Chapter 3

Nutrition recommendations – background and principles

Contents

Background

The Nordic Nutrition Recommendations (NNR) constitute the scientific basis for planning of diets for population groups, including the development of food-based dietary guidelines in the Nordic countries. The recommendations also serve as a basis for assessing nutrient intakes for groups of healthy individuals, for national and regional nutrition policies, for nutritional educational programs, and for 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 disease(s) and for other groups with special needs, the dietary composition and energy content may have to be adjusted accordingly. The NNR give values for the intake of and balance between individual nutrients which, based on current scientific knowledge, are adequate for development and optimal function and reduce the risk of development of 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, 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 NNR are primarily valid for groups of healthy individuals with various levels of physical activity (excluding competitive athletes) and are not to be used for judging the intake at individual level

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

The concept of setting recommended dietary intakes goes 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 (League of Nations 1936) 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, US, to serve as a guide for planning adequate nutrition for the general population (IoM, 2001). Since then the concept has evolved to take into account not only the avoidance of clinical or subclinical deficiencies, but also reduction in the risk of development of overweight and obesity and major lifestyle diseases, including 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, defined as an intake level that maximises the physiological and mental functions and minimises the risk of development of chronic diseases (**Fig 3.1**). Since 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. Consequently nutrition recommendations 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 may even lead to adverse health effects.

For more than four decades, nutritionists in the Nordic countries have emphasised that in order to follow the NNR the ratio between the macronutrients (energy-providing nutrients) should be changed in diets of most population groups. Initially, these recommendations emphasised a reduction in the intake of fat, especially saturated fat, and refined sugars and an increase in the intake of complex carbohydrates and dietary fibre. In recent editions of NNR more emphasis has been put on fat quality, i.e. replacing saturated fat and trans-fatty acids with unsaturated fat and the importance of both n-3 and n-6 fatty acids. Recommendations on physical activity have been included and certain aspects of food-based dietary guidelines, i.e. cereals, fruit and vegetables and fish, potatoes, milk products and meat. During recent years nutrient recommendations and food based dietary guidelines have been published by international and national organisations (WHO, 2003; IoM 2002/2005; WCRF 2007, USDA 2010, Helsedirektoratet 2011).

General approach

The main objective of the nutrition recommendations is, on the basis of the best available scientific evidence, to ensure a diet that provides energy and nutrients for optimal growth, development, function and health during the whole life. It should be noted that a certain recommendation e.g. 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 for example during short-term mild infections or certain medical treatments. The recommended amounts are usually not suited during 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 but not specifically meant for treatment of diseases or significant weight reduction. NNR, however, cover dietary approaches for sustainable weight maintenance after significant, intentional weight reduction. For individuals with disease and for other groups with special needs dietary composition may have to be adjusted accordingly.

The 5th edition of 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 applied, including 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 made 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 (RCT) have been used where possible. Animal and in vitro studies have been included when needed to explain mechanisms in action, i.e. the NNR values have been based on the totality of available evidence (Blumberg et al, 2010; Mann JI, 2010).

Terminology and definitions

The term NNR refers to a set of dietary reference values to define the complete set of dietary reference values for essential nutrients: average requirements (AR), recommended intakes (RI), upper intake level (UL), lower intake level (LI) and reference values for energy, all expressed on daily basis, and recommended range of macronutrient intakes.

Average requirement (AR)

The requirement is defined as the lowest long-term intake level of a nutrient that will maintain a defined level of nutritional status in an individual. The term *average requirement* (AR) 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 a normal distribution of the requirement (**Fig 3.2**).

In the NNR the selected criteria for establishing the *AR* in general apply to micronutrients and are usually based on data on biochemical markers of adequate nutritional status. However, 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 and neurological symptoms due to vitamin B_{12} deficiency would arise. Data on biochemical markers may 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 may be associated with deficiency symptoms or impaired function. Moreover, it is possible to define an interval between manifest deficiency and optimal intake level, where clinical symptoms are more diffuse or do not exist at all. This level is sometimes called latently insufficient (**Fig 3.1**). 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 (DoH, 1991; IOM, 2002). The European Food Safety Authority (EFSA) uses the term 'Average Requirement' (EFSA, 2010).

Recommended intake (RI)

The term *recommended intake (RI)* refers to the amount of a nutrient that according to present scientific knowledge and information on dietary patterns can meet the known requirement and maintain good nutritional status among practically all healthy individuals in a particular life stage and 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 (**Fig. 3.2**):

$$RI = AR + 2\ SD_{AR}$$

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 percent may be used (see Fig 3.2).

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

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

High doses of certain vitamins and minerals may have pharmacological effects different from their primary nutritional effects. Generally, this concerns amounts which the target group cannot

normally obtain from the diet. High doses of nicotinic acid have been used as a lipid-lowering agent and the effect of fluoride on dental caries may also be considered a pharmacological rather than a nutritional effect. 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 arising from diseases, such as infections. In general, the RIs are only applicable when the supply of other nutrients and energy is adequate.

The definition of *RI* corresponds to the term 'Recommended Intake' (RI)' used in the UK and 'Recommended Dietary Allowance' (RDA) used in the US (IoM, 2002). The European Food Safety Authority (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" (EFSA, 2010).

Setting RI for micronutrients

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

The first step includes an evaluation of the average physiological requirement for the population group in question, judged by criteria that have to be set specifically for every individual nutrient. The establishment of these criteria includes considerations about clinical and biochemical deficiency symptoms, body stores, body pool turn-over and tissue levels. The nutritional requirements are influenced mainly by different biological factors like 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 (**Fig 3.2**).

Upper intake level (UL)

For most nutrients, high intakes may 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 to humans. The threshold for any given adverse effect varies depending on life-stage, sex and other individual characteristics, as it does for any nutrient requirement. However, there are insufficient human data to establish

distributions of thresholds for each adverse effect. In setting the *UL* the different steps taken include the identification of the critical endpoint, which is the adverse effect occurring at the lowest dose, and using a surrogate measure for the threshold (**Fig 3.3**). 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, an *UL* is derived taking into account the scientific uncertainties in the data by dividing the *NOAEL* by an uncertainty factor (UF) (**Fig 3.3**). This factor should account for uncertainties in human inter-variability and, in the case of lack of adequate human data, an extra-polation 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 (IoM, 2002), and by the European Food Safety Authority (EFSA, 2010).

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 a *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 intake' (LRNI) used in the UK (DoH, 1991) which is defined as EAR minus 2 SD (DoH, 1991). The European Food Safety Authority 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 (EFSA, 2010).

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, age, sex and various levels of physical activity. Setting the *reference value for energy intake* requires a different approach compared with the reference values for vitamins and minerals. For some vitamins and minerals *RI*s can be given with large margins, since the absorption can be limited or the excess broken down or secreted. The *RI*s may 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 which may affect health adversely. 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 of 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 of macronutrients

The term *recommended intake of macronutrients* is used to emphasise the importance of the distribution of energy between energy-providing nutrients, *i.e.* macronutrients. The background is that the current major lifestyle diseases mainly result from over-nutrition and nutritional imbalances, rather than the under-nutrition and deficiency symptoms. The intention of setting the *recommended intake of macronutrients* is thus to derive at a dietary macronutrient composition that will provide an adequate intake of essential nutrients, associated with optimal health and a reduced risk of major lifestyle diseases **(Fig 3.1)**.

The *recommended intake of macronutrients* is based on an overall assessment of the present knowledge about the impact of macronutrient intake on health and/or risk of disease. This requires various types of scientific data, primarily from controlled clinical trials (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 to for example interaction 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 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 actual composition of available foods in the Nordic countries. On this basis, the *recommended intake of macronutrients* should be considered as 'optimal' in Nordic conditions.

The *recommended intake of macronutrients* refers to average intakes for groups and should be considered as goals for dietary changes and dietary advice (planning). Using acceptable ranges for the percentage of energy provided by carbohydrate, protein, and fat and their subclasses in the diet, refers to appropriate ranges of usual intake in the majority of the population (King et al,

2007). The *recommended intake for protein* also includes considerations of an average requirement (AR) level.

Food based dietary guidelines

Food based dietary guidelines are based on an overall assessment of the present knowledge about the impact of food/food groups on health and/or risk of disease. Setting food based dietary guidelines requires various types of scientific data, especially prospective cohort studies and other epidemiological studies and controlled clinical trials (RCTs). 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 actual composition of available foods in the Nordic countries. On this basis, the FBDG should be considered as 'optimal' in Nordic countries.

Physical activity

Guidelines for physical activity are an integral part of NNR. Physical activity (and inactivity) influence growth, development and long-term health, and also interact with food intake and dietary patterns. The physical activity guidelines generally apply to a physical activity level corresponding to an "active lifestyle" 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 ARs and RIs are derived from data on maintenance of body stores and/or function and 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 (WHO 2003) forms the basis for setting RIs, see above (**Fig 3.4**). A similar approach is also used for deriving guidelines on breastfeeding and physical activity.

In deriving values for the NNR original data for various life-stage groups have been preferred (Atkinson & Koletzko, 2007). Where original data are lacking or due to paucity of 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 (IoM 2000). This approach has also been applied in the current NNR.

Interpretation of nutrition epidemiology studies

In NNR evidence from observational studies, mainly prospective cohort studies, is used extensively to assess diet/nutrient-health relationships. A number of issues influences the quality and interpretation of the results and relate to e.g. the complexity of foods and diets, subject characteristics, dietary assessment method and statistical approaches used in analyzing the data.

In addition to energy and essential nutrients, foods also contain a large number of other bio-active components with potential important effects on metabolic processes and health; diet is thus an extremely complex matrix of exposure. Some important issues to consider include:

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

In dietary assessments, food records and 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 (i.e., "usual diet"). Some other important issues to consider include:

- Food choices may vary greatly from one day to the next. Many repeated records (or recalls) or records covering a longer time period may therefore be needed (when using "current diet" dietary assessment methods) to capture the "usual" (habitual, average) nutrient intake of an individual. This varies between nutrients, and depends on how often food 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 may be common. As a consequence it may 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.

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

- Personal characteristics like a desire to please others (social desirability) or dietary concerns, may cause the individual to describe their food habits in a way that doesn´t mirror their actual diet.

•Nutrition epidemiological studies usually examine the relative ranking of individuals. So although dietary intake variables often are 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 unwanted strong influences of extreme (uncertain) values.

Thus, the interpretation of results in nutrition epidemiology is a challenge; the researcher needs to take several confounders into account; lack of data about the composition of foods and foodpractices 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 update of the NNR consists of two approaches:

1. A systematic review (SR) is applied to a selected group of nutrients where new data considered being of specific importance for setting NNR were available since the last version of NNR (see www.NNR5.org). The SR approach is also applied to nutrition for specific groups (e.g. children, elderly, overweight/obese) and for food-based dietary guidelines, meal patterns and alternative diets (**Table 3.1**).
2. A less stringent **updating of current reference values** is applied for the other nutrients not subject to SR (**Table 3.1**).

Systematic review

A Systematic review (SR) approach is used to strengthen 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 (Chung et al, 2010).

The key characteristics of the SR include:

- a clearly stated set of objectives and research questions with pre-defined eligibility criteria for 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.

The first step in the SR is identifying and defining 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 3.1**. In the next step, the protocol and search strategy is performed, and appointed experts for each nutrient/topic collaborate closely together with a methodologist specialised in performing database searches (**Fig 3.5**). After the literature search, abstracts of articles identified in the database searches are screened by minimum two independent experts by eligibility criteria for potentially relevant articles in a consistent, comprehensive manner (first selection). 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 systematic review are listed with reasons for exclusion according to predefined eligibility criteria. The methodological quality of the remaining articles is assessed using a three-category quality grading system (**Box 3.2**). 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 (www.nnr5.org).

After the quality assessment of the individual studies, the studies not fulfilling the quality criteria (i.e. have so serious bias that the results are invalidated 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 made for 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 with clear indication of the source. Basic statistical information is included in order to indicate the strength of the findings (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 the WCRF criteria with minor modifications (**Box 3.3**). The grading of evidence is based on the analysis of the scientific basis (the study quality, consensus, generalisability, effect size, risk for publication bias, imprecise data or other aspects such as correlation of dose-response) done 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’, ‘limited — no conclusion’ (**Box 3.3; Fig 3.5**).

The conclusions of the SR summarise the overall reviewed evidence. The conclusions also point out principal areas of uncertainty and areas of further research required, where appropriate. The guide for conducting SR and information on experts engaged in the NNR 5 process is available on the webpage (www.nnr5.org).

Other nutrients/topics

Some nutrients/topics have not been subject to an SR (**Table 3.1**). The reason for this is that comprehensive scientific reports were already available; that few major new scientific data were available and/or that the nutrient is of little public health concern. The reference values/topics have been updated with a similar approach as was used in the previous NNR, building on the evidence included in the 4th edition from 2004. The review of the literature is concentrated on papers and other reports published after 2000, primarily using Medline as a database source. Studies on Nordic population groups have been included where available. Other important data sources include scientific reports and recommendations published by national and international institutions and expert groups. Additional papers and reports are identified during the work through e.g. reference lists. When available, systematic reviews were supplemented with papers on individual studies and investigations. The reference lists for 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 literature that may be relevant to the basic issues of each nutrient/topic.

Derivation of Nordic Nutrition Recommendations

The framework that has evolved during recent years for the development of dietary reference values is increasingly recognized as similar to that developed in other fields and referred to as risk analysis (IoM 2008). However, when setting dietary reference values 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 e.g. chronic disease (EFSA 2010). Thus it is appropriate to use the term risk-benefit analysis. In the development of NNR, the step known as risk assessment in a risk analysis can be compared to the process of conducting systematic reviews (SR). The next step of the risk analysis, i.e. the risk management, also plays a role in the development of NNR. The process of deriving NNRs will include considerations on the evidence for each nutrient/topic, as well as possible inter-relations and consequences for the diet as a whole. Further, classic risk analysis also includes consideration of risk communication.

Generally, it can be said that an assessment of evidence as “convincing” or “probable” (**Box 3.3**) justifies a recommendation while evidence judged as limited-suggestive or limited-no conclusion does not justify a recommendation. However, rating quality of evidence and strength of 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 (NNR). The process of deriving NNR includes considerations on whole-diet approach and current dietary practices. This evaluation was done by the NNR5 working group and was not a part of the SR conducted by the expert groups. The systematic reviews are used as primary and independent components - but not the only components – for the decision-making-processes performed by the NNR 5 working group who is responsible for developing the NNR.

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Table 3.1

Overview of the two approaches used in setting recommendations for each nutrient/topic

Nutrient/topic	SR	Update	Comments
Breastfeeding	✓		
Food based dietary guidelines	✓		SR on wholegrain, potatoes, berries, milk and meat
Meal patterns	✓		Called Eating patterns in NNR4
Fluid and water balance		✓	
Energy		✓	
Physical activity		✓	
Fat	✓		Including quantity and quality
Carbohydrates (including sugars and fibre)	✓		Including quantity and quality
Protein	✓		
Alcohol	✓		
Dietary antioxidants		✓	
Vitamin A		✓	
Vitamin D	✓		SR on recent reviews mainly
Vitamin E		✓	
Vitamin K		✓	
Thiamin		✓	
Riboflavin		✓	
Niacin		✓	
Vitamin B6		✓	
Folate	✓		
Vitamin B12		✓	
Biotin		✓	
Pantothenic acid		✓	
Vitamin C		✓	
Calcium	✓		SR on recent reviews mainly
Phosphorus		✓	
Magnesium		✓	
Sodium as salt		✓	
Potassium		✓	

Nutrient/topic	SR	Update	Comments
Iron	✓		
Zinc		✓	
Iodine	✓		
Selenium		✓	
Copper		✓	
Chromium		✓	
Manganese		✓	
Molybdenum		✓	
Fluoride		✓	

New topics in NNR5			
Alternative diets	✓		With focus on vegetarian, macrobiotic, ketogenic and low GI diets
Obesity and overweight	✓		With focus on primary prevention of weight gain and prevention of weight gain after weight loss
Population groups in dietary transition	✓		Modified SR. The SR approach was used but the work was done by one expert only
Environmental aspects			Overview on recently published reports

Nutrition recommendations in pregnancy and lactation, for infants and children and elderly are incorporated in each chapter after separate SRs. In addition, separate SRs were also conducted on health effects of weightloss prior to conception and the impact of milk/dairy consumption on birth weight and fetal growth.

Box 3.1 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 composition* on long-term (≥1 y) change in weight/waist circumference/body fat in general adult population?

Box 3.2. 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 with 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", they have some deficiencies but none likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.

C Studies have significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; there are large amounts of missing information, or discrepancies in reporting.

Box 3.3. 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', '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 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 RCT may be sufficient.
- Evidence from at least two independent cohort studies (cf. 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 exclude with confidence the possibility that the observed association, or absence of association, results from random or systematic error, including confounding, measurement error, and 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 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 RCT may 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 exclude with confidence the possibility that the observed association, or absence of association. results from random or systematic error, including confounding, measurement error, and selection bias.
- Evidence for biological plausibility, in 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 may have methodological flaws, or be limited in quantity, but shows a generally consistent direction of effect. All 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 may 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 of direction of effect, by poor quality of 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 2 or more high (A) or moderate (B) quality studies with contradicting or null results.

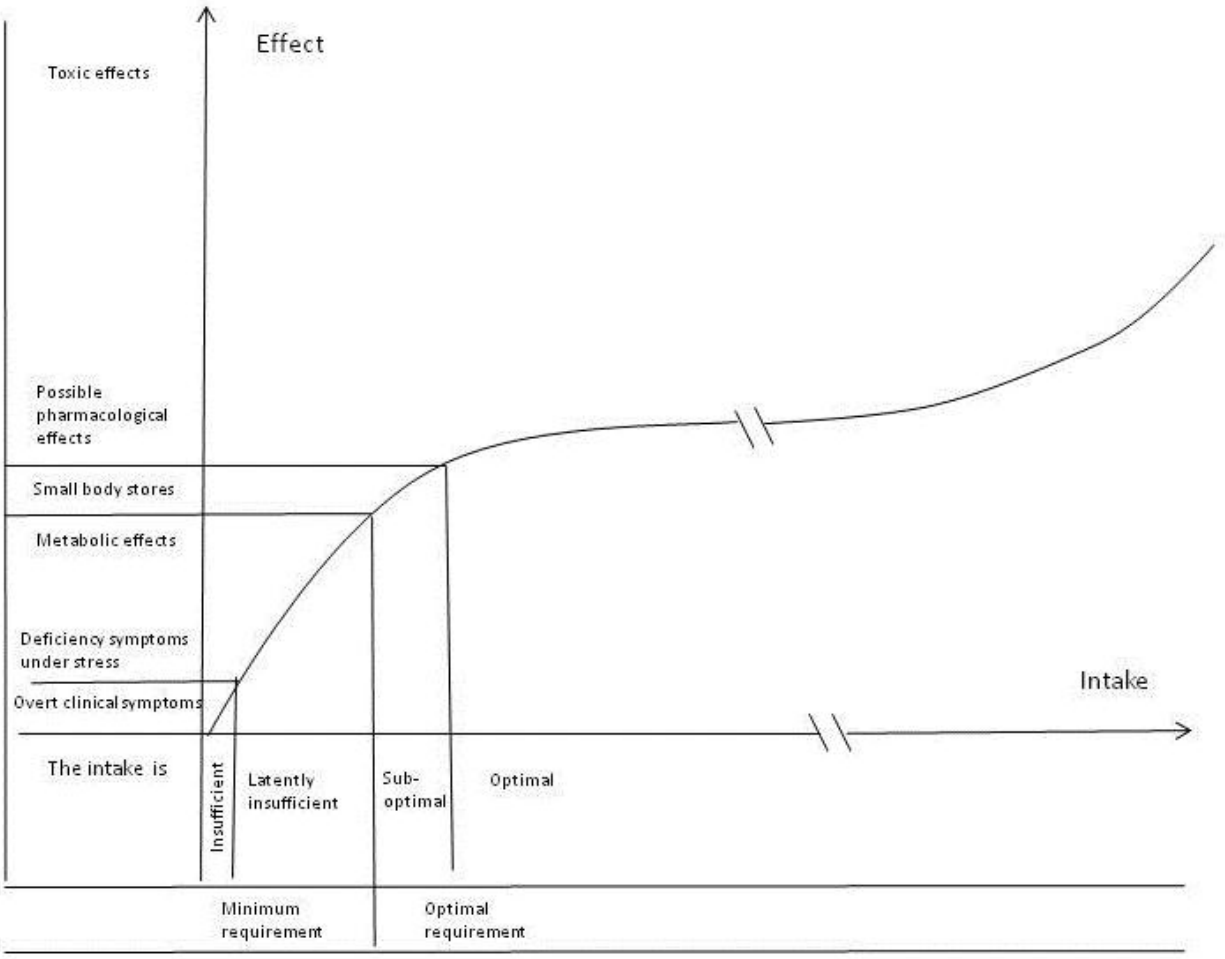

Figure 3.1. The theoretical relationship between intake of a nutrient and the effect on the organism

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 nutrients. There is also a transitional phase between overt toxic effects at very high intakes and milder adverse effects at lower intakes.

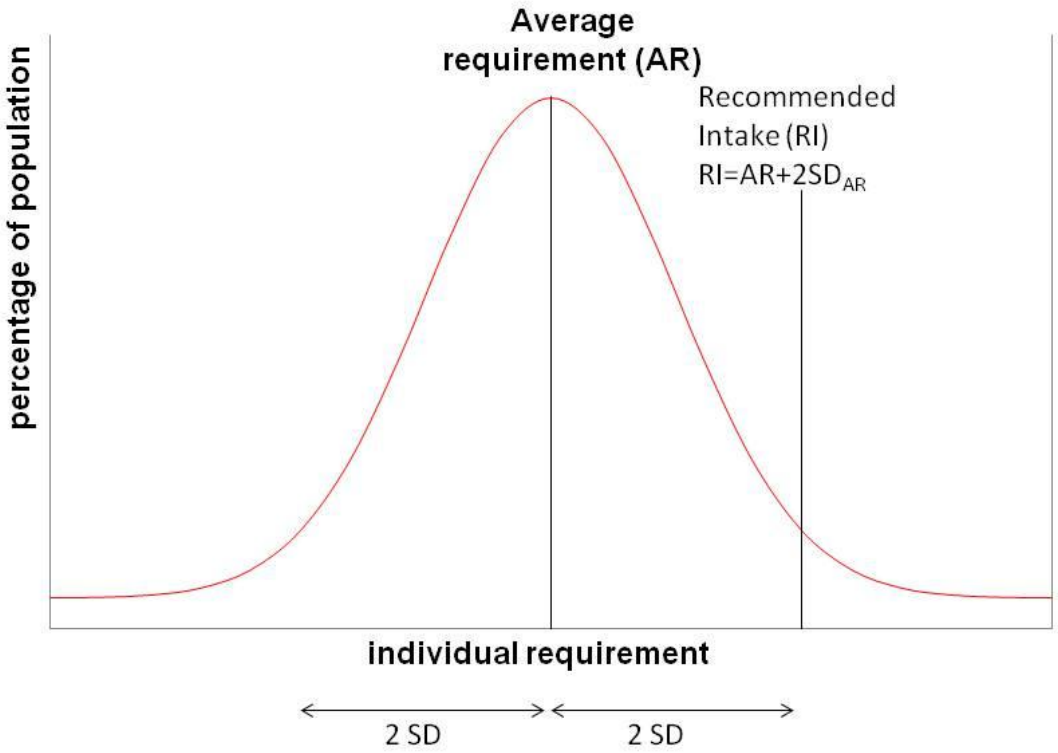

Figure 3.2. Frequency distribution of individual nutrient requirement

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 **(Fig 3.2)**. Depending on the criteria used for setting the average requirement, the margin between average requirement and recommended intake may vary.

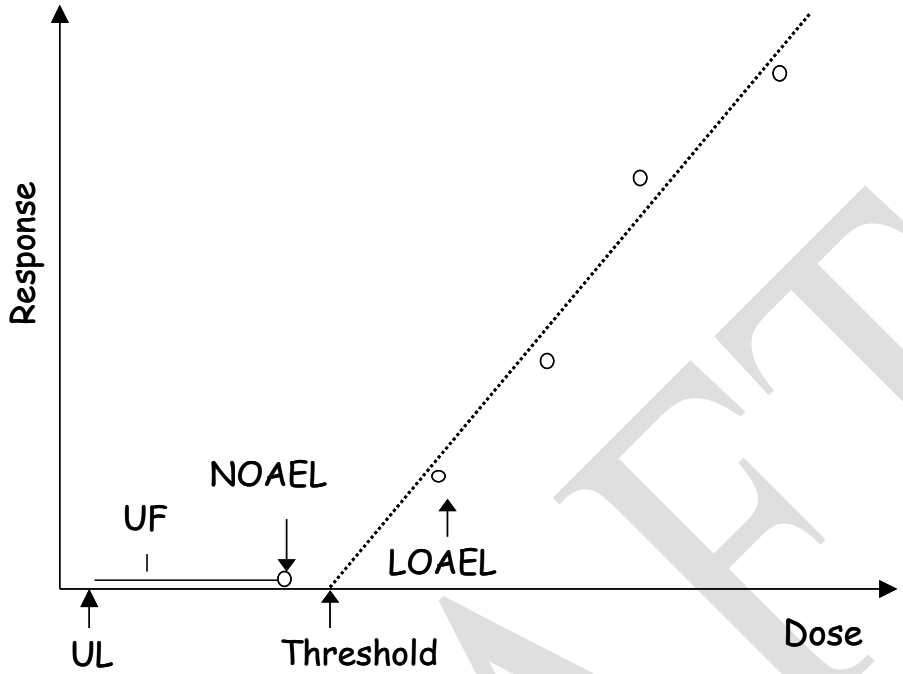

Figure 3.3. Derivation of Upper Intake Level (UL)

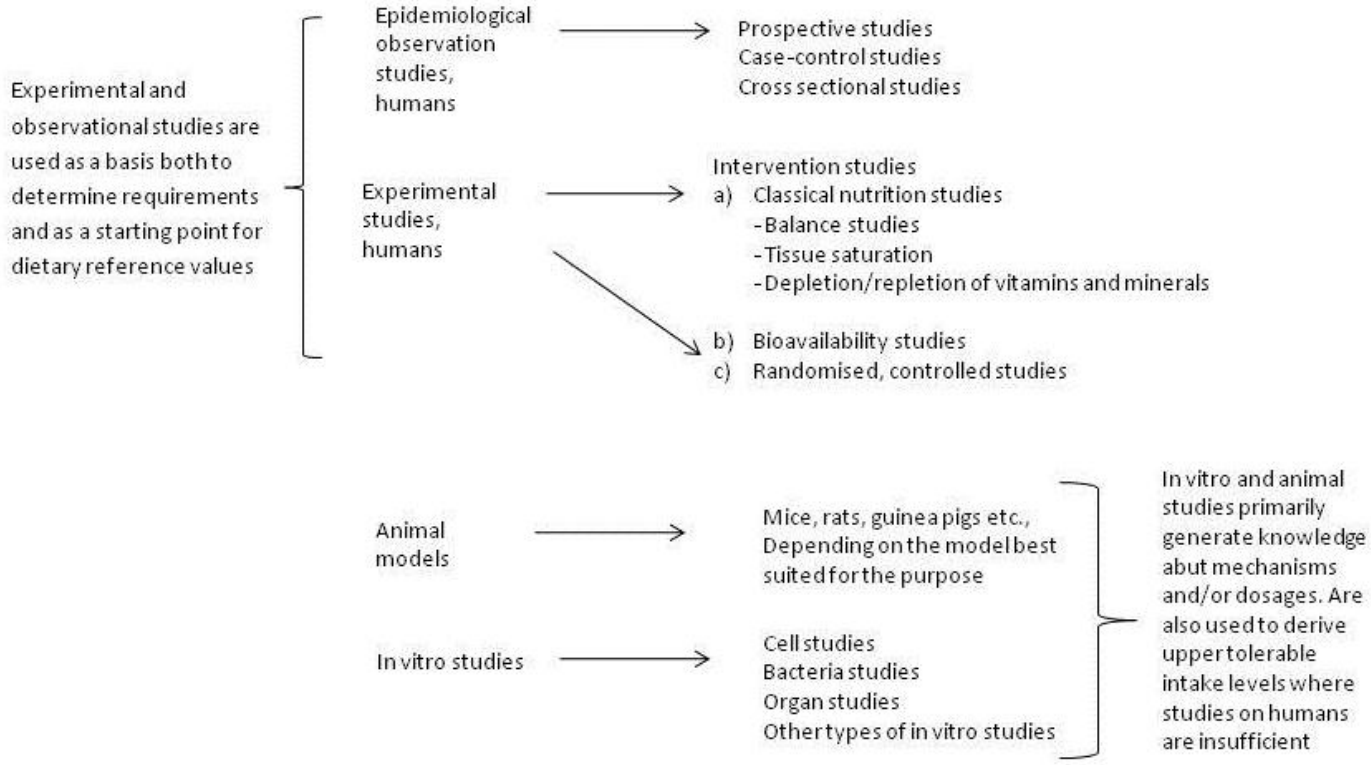

Figure 3.4 Types of studies used as a basis for dietary reference values

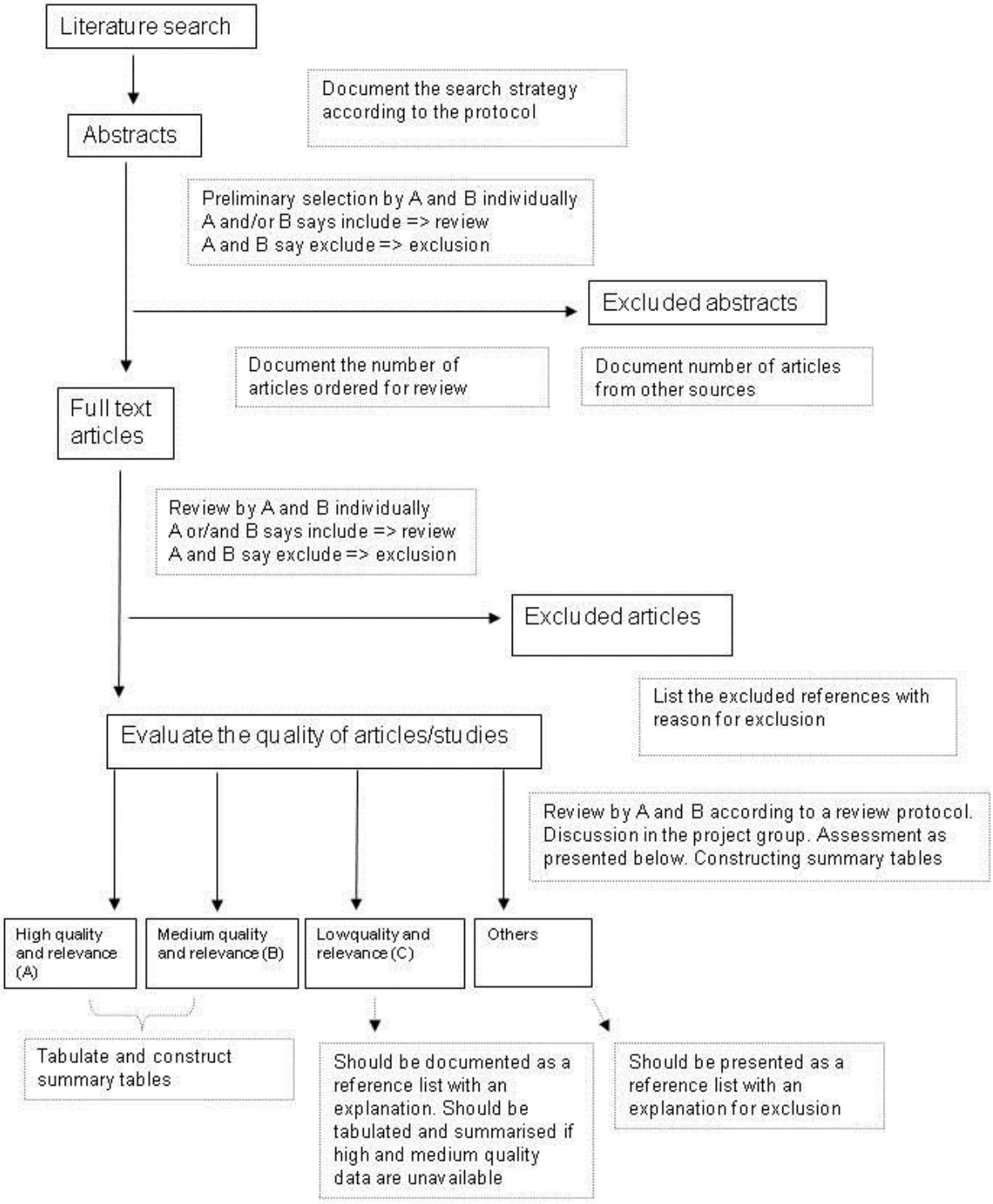

Figure 3.5. Flow chart on the reviewing process in the Systematic Review (SR)