential trace element (3).

A number of chromium supplementation studies have been published that have investigated the effects of chromium on insulin and blood glucose levels (8) (9). In 20 randomized controlled trials (RCTs) included in a meta-analysis from 2002 (8), no effect of chromium on glucose or insulin

concentrations was seen in non-diabetic subjects. Although some studies suggested beneficial effects of chromium supplementation in individuals with type 2 diabetes (9), the results were inconclusive and further studies are needed to be able to make any claims about the benefits of chromium supplementation in this group (8–10).

Several studies have also investigated chromium supplementation in relation to body composition and lipid metabolism (10). Supplementation with 200–240 µg/d has been suggested to reduce concentrations of total and LDL cholesterol (10), but the number of studies in this area is still small and the studies that demonstrate such an effect have a high risk of being biased (10). The effects of chromium supplementation on body composition, therefore, remain inconclusive (10).

Requirements and recommended intake

As described above, the role of chromium as an essential nutrient is still unclear. If chromium is an essential trace element, it must have a specific role as an enzyme cofactor and a deficiency should produce a disease or impairment of function. Methods for evaluating chromium status are lacking, and there is still uncertainty about how chromium deficiency in humans manifests itself. Thus the requirement for chromium is not currently known.

The EU Scientific Committee for Food (SCF) (11) stated that "since data on the essentiality and metabolism of chromium are so sparse, the Committee is unable to specify any requirements". The UK Committee on Medical Aspects of Food Policy (12), however, used balance studies and regression equations to calculate a theoretical requirement for adults of 23 µg/d and stated that a safe and adequate intake level is believed to be greater than 25 µg/d for adults. The U.S. Food and Nutrition Board (13) estimated adequate intakes (AI) for chromium for different age groups based on calculations of well-balanced diets. For adults aged 19 to 50 years, the adequate intake was estimated to be 35 µg/d for men and 25 µg/d for women. Despite these estimates, the authors of a scientific report submitted to the European Food Safety Authority (EFSA) in 2012 came to the conclusion that evidence was still inadequate for setting dietary reference values for chromium (10). This conclusion was based on a systematic review including several relevant studies published between 1990 and 2011.

The Nordic Nutrition Recommendations of 2004 did not include recommendations for chromium intake. Because very few relevant human

studies have been conducted since then, it is still impossible to establish requirements and no recommendations have been set for any age group. Data are also lacking on the requirements for chromium during pregnancy, but the U.S. Food and Nutrition Board (13) suggests an increase of 5 µg/d during pregnancy over the usual chromium intake.

Within Europe, chromium concentrations in human breast milk range between 0.09 and 19.8 µg/L (10), and the chromium concentration appears to be independent of maternal chromium intake (14–16). A study on lactating Finnish mothers found an average concentration of chromium in breast milk of 0.4 µg/L (range 0.2–0.7 µg/L) (17).

Upper intake levels and toxicity

Trivalent chromium has generally low toxicity, no adverse effects were observed at intakes of 1,000–2,000 µg/d. Due to the lack of adequate data, the EU Scientific Committee for Food (11) has not suggested a Tolerable Upper Intake Level (UL) for chromium (III) salts. The same conclusion was reached by the U.S. Food and Nutrition Board (13) and the UK Expert Group on Vitamins and Minerals (11).

The consumption of chromium picolinate, a trivalent chromium compound popular in many food supplements, is currently being debated because of possible adverse health effects. This compound might influence the central nervous system and, therefore, behaviour (18), and high doses have been associated with kidney damage (19) and potential clastogenicity has also been reported (20). It is still unclear whether these effects are due to the picolinate formulation or to a higher degree of chromium absorption. The UK Food Standards Agency (21) advises people not to take chromium picolinate and has consulted on a proposal to ban the use of this form of chromium in the manufacture of food supplements because there is a chance that it could cause cancer. A review from 2004 (22), however, evaluated one particular brand of chromium picolinate and found it to be safe.

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39 Manganese

No recommendation given due to lack of sufficient evidence

Introduction

Manganese is chemically similar to iron. It is a catalytic cofactor for arginase, pyruvate carboxylase, and mitochondrial superoxide dismutase (SOD). Manganese also functions as a specific or unspecific activator for a large number of other enzymes, some of which participate in the synthesis of proteins, mucopolysaccharides, and cholesterol.

Dietary sources and intake

Wholegrain cereals, nuts, and leafy vegetables have high manganese contents. Tea may also substantially contribute to manganese intake. Manganese intake varies from very low (<2 mg/d) to high (>8 mg/d) depending on the diet. In the Swedish market basket study in 2010 (1), the daily estimated per capita intake of manganese was 4.0 mg. A Danish study in which 100 men collected duplicate portions of their regular diets for 48 hours showed a manganese intake of 3.9 mg/d (2). The manganese intake of Finnish children 3–18 years of age was in the range of 3–7 mg/d calculated from food consumption data and food contents (2). These data indicate that manganese intake is adequate in these countries. Multivitamin-mineral and mineral supplements for adults usually provide 2–5 mg per dose.

Physiology and metabolism

The total body content of manganese is estimated to be 10–20 mg. The concentration is relatively high in bone and in organs rich in mitochondria, such as the liver, pancreas, and kidney, and concentrations are low in

muscle and plasma. Absorption from the diet is low, approximately 5%, and excretion is primarily through the bile. Animal studies have shown that iron, calcium, and phytic acid reduce the absorption of manganese (3). A negative effect of calcium has been shown in humans, but the effect of iron and phytic acid in humans does not seem to be pronounced (4). High intakes of manganese inhibit iron absorption (5), and a higher absorption of manganese has been reported in cases of iron deficiency (6, 7).

Manganese deficiency in experimental animal models results in reduced growth, skeletal abnormalities, and defects in lipid and carbohydrate metabolism (3). In humans, only a limited number of deficiency symptoms attributed to lack of manganese, have been described in experimental studies with a manganese-deficient diet (8). Dermal changes and hypercholesterolemia are possible signs of manganese deficiency, as well as diffuse bone demineralization and poor growth in children. Very little information is available concerning the relationship between manganese intake and health endpoints or disease prevention (9).

Requirement and recommended intake

Our knowledge of manganese metabolism and the consequences of low intakes are insufficient for determining requirements and recommended daily intakes for humans. Balance studies have suggested that an intake of 0.74 mg/d should be sufficient to replace daily losses of manganese (10). Intakes over 1 mg/d generally result in a positive manganese balance (9).

The U.S. Food and Nutrition Board (11) found data to be insufficient for setting an Estimated Average Requirement (EAR) for manganese but used median intakes reported from the U.S. Total Diet Study 1982–9 as a basis for setting adequate intakes (12). An Adequate Intake (AI) for adult men and women is set at 2.3 and 1.8 mg/d, respectively. In 1993, the EU Scientific Committee for Food (13) suggested 1–10 mg/d to be an acceptable intake of manganese.

The NNR 2004 (14) did not include recommendations for manganese intake. Because very few relevant human studies have been conducted since then, requirements are still difficult to determine and, therefore, recommendations are not given for any age group.

Data are also too limited to determine requirements for manganese during pregnancy and lactation, and manganese deficiency has not been observed in pregnant or lactating women. Manganese excretion from breast milk is estimated to be below 1% of the total manganese excretion, and

there is no clear correlation between dietary intake and the concentration of manganese in breast milk (9). A systematic literature review of 15 studies published from January 1990 to October 2011 reported breast milk manganese concentrations of 0.8–30 µg/L (9). The median (SD) manganese concentration of 31 Swedish milk samples was found to be 3.23 (0.27) µg/L (15).

Upper intake levels and toxicity

Manganese toxicity, which manifests as psychological and neurological changes, has been observed in workers in manganese mines (7), and the neurological symptoms are reminiscent of those seen in Parkinson's disease. Inhalation of manganese dust is the likely explanation for these effects because toxicity due to a high dietary intake is unknown. Epidemiological studies, mostly cross-sectional, indicate that manganese exposure from drinking water might have a negative effect on the nervous system of children (16, 17). The EU Scientific Committee for Food (18) found that data for setting a Tolerable Upper Intake Level (UL) of manganese were too uncertain, and the UK Foods Standards Agency (19) has also found data to be insufficient to establish a Safe Upper Level for manganese.

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40 Molybdenum

No recommendation given due to lack of sufficient evidence

Introduction

Molybdenum has a number of valences and functions in oxidation-reduction reactions in plants and lower organisms. In humans only three molybdenum-containing enzymes are known: sulphite oxidase, xanthine oxidase, and aldehyde oxidase. These enzymes are involved in catabolism of sulphur-containing amino acids and heterocyclic compounds, including purines and pyridines.

Dietary sources and intake

Molybdenum is ubiquitous in food and water as soluble molybdates, but the content of molybdenum in plants varies widely with the soil concentration of molybdenum and pH. Good food sources are grains, legumes, nuts, offal, dairy products, and eggs. Fruits, root vegetables, and muscle meat are poor sources (1). High concentrations have been found in shellfish. Molybdenum levels in drinking water are mostly low, typically less than 0.01mg/L. However, in areas near mining sites molybdenum concentrations in the water of up to 0.2 mg/L have been reported (2).

There are few published studies on the dietary intake of molybdenum in the Nordic countries. Typical intakes according to supermarket baskets or dietary surveys are in the range of 100 µg/d to 150 µg/d (3–5). In the Swedish market basket study in 2010 (6), the daily estimated per capita consumption of molybdenum was 157 µg. Many multivitamin-mineral supplements contain molybdenum and these must be taken into consideration when estimating total dietary intake.

Physiology and metabolism

Molybdenum absorption from the diet is efficient (>80%), and the body content is primarily regulated via the kidneys.

There is only one recorded case of apparent molybdenum deficiency in humans, and this occurred in a subject receiving total parenteral nutrition (50 µg/d) for 18 months due to Crohn's disease (7, 8). Unconsciousness, heart disturbances, and night blindness were observed, and the symptoms disappeared after supplementation with 160 µg/d of molybdenum.

Stable isotopes have been used to investigate molybdenum metabolism in healthy men aged 22–33 years (9–12). Molybdenum absorption was efficient (about 90%) when subjects ingested diets containing five levels of the metal (ranging from 22 µg/d to 1,490 µg/d) for 24 days each. Excess molybdenum was rapidly excreted in urine, but whole-body retention was increased when the dietary level was low. Molybdenum status is difficult to determine because low plasma levels are tightly maintained by up-regulated urinary excretion in response to increased intakes (8).

Requirement and recommended intake

Adult men fed a diet with only 22 µg/d molybdenum for 102 days did not develop any symptoms of molybdenum deficiency leading Turnlund and co-workers (11) to suggest that the minimum daily requirement for this trace element is about 25 µg.

Based on these findings, the U.S. Food and Nutrition Board (13) set a Recommended Dietary Allowance (RDA) for adult men and women at 45 µg/d. The average dietary intake of molybdenum in U.S. men and women is more than twice this level.

The NNR 2004 (14) did not include recommendations for molybdenum intake. The evidence regarding molybdenum in relation to setting dietary reference values is still limited (8) and is not considered sufficient to establish requirements. Accordingly, recommendations are not given for any age group.

Upper intake levels and toxicity

The absence of toxicity symptoms in men with a daily intake of 1,490 µg molybdenum for 24 days (10) provides a working upper boundary for further studies. The U.S. Food and Nutrition Board (13) set a Tolerable

Upper Intake Level (UL) of 2 mg/d based on impaired reproduction and growth in animals. A British expert group concluded that there are insufficient data from animal and human studies to establish a Safe Upper Level for molybdenum (15). The Scientific Committee on Food (SCF) set the UL at 0.6 mg/d for adults and between 0.1 mg/d and 0.5 mg/d for children aged 1–17 years (16).

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41 Fluoride

No recommendation given due to lack of sufficient evidence

Introduction

Fluoride is found in food and drinking water either in an ionic form or bound in complexes. Fluoride has a well-documented role in the prevention and treatment of dental caries, but the mechanism is attributed to local effects on the tooth enamel surface rather than systemic effects. Fluoride is not considered essential for humans.

Dietary sources and intake

Fluoride levels in foods (except water) are generally low with a few exceptions. Fish eaten with the bones, such as canned sardines, some teas and mineral waters, and drinking water in some areas have the highest content. Little data on fluoride intake from food is available, but according to the EFSA (1) fluoride intakes from food (except for fruit juice, mineral water, and tea) for young children, older children, and adults are reported to be 0.04, 0.11, and 0.12 mg/d, respectively. Fruit juice, mineral water, and tea are estimated to contribute with 0.01 mg, 0.06 mg, and 0.26 mg fluoride, respectively. Tap water and other water sources such as mineral waters can contribute various amounts of fluoride depending on the concentration in the water. In the EFSA report, the contribution of fluoride from tap water in adults was reported to be around 0.06 mg/d at a concentration of 0.13 mg/L and about 0.5 mg/d at a concentration of 1.0 mg/L (1). Toothpaste can also contribute to the ingested fluoride, especially in small children. It is estimated that in adults <10% of the toothpaste is ingested because the spitting reflex is well developed, but the intake in children has been reported to be as high as 48% in 2 to 3 year olds, 42% in 4 year

olds, 34% in 5 year olds, and 25% in 6 year olds. In children aged 8 to 12 years, the ingestion is reported to be ~10% (2).

Physiology and metabolism

Fluoride in drinking water is effectively absorbed (>90%), but complex-bound fluoride in foods is less well absorbed. Approximately 50% of the absorbed fluoride is excreted via the kidneys, and the rest is incorporated into the bones and, in childhood, into the teeth. Thus, the main proportion of fluoride in the body is complex-bound to calcium in the skeleton and tooth tissues. These fluoride complexes can replace the hydroxyl ions in hydroxyapatite crystals – making the crystals less acid-soluble – and this was previously believed to be the basis for fluoride's ability to prevent dental caries. However, the presence of fluoride in the mouth and subsequent deposition of CaF_2 onto the tooth biofilm acts as a fluoride reservoir that can influence the balance between enamel demineralisation and remineralisation, and this is now recognized as the basis for the cariostatic effect of fluoride (3). Aside from this local effect, the biological functions of fluoride in humans remain uncertain.

Requirement and recommended intake

No recommendation for daily fluoride intake is given because it is not considered an essential trace element. This agrees with the EC Scientific Committee for Foods, which also did not set any recommended intake (4). The U.S. Institute of Medicine was unable to establish an RDA but has set an adequate intake for fluoride that is based on the observed estimated intake judged to reduce the incidence of dental caries in a group of healthy adults (5). For adults, this level was set to 3 mg/d and 4 mg/d for women and men, respectively (5).

Upper intake levels and toxicity

An intake of 2.2 g/kg bodyweight is lethal in adults. In children, 15 mg/kg bodyweight is lethal and 5 mg/kg bodyweight causes acute symptoms such as nausea, stomach pain, and vomiting. Chronic high intakes can affect skeletal mineralisation and kidney function (6). The most common side effect of high fluoride intake is enamel fluorosis or "mottled teeth". Fluorosed enamel is composed of hypomineralized sub-surface enamel

covered by well-mineralized enamel, but the exact mechanisms of dental fluorosis development have not been fully elucidated (7). High fluoride intake/exposure has been associated with effects on thyroid metabolism. However, the exposures necessary for caries prevention provided from toothpaste or drinking water have not been shown to affect thyroid function (1, 8, 9).

The EFSA (1) considered that a daily intake of up to 0.1 mg of fluoride per kg bodyweight in children up to 8 years old leads to no significant occurrence of "moderate" forms of fluorosis in permanent teeth. Based on this, a UL was set to 1.5 mg/d for children 1–3 years old, 2.5 mg/d for children 4–8 years old, 5 mg/d for children 9–14 years old, and 7 mg/d for older children and adults.

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42 Intake of vitamins and minerals in the Nordic countries

If a diet provides enough food to cover the energy requirements, complies with the ranges for distribution of energy from macronutrients, is varied and includes food from all food groups, the requirements for practically all nutrients will be covered. Exceptions might be vitamin D, iron, iodine and folate in subgroups of the population. The nutrient density of average diets in the Nordic countries is presented in Table 1. Data are calculated from recent national dietary surveys. Some of the pronounced differences may be explained by different dietary patterns (i.e. consumption of fish), levels of micronutrients added to foods (vitamin D, thiamin, riboflavin, vitamin B_6, iron and iodine) or differences in soil and composition of fertilizers (selenium). There may also be significant differences caused by the various survey methods and calculation procedures, e.g. recipes and correction for losses in cooking. Contributions to intakes of vitamins and minerals from supplements are not included.

For comparison the NNR 2012 recommended nutrient density for planning of diets (Chapter 1, Table 1.4.) is included in Table 1. These values are intended for groups of individuals with a heterogeneous age and sex distribution and they form a rather strict reference based on the principle of the 'most demanding subject' (explained in Chapter 3, use of Nordic Nutrition Recommendations). It is obvious that the average diets do not meet the reference nutrient density for all micronutrients. However, this does not mean that food supply is inadequate, but rather it should be seen as a reminder to the diet planner of where to focus.

Table 1. Nutrient density (per 10 MJ) of selected vitamins and minerals in the average diet in the Nordic countries

		Denmark	Finland	Iceland	Norway	Sweden	Reference values for heterogeneous groups
Vitamin A	RE	1,241	1,085	1,319	961	1,117	800
Vitamin D	µg	3.5[3]	12.8	9.8	6.2	8.8	14
Vitamin E	α-TE	7.9	13.0	12.0	12.1	15.8[1]	9
Thiamin	mg	1.4	1.62	1.5	1.7	1.5	1.2
Riboflavin	mg	1.8	2.4	2.0	2.0	1.9	1.4
Niacin	NE	33	42	42	–	43	16
Vitamin B_6	mg	1.6	2.4	1.9	1.9	2.5	1.3
Folate	µg	350	322	329	280	349	450
Vitamin B_{12}	µg	5.7	7.6	8.0	8.0	6.9	2
Vitamin C	mg	124	152	125	123	132	80
Calcium	mg	1.207	1,417	1,087	995	1,114	1000
Phosphorus	mg	1,563	1,941	1,820	1,871	1,697	800
Potassium	g	3.7	4.8	3.6	4.2	4.0	3.5
Magnesium	mg	382	479	354	428	419	320
Iron	mg	11.0	14.3	13.0	12.2	13.1	16
Zinc	mg	11.7	14.4	12	12.5	13.1	12
Iodine	µg	217	263	204	–	–	170
Selenium	µg	47	86	85	63	58	57
Corrected for cooking losses		Yes	Yes	Yes	No	Yes[2]	
Age group	years	4–75	25–74	15–80	18–70	18–80	
Survey method		7-d food record	48-h recall	24-h recall	24-h recall	4-d food record	
Reference		3	2	4	5	1	

1 Calculated from α-tocopherol.
2 Refers to thiamin, riboflavin, preformed niacin, vitamin B_6 and vitamin C.
3 Contribution from β-carotene is calculated as 1/12.

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