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A guide for conducting SLR for NNR5

How to undertake a systematic review of nutrition recommendations

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A guide for conducting Systematic Literature Reviews for the 5th edition of the Nordic Nutrition Recommendations

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A guide for conducting Systematic Literature Reviews for the 5th edition of the Nordic Nutrition Recommendations

Contents

FOREWORD

This guide in conducting systematic literature reviews was developed for the revision of the 4th edition of the Nordic nutrition recommendations (NNR5 project). It is based on other handbooks and guides such as Cochrane handbook for systematic reviews of interventions, Application of systematic review methodology to the field of nutrition by the Agency for Healthcare Research and Quality (AHRQ), the unpublished handbook by the Swedish Council on Health Technology Assessment, The World Cancer Research Fund´s/American Institute of Cancer research´ report on Food, nutrition and the prevention of cancer and other relevant literature specified in the reference list.

The guide was devised by the NNR 5 working group nominated by the Nordic Working Group for Diet, Food & Toxicology (NKMT), under the Secretariat for the Nordic Committee of Senior Officials for Fisheries and Aquaculture, Agriculture, Food and Forestry (ÄK-FJLS Food). The working group was established in 2009. The project group consists of Wulf Becker (chair), Ulla-Kaisa Koivisto Hursti (scientific secretary) and Elisabet Wirfält, Sweden; Agnes N Pedersen and Inge Tetens, Denmark;

Mikael Fogelholm and Ursula Schwab, Finland; Ingibjörg Gunnarsdóttir and Inga Thorsdottir, Iceland; Sigmund A Anderssen and Helle Margrete Meltzer, Norway.

The aim of this guide is to give instructions on how to conduct systematic literature reviews for the experts engaged in the NNR 5 project. This guide is a working document and has been submitted to and approved of by the NNR 5 reference group that consists of senior experts representing various fields of nutrition science, both within and outside the Nordic countries.

BACKGROUND

The aim of the project is to review and where necessary update the 4th edition of the Nordic Nutrition Recommendations (NNR) issued in 2004 (Nord 2004:13). The work will mainly focus on a revision of those areas in which new scientific knowledge has emerged. This includes fat and carbohydrate quantity and quality, protein, alcohol, vitamin D, calcium, folate, iodine, iron, meal patterns and food-based dietary guidelines. Chapters on nutrition in specific groups (e.g. children, elderly, overweight) will be incorporated and the need for new areas, e.g. alternative diets and environmental aspects will be considered.

The work will focus on a review of existing scientific evidence in order to enable an update of NNR reference values in the context of a balanced diet which, when part of an overall healthy lifestyle, contribute to good health through optimal nutrition and prevent lifestyle related diseases such as cardiovascular disease, osteoporosis and certain types of cancer, diabetes type 2 and related risk factors.

Systematic literature reviews (SLR) will be performed to minimise potential reporting bias through comprehensive and reproducible searches using clearly defined and described selections and reporting protocols. Established criteria for evaluating the methodological quality of the included studies and the overall strength of the scientific evidence will be used and the work process will

include several stakeholders in a transparent process. This will be ensured through detailed documentation of the decision making process (Figure 1). The SLRs will be evaluated by external reviewers. Also, a scientific reference group will be assigned to the project, which will be consulted for general overview and on specific matters.

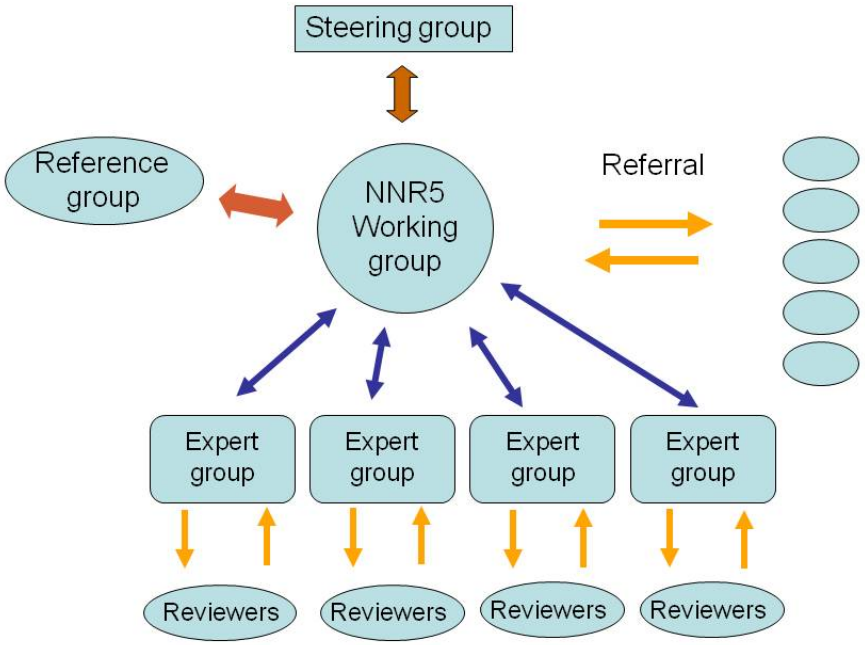

Figure 1. The proposed decision making process

The work process

The revision will be led by the NNR5 working group nominated by the Nordic Council of Ministers. The NNR5 working group will be responsible for the revision process and for the final proposal for the 5th edition of the NNR. The NNR5 working group will frequently report to the project steering group (consisting of members of the Nordic Working Group for Diet, Food & Toxicology, NKMT) who will monitor progress of the project and ensure adherence to the project plan. A scientific secretary included in the NNR5 working group will administer the work process. Documentation from the project will be available on the project website (www.nnr5.org) in order to guarantee transparency and enable external review of the process. Information of the project will also be available on the Nordic Council of Minister´s website (www.norden.org) and will be distributed to universities, research institutes, government agencies and other organisations within the field of nutrition and public health.

The experts involved in conducting SLR, nominated by the NNR5 working group, will be posted on the project website together with their CVs and Declaration of interest forms. The new edition of the NNR will be published as a Nord publication and also be available in electronic form.

Systematic Literature Reviews

According to Cochrane handbook for systematic reviews of interventions [1] a systematic review attempts to collate all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question (http://www.cochrane-handbook.org/). It uses explicit, systematic methods that are selected with a view to minimising bias, thus providing more reliable findings from which conclusions can be drawn and decisions made. The key characteristics of a systematic review are:

- a clearly stated set of objectives 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, for example through the assessment of risk of bias; and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies.

It is important that all the phases in the process are well defined and described [2] (Figure 2).

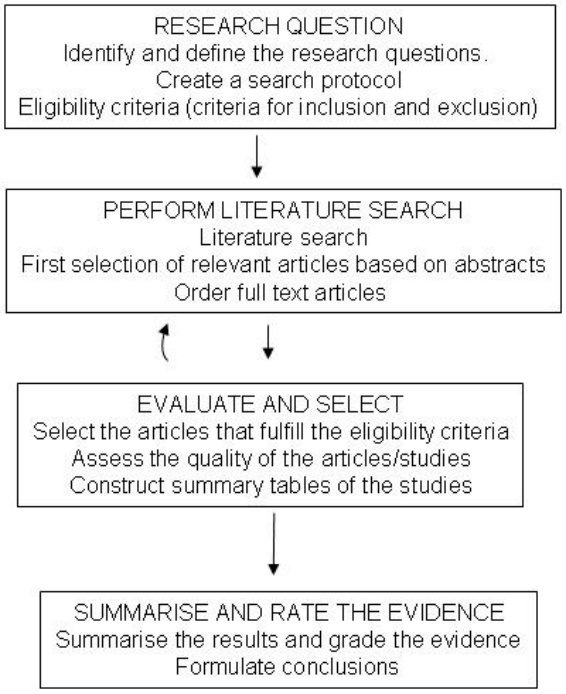

Figure 2. Flow chart on the review process [2]

RESEARCH QUESTION

Identify and define the research questions

In this first phase it is important to identify the most important research questions, to pose questions that are possible to answer and to define criteria for inclusion and exclusion of studies. To enable a

focused literature search the research questions should be formulated so that they can be responded to by data from observational or clinical studies, randomised controlled trials or human physiological studies. In some cases also animal studies and cellular and molecular studies may be relevant. Here, it is useful to develop an analytical framework as e.g. visual maps outlining relations within the target population with respect to exposures, modifying factors, biological role of a nutrient, and outcomes of interest. The framework will facilitate identification and definition of appropriate research questions [3-5]. The PICO approach is commonly used to formulate research questions. The following components should be defined for all the research questions: Population/Participants, Intervention/Exposure, Control and Outcome.

Box 1. Components of the research question. Example from an intervention study			
Population/participants	**Intervention/method**	**Control**	**Outcome**
Description of the study population e.g. - Age - Sex - Diagnosis - Life-style factors - Socioeconomic characteristics - Other risk factors - Other diseases	Definition and description of the methods - intervention procedure - dietary modification (use of "normal foods") - minimum duration - compliance - relevance to Nordic population	Definition and description of the method for control - placebo - other treatment	Outcome measures that are related to the individual such as survival, quality of life, illness or changes in symptoms, well established risk factors and markers. Also, complications or side-effects of the intervention should be considered as outcome measures.

The Scientific Advisory Committee on Nutrition (SACN) of the UK Food Standards Agency (FSA) has set a framework for evaluation of evidence that relates food and nutrients to health [6]. According to SACN the following issues should be considered in identifying the research questions.

- Principal nutrients or foods under consideration
- Relevant health or disease endpoints/outcomes of the evaluation
- Putative role of foods or nutrients in process (i.e. characterisation of the possible role of nutrition in this area)

Dietary modification may consist of one or several components of the diet. However, it should be clearly defined which part is studied and how (methodology).

Create a search protocol

In order to construct an effective set of search terms the research question should be broken down into components according to the PICO approach (Population/Participants, Intervention/Exposure, Control and Outcome). Search strategies are usually built up from a series of test searches and discussions of the results of those searches among the review team [7] (Figure 3). In the NNR 5 project the appointed experts for each subject/area will, in collaboration with a librarian (specialised in performing systematic literature searches), be responsible for developing search strategies.

Intervention/Exposure

Study types that will be included in the systematic literature reviews include controlled intervention studies, prospective cohort studies, case-control studies and systematic reviews. This includes studies assessing net losses of nutrients, nutrient balances, factorial calculations etc. Also, multi-factorial intervention studies including diet and physical activity will be considered. Retrospective case-control studies where the measure of exposure occurred after or concurrent with the outcome will only be used when results from other study types are not available. Cross-sectional studies will

primarily be used for describing prevalence and animal studies will not be used apart from describing mechanisms

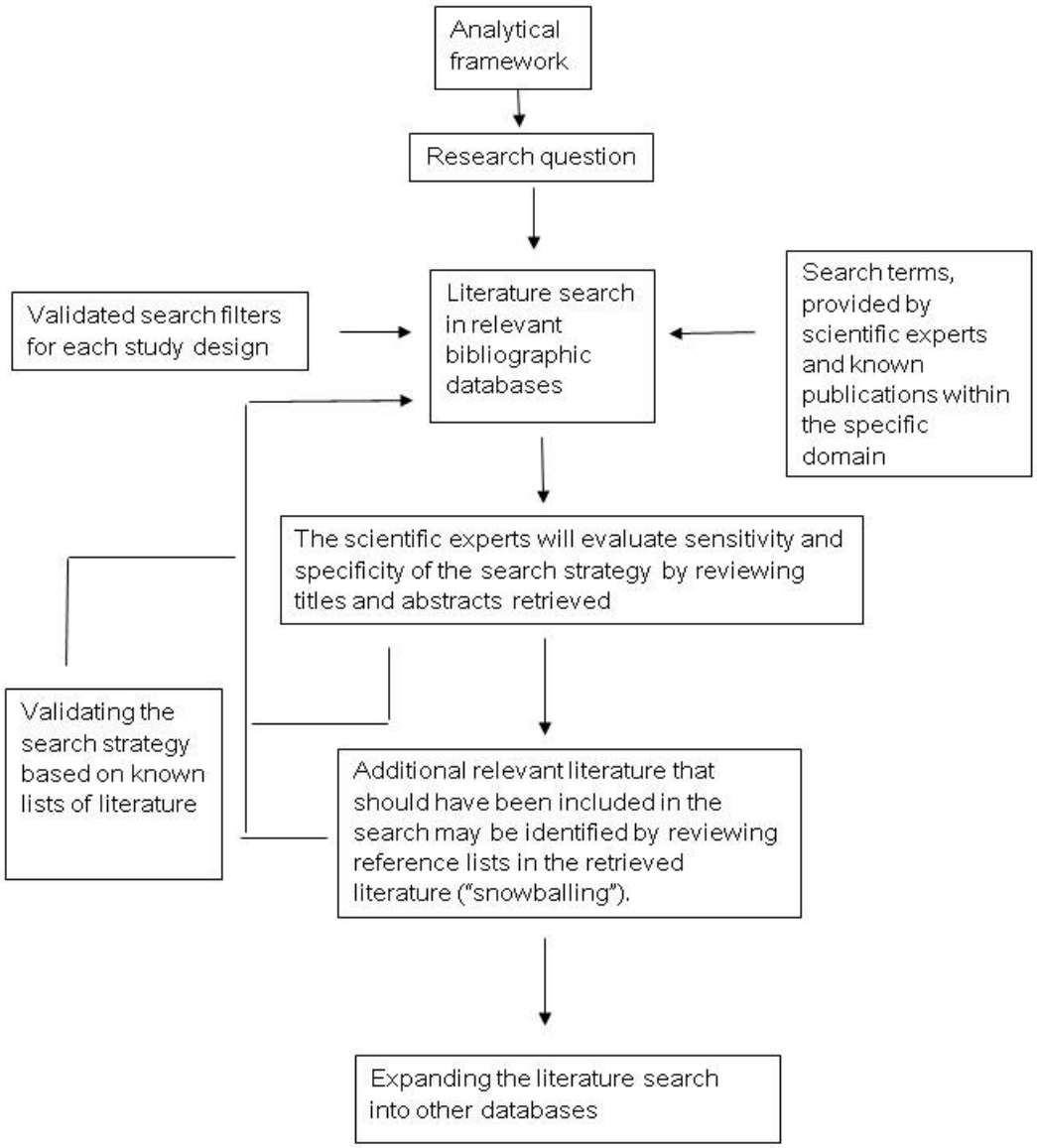

Figure 3. Flowchart for constructing and optimising the search strategy [2]

Eligibility criteria

The PICO components define much of the eligibility criteria for selecting the studies. Additional criteria include study design, dose levels (plausibility at dietary level), minimum number of subjects per study arm, background diets, baseline nutritional status, minimum study period and statistical analysis [3].

Box 2. Examples of aspects that should be considered when defining eligibility criteria

- Disease or healthy subjects only
- Intervention/exposure of interest
- Outcome measure
- Type of study
- Number of participants – study size
- Dietary assessment methods
- Publication language
- Publication type (original articles, conference abstracts etc)
- Time period for publication (2000 onwards →)
- Length of follow up
- Length of intervention period
- Drop-out rate
- Compliance
- Other simultaneous interventions
- Comorbidity
- Previous interventions

The primary target population for NNR5 is defined as the general healthy population. This means that studies focusing on treatment of patients with overt diseases will be excluded. Studies involving subjects with increased metabolic risks or pre-disease states, e.g. with established risk factors, will be considered.

For intervention studies the following criteria should be predefined

- Minimum duration. Should be at least 4 weeks, specific criteria should be defined depending on outcome
- Drop-out/attrition
- Complience
- Minimal no. of subjects

For observational studies the following criteria should be defined

- Minimum follow-up period. Should be at least 4-5 years, longer periods may be required depending on dietary exposure and outcome
- Drop-out during follow-up (less than 30 %)

For all the study types, the intake ranges for nutrients and dietary sources should be relevant to the Nordic setting.

Selection of databases to be used

PubMed, EMBASE and Cochrane library are the main information sources in the field of nutrition and medicine. Other databases and online hosts such as SveMed+ and DialogSelect will be considered. To be comprehensive, multiple databases as well as reference list of relevant retrieved articles should be searched, supplemented by contributions of scientific experts.

Identification of search terms

The search terms must be adequate in scope to capture all of the relevant literature but narrow enough to avoid capturing too much extraneous literature [3]. MeSH-terms, used to index publications in MEDLINE/PubMed, will be used.

PERFORM LITERATURE SEARCH

Literature search

The literature search will be performed in collaboration with and the results summarised by a librarian in order to ensure objectivity. The search strategy used and bibliographic databases searched will be clearly documented. It makes it possible for others to reproduce the systematic reviews, allows comparison across reviewers and serves as a foundation for an efficient updating of the systematic review as new findings emerge. The full search strategies for each database will need to be included in an Appendix of the review. The search strategies will need to be copied and pasted exactly as run and included in full, together with the search set numbers and the number of records retrieved. The number of records retrieved will need to be recorded in the Results section of the review, under the heading 'Results of the search'. The search strategies should not be re-typed as this can introduce errors [1].

The World Cancer Research Fund published a large systematic literature review on Food, nutrition, physical activity and the prevention of cancer in 2007 [8]. Also, a systematic literature review specification manual has been published [9]. These two reports offer useful guidance in conducting systematic literature reviews and reporting the results.

As the primary aim of the NNR 5 is to revise the previous 4th edition of NNR the focus will lie on publications after 2000.

First selection based on abstracts

In this phase abstracts of articles identified in the database searches are reviewed and those not fulfilling the predefined inclusion criteria are excluded. For the remaining articles, including those for which some relevant information is missing, full-text papers are collected.

EVALUATE AND SELECT

The abstracts should be screened guided by eligibility criteria for potentially relevant articles in a consistent, comprehensive and efficient manner (Figure 4). All the potentially relevant articles should be reviewed by two independent experts.

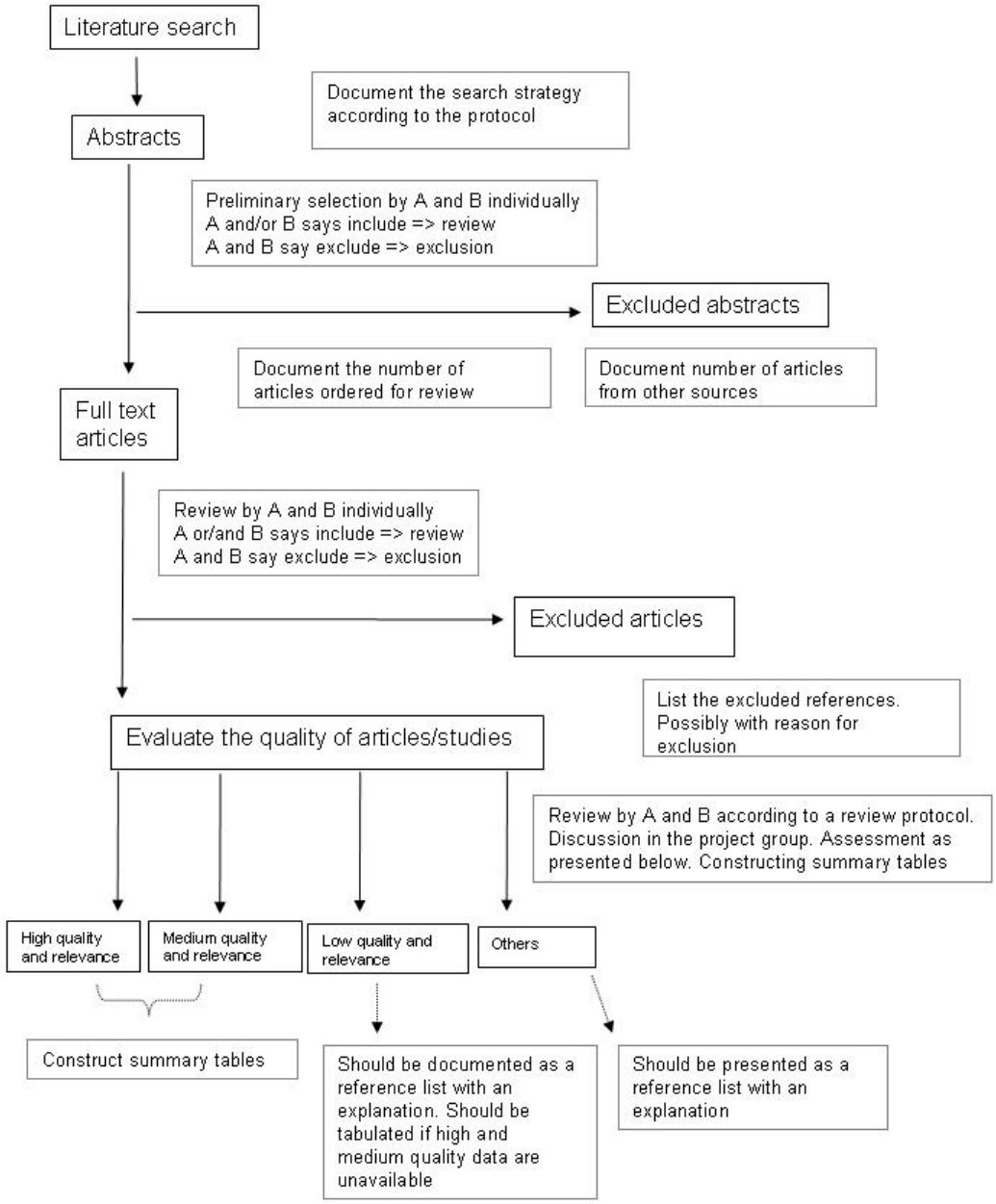

Figure 4. Study selection process [2]

Constructing evidence and summary tables, extracting study data

One of the most important tasks for the experts is to extract study data and construct evidence tables of the studies. These will include data that are important in evaluating the quality and relevance of a study using nutrient-specific criteria in addition to those criteria commonly used.

Nutrient intake information might include intake/dose, source of nutrient, mode of administration (supplement/foods), chemical form, background diet and nutritional status. Additional types of information that are relevant include level of nutrient in the background diet, method used to

estimate intake, analytical methods used to assess nutrient status and whether a nutrient biomarker or other approach was used to validate the dietary data. Also, it is essential to document the food composition database used and definitions of the nutrients, and where necessary methods of analysis or the algorithms used for estimation of content of nutrients in foods. See [3] for more details on unique considerations when conducting nutrition related systematic reviews.

All the data elements (Table 1) to be extracted should be a priori defined and summarized in tabular form. The evidence tables will give the reader possibility to judge the reliability of the conclusions and should include information on the source reference, research question, methods, study design, the carrying through, results and methodological quality. Table 1 gives an example on evidence table headings providing some of the main relevant data elements.

The data collection form is a bridge between what is reported by the original investigators in journal articles and what is ultimately reported by the review authors. The form is linked directly to the review question and criteria for assessing eligibility of studies, and provides a clear summary of these that can be applied to identified study reports. Further, the data collection form is the historical record of the multitude of decisions (and changes to decisions) that occurs throughout the review process. Also, the form is the source of data for inclusion in an analysis [1].

Table 1. Example on evidence table headings

Reference details, First author, Year, Country	**Study design** (RCT, CT, cohort, case control etc.)	**Population, subject characteristics,** Inclusion/exclusion criteria Setting, No at baseline, Male/Female, Age, Ethnicity of the subjects	**Outcome measures** Disease, biological measures	**Intervention/ exposure**	**Time between baseline exposure and outcome assessment**	**Dietary assessment method** FFQ, food record **Internal validation** y/n *see separate table for more details*	**No of subjects analysed**	**Intervention** Intervention (I) (dose interval, duration) Control (C) (active, placebo, usual care etc), compliance, achieved dietary change, adherence to dietary targets, actual dietary change	**Follow- up period, drop-out rate** (from baseline to follow-up, or from end of intervention to follow-up) Drop out (%)	**Results** Results (I, C) (Absolute difference, RR, OR, p-value, confidence interval, sensitivity, specificity, observer reliability?, etc)	**Confounders adjusted for**	**Study quality and relevance, Comments** A-C

Dietary information*

SI	Author Year Study Name	Expo-sure	Dietary Assessment Method**	Food Composition Database*** Definition of relevant nutrient ****	Internal Calibration (or Validity) of Dietary Assessment? (y/n). If Yes, Provide Data	Biomarker Assay*****	Analytical Validity of Biomarker Data Reported? (y/n). If Yes, Provide Data	Time between Biomarker Sampling and Analysis	Season/Date when biomarker samples were drawn	Background exposure data

* Write "nd" if there was no data reported. Please do not leave blank
**Please refer to brief name indicated in dietary assessment method table. If other method was used, please describe the detail.
*** Specify database used to calculate nutrient intakes. Other nutrient analysis, please specify.
****Eg. are carbohydrates expressed as available carbohydrates or carbohydrates by difference, is fibre included in the carbohydrates or not, retinol equivalent or retinol activity etc. Chemical form of the nutrient.
*****ONLY biomarker of interest for outcome

ASSESSING METHODOLOGICAL QUALITY AND APPLICABILITY OF STUDIES

Study quality and relevance refers to the scientific quality of each individual study and its ability to give a reliable answer to the research question.

A three-category quality grading system of the AHRQ (Agency for Healthcare Research and Quality) Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews should be used for grading the quality of each individual study. This system defines a generic grading system that is applicable to each type of study design including interventional and observational studies (Box 1).

Box 1. Assessing methodological quality of the studies: The three category quality grading system

The studies should be evaluated and graded within their own design strata

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.

Criteria for checklists

When evaluating results from scientific studies a number of criteria can be used to assess the reliability as well as their usefulness and relevance for establishing dietary reference values (DRV). Some criteria are common to different study types, while others are specific to e.g. intervention or observational studies.

In order to assess study quality checklists with a number of questions regarding several aspects of the study will be used. These have been derived from guidance documents used by various scientific expert groups [6]. For checklists for studies see appendix 1-6.

The approach to evaluate the literature should be described. If certain types of evidence are not to be considered (e.g. animal or cell studies), this should be noted giving reasons for non-inclusion.

Evidence from systematic reviews and meta-analysis

Results of *systematic reviews and meta-analysis* should be quality assessed and evaluated with the NNR5 modified AMSTAR quality assessment tool and incorporated in the evidence tables. A similar categorisation to that of individual studies has been included, based on answers to each question.

Meta-analysis uses statistical methods to combine multiple studies addressing the same research question. It is often part of a systematic review and can identify significant results when individual studies are inadequately powered. Most meta-analyses combine results across studies in order to arrive at an overall estimate. When data are available, meta-regression can be performed to explain discrepancies across studies and to explore variations of effects such as dose-response relationships. Sometimes meta-analyses may shed new insights that studies examined individually may fail to reveal because of power limitations. Statistical methods to perform meta-analyses have advanced in the past two decades and the strengths and limitations are well understood. A key issue in performing a meta-analysis is the appropriateness of combining studies. This decision should be weighted in the context of the nature of the data and how the results will be used. Because several meta-analyses addressing similar questions may result in dissimilar conclusions, often due to differences in the questions asked and search protocol e.g. the inclusion criteria applied, the method of assessing methodological quality, and the applicability of studies included, it is important when interpreting the results to consider the questions and eligibility criteria very carefully.

In systematic reviews, a meta-analysis of the results from some of the included studies is often conducted. Potential advantages of meta-analyses include an increase in power, an improvement in precision, the ability to answer questions not posed by individual studies, and the opportunity to settle controversies arising from conflicting claims. However, they also have the potential to mislead seriously, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not carefully considered [1].

A subgroup analysis is sometimes undertaken to assess treatment effects for a specific subgroup. If sub-group analyses are undertaken they should be predefined and the interpretation of subgroup differences cautious [12].

Forests plots can be used to illustrate estimates and confidence-intervals for both individual studies and meta-analyses. Each study is represented by a block at the point estimate of intervention effect with a horizontal line extending either side of the block. The area of the block indicates the weight assigned to that study in the meta-analysis while the horizontal line depicts the confidence interval (usually with a 95% level of confidence). The area of the block and the confidence interval convey similar information, but both make different contributions to the graphic. The confidence interval depicts the range of intervention effects compatible with the study's result and indicates whether each was individually statistically significant. The size of the block draws the eye towards the studies with larger weight (usually those with narrower confidence intervals), which dominate the calculation of the pooled result [1].

SUMMARISE THE RESULTS AND GRADE THE EVIDENCE

Quality assessment of each individual study is the first step in the process of rating the quality of the evidence (Figure 1). After the quality assessment of individual studies, the results of the quality assessment should be summarised and the quality and strength of the evidence should be evaluated based on the summary of the results and quality assessment of all the individual studies. That is, how convincing is the evidence, taken the results from all the studies included in the review to support a judgement on a relationship. The expert groups grade the quality of a body of evidence separately for each outcome.

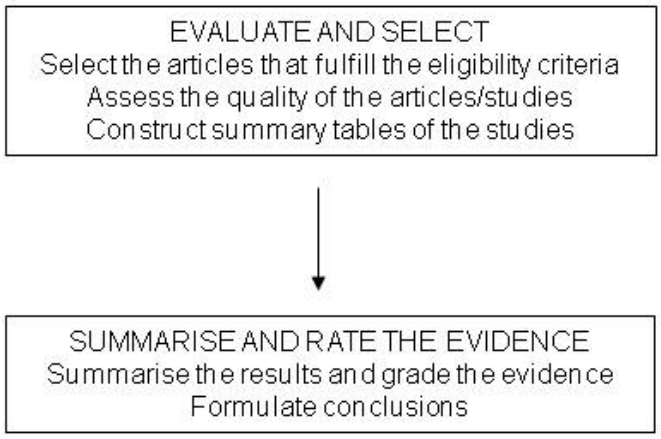

Figure 1. The review process: Quality assessment and grading the quality and strength of the evidence

When all the studies included in the systematic literature review are tabulated and quality assessed the results should be summarised and evaluated (Figure 1). This synthesis should be done in an open, transparent and reproducible manner. The risk for systematic errors should be minimised.

When summarising the findings the methods used for the review should be described - including details of data sources, databases searched and search strategies. Preference should be for data published in peer-reviewed journals, but other sources such as official or expert reports and government funded research, may provide some valuable information. Where such data are used, the source should be provided. The findings of the review and the conclusions drawn should be clearly and consistently described. Descriptors should allow ready assessment of study quality and the validity of findings. Basic statistical information needs to be included so that the strength of the findings can be seen (at least the number of cases included in the analysis and the 95% confidence interval).

In the 2007 WCRF cancer report [8] a number of predefined criteria were used to grade the strength of evidence (Box 2). This system was developed as an alternative for the GRADE evidence grading system [11] which is mainly used in health care methodology assessment where randomised clinical trials are the primary type of studies used as the evidence base. In the WCRF report, on the other hand, many conclusions were based on evidence from observational studies, and other types of studies provided supportive evidence.

As many of the studies used as evidence base within the NNR 5 project will be observational studies the system developed by the WCRF will also be used within the NNR 5 project. In order to guarantee transparency and openness of the process, the grading of the evidence should be strictly based on the quality assessment of the individual studies (Box 2).

Box 2. 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 shown here 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 riskfactors) 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 riskfactors) 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.

Constructing summary tables

The main results should be tabulated or listed in a summary table. A summary table is a distillation and synthesis of information from evidence tables. It is used to present study characteristics and results to support the interpretation of the evidence addressing a specific question [3]. All the relevant outcome variables should be reported separately (e.g. morbidity, mortality, biological effects). The outcome variables should include not only the positive effects but also possible negative effects (like elevated risk, side effects and complications) and be presented separately in the summary table. The outcome variables should be tabulated hierarchically with the more important variables presented before the less important ones. In some cases also outcome variables with less relevance can be included but should be presented at the end of the summary table. Markers of study quality should be included. Table 2 is an example of a summary table. There are a number of ways in which studies could be grouped for presentation. Grouping could be done according to study design or other major factors that may influence the results. Forest plots of results can be used to illustrate results of individual studies.

Summarising the grade of evidence

The process of summarising the grade of evidence should be 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 should be specified. Also, it is important to separately evaluate the quality of each study included according to the three category quality grading system (Box 1) before summarising the evidence.

FORMULATE CONCLUSIONS

There are several important factors to consider when formulating conclusions based on the systematic literature review (SLR). The aim of conducting a SLR is to strengthen the available evidence to allow firm conclusions to be drawn that will serve as the basis for advice to the public. The conclusions should summarise the evidence, be clearly worded and based solely on the reviewed evidence. They should also point out principal areas of uncertainty and areas where further research is required.

DERIVATION OF REFERENCE VALUES

Generally, it could be said that a judgement of evidence as convincing or probable justifies a recommendation, while evidence judged as limited-suggestive or limited-no conclusion do not justify a recommendation. However, rating the quality of evidence and the strength of conclusions is not the last stage in the evaluation process. The SLR and rating of the evidence will be the basis for deriving dietary reference values (DRV). The process of deriving DRVs will include considerations of how realistic the conclusions from the SLR are (i.e. is it possible to achieve suggested intake levels by eating “normal foods” or will it be necessary to take supplements) and the relevance for the Nordic setting. This evaluation will be done by the NNR5 working group and should not be part of the SLR conducted by the expert group. It is, however, important for the expert groups to remember that the systematic reviews are primary and independent components - but not the only components – of the decision making processes performed by those responsible for developing science-based dietary recommendations.

Table 2. Example on summary table headings

Exposure/Intervention	No of participants (No of studies)	Outcome variable (primary or secondary)	RR (95% CI)	Effect	Number of studies rated as A B C	Strength of evidence (convincing, probable, limited-suggestive, limited-no conclusion)	Comments

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APPENDICES

Appendix 1. Quality assessment tool for clinical trials

Author:_____ Year:_____ Reference nr:_____

1. General question and study design					Requires Yes for level A	B	C
a) Research question/hypothesis clearly formulated?	Yes	No	Can´t tell	NA	x	x	
b) Was the study design suited to test the research hypothesis?	Yes	No	Can´t tell	NA	x	x	
c) Was the duration of the study suited to test the research hypothesis?	Yes	No	Can´t tell	NA	x		
d) Sample size and power calculation reported/considered (relevant for the main outcome variable)?	Yes	No	Can´t tell	NA	x		
2. Participants and compliance							
a) Population (target group) well described and relevant (for NNR)?	Yes	No	Can´t tell	NA	x	x	
b) Sample (possible participants) recruited in an acceptable way?	Yes	No	Can´t tell	NA	x	x	
c) Criteria for inclusion/exclusion clearly formulated and acceptable?	Yes	No	Can´t tell	NA	x		
d) Actual participants comparable with the relevant (target) population?	Yes	No	Can´t tell	NA	x		
e) Method of randomization allocation stated and appropriate?	Yes	No	Can´t tell	NA	x		
f) Was there an account of the comparability of groups with regard to relevant/possible factors that might affect outcome?	Yes	No	Can´t tell	NA	x		
g) Compliance reported in an acceptable way? Compliance acceptable?	Yes	No	Can´t tell	NA	x		
h) Drop-out rate within an acceptable range? 6mo<30%, 12mo<40%, 24 mo<50%	Yes	No	Can´t tell	NA	x		
i) The drop-outs did not differ from the participants?	Yes	No	Can´t tell	NA	x		
3. Dietary intervention and assessment							
a) Intervention diets clearly defined and characterised (foods and nutrients)?	Yes	No	Can´t tell	NA	x	x	
b) Method used for dietary assessment valid/ adequately validated?	Yes	No	Can´t tell	NA	x		
c) Intervention diets consist of normal foods / relevance to research question?	Yes	No	Can´t tell	NA	x		
d) Measurement errors in dietary reporting considered?	Yes	No	Can´t tell	NA	x		
e) Energy intake at a credible level? Were the results adjusted for energy intake?	Yes	No	Can´t tell	NA	x	x	
c) Food composition database reported?	Yes	No	Can´t tell	NA	X		
4. Outcome, results and analysis							
a) Acceptable and clear definition of the outcome/endpoint?	Yes	No	Can´t tell	NA	x	x	
b) Biological mechanism for endpoint plausible?	Yes	No	Can´t tell	NA	x	x	

c) Results analysed blind?	Yes	No	Can´t tell	NA	
d) Attempts in the analysis phase made to adjust for imbalances between treatment arms with regard to important determinants for the outcome (e.g. through multivariate modelling)?	Yes	No	Can´t tell	NA	x
e) Valid biomarkers used to study compliance with the dietary exposure?	Yes	No	Can´t tell	NA	x if relevant
f) Possible use of medication/supplements taken into account?	Yes	No	Can´t tell	NA	x if relevant
g) Between measurement variation minimised/standardised?	Yes	No	Can´t tell	NA	
h) Smallest effect clinically relevant/reasonable?	Yes	No	Can´t tell	NA	
i) No possible conflicts of interests affecting the study quality?	Yes	No	Can´t tell	NA	x
5. Summary of the study quality	A	B	C		

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; no reporting errors; 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.

Appendix 2. Quality assessment tool for prospective cohort studies

Author:_____ Year:_____ Reference nr:_____

1. General questions and study design					Requires Yes for level A B C
a) Research question clearly formulated?	Yes	No	Can´t tell	NA	x x
b) Endpoint/outcome clearly defined?	Yes	No	Can´t tell	NA	x x
c) Was the study design suited to test the research hypothesis?	Yes	No	Can´t tell	NA	x x
2. Sampling (*Ascertainment of cases and non-cases)*					
a) Source population/study base well defined? Recruitement done in an acceptable way?	Yes	No	Can´t tell	NA	x x
b) Response rate reported and acceptable?	Yes	No	Can´t tell	NA	x x
c) Criteria for inclusion/exclusion clearly formulated and acceptable?	Yes	No	Can´t tell	NA	x x
d) Participants and non-participants comparable with Nordic population?	Yes	No	Can´t tell	NA	x
e) Time period of baseline examinations clearly identified?	Yes	No	Can´t tell	NA	x
f) Endpoint clearly ascertained and assessed in a valid way?	Yes	No	Can´t tell	NA	x x
g) Follow-up period clearly identified?	Yes	No	Can´t tell	NA	x
h) Time-exposure-variable clearly defined (i.e., period non-cases being exposed)?	Yes	No	Can´t tell	NA	x
i) Loss to follow up < 20%?	Yes	No	Can´t tell	NA	x
3. Dietary exposure					
a) Type of exposure (nutrients, food groups etc) reported in sufficient detail?	Yes	No	Can´t tell	NA	x x
b) Particulars of dietary assessment tool reported in sufficient detail?	Yes	No	Can´t tell	NA	x
c) Food composition database reported?	Yes	No	Can´t tell	NA	x
d) Concurrent validity (validation coefficients) of specific exposures reported?	Yes	No	Can´t tell	NA	x
e) Associations between dietary exposures reported?	Yes	No	Can´t tell	NA	x
f) Measurement errors in dietary reporting considered?	Yes	No	Can´t tell	NA	x x
g) Energy intake at a credible level?	Yes	No	Can´t tell	NA	x x

h) Energy adjustment adequately done?	Yes	No	Can´t tell	NA	x
i) Repeat assessment of diet during follow up?	Yes	No	Can´t tell	NA	x
j) Use of dietary biomarkers adequate? Details of assessment and handling reported? Valid biomarker assay?	Yes	No	Can´t tell	NA	x if relevant
k) Time period between biomarker assessment and diagnosis acceptable?	Yes	No	Can´t tell	NA	x if relevant
4. Anthropometry					
a) Assessment details clearly reported and assessment adequately performed?	Yes	No	Can´t tell	NA	x
5. Physical activity					
a) Assessment details clearly reported and assessment adequately performed?	Yes	No	Can´t tell	NA	x
6. Confounding					
a) Were important confounders identified/ascertained and considered by authors?	Yes	No	Can´t tell	NA	x x
b) The distribution of confounders similar in cases and non-cases?	Yes	No	Can´t tell	NA	x
7. Statistical power					
a) Was the study power considered and sample size and power calculations reported?	Yes	No	Can´t tell	NA	x
b) In view of multiple tests, were by chance findings considered?	Yes	No	Can´t tell	NA	x
c) Sufficient size of study population and no. of outcomes/cases?	Yes	No	Can´t tell	NA	x
8. Statistical analysis					
a) Appropriately handled?	Yes	No	Can´t tell	NA	x
b) Relevant confounders adequately handled: Restriction, Stratified analysis, Multivariate modelling, Interaction tested?	Yes	No	Can´t tell	NA	x x
c) Ascertainment/detection bias considered (eg. cases detected due to screening)?	Yes	No	Can´t tell	NA	x
d) Cases detected early during the follow-up period removed?	Yes	No	Can´t tell	NA	x
9. Summary of the study quality	A	B	C		

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; no reporting errors; 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.

Appendix 3. Quality assessment tool for nested case-control studies

Author:_____ Year:_____ Reference nr:_____

1. General questions and study design					Requires Yes for level A	B	C
a) Research question clearly formulated?	Yes	No	Can´t tell	NA	x	x	
b) Endpoint/outcome clearly defined?	Yes	No	Can´t tell	NA	x	x	
c) Was the study design suited to test the research hypothesis?	Yes	No	Can´t tell	NA	x	x	
2. Sampling (*Ascertainment of cases and controls)*							
a) Source population well defined and recruitment done in an acceptable way?	Yes	No	Can´t tell	NA	x	x	
b) Time period for baseline examinations reported and adequate?	Yes	No	Can´t tell	NA	x	x	
c) Criteria for inclusion/exclusion clearly formulated and acceptable?	Yes	No	Can´t tell	NA	x	x	
d) Repeat exposure assessment during follow up adequately done?	Yes	No	Can´t tell	NA	X		
e) Endpoint clearly ascertained and validly assessed?	Yes	No	Can´t tell	NA	x	x	
f) Follow-up period clearly defined?	Yes	No	Can´t tell	NA	X		
g) Matching criteria clearly formulated?	Yes	No	Can´t tell	NA	X		
h) Criteria for inclusion/exclusion of controls clearly formulated and acceptable?	Yes	No	Can´t tell	NA	X		
i) Characteristics of cases versus controls examined and reported?	Yes	No	Can´t tell	NA	X		
3. Dietary exposure							
a) Type of exposure (nutrients, food groups etc) reported in sufficient detail?	Yes	No	Can´t tell	NA	x	x	
b) Particulars of dietary assessment reported in sufficient detail?	Yes	No	Can´t tell	NA	x	x	
c) Concurrent validity (validation coeff.) of specific exposures reported?	Yes	No	Can´t tell	NA	x		
d) Associations/correlations between dietary variables reported?	Yes	No	Can´t tell	NA	X		
e) Measurement errors in dietary reporting accounted for/considered?	Yes	No	Can´t tell	NA	x	x	
f) Energy intake at a credible level?	Yes	No	Can´t tell	NA	x	x	
g) Energy adjustment adequately done	Yes	No	Can´t tell	NA	x		
h) Repeat assessment of diet during follow up?	Yes	No	Can´t tell	NA	x		
i) Use of dietary biomarkers adequate? Details of assessment and handling reported?	Yes	No	Can´t tell	NA	x if relevant		
j) Coefficient of variation of assay?	Yes	No	Can´t tell	NA	x		
k) Time period between biomarker assessment and diagnosis acceptable?	Yes	No	Can´t tell	NA	x if relevant		

4. Anthropometry			
a) Assessment details clearly reported and assessment adequately performed?	Yes No Can´t tell NA	x	
5. Physical activity			
a) Assessment details clearly reported and assessment adequately performed?	Yes No Can´t tell NA	x	
6. Confounding			
a) Were important confounders identified/considered by authors?	Yes No Can´t tell NA	x	x
b) Relevant confounders ascertained at baseline?	Yes No Can´t tell NA	x	x
c) The distribution of confounders similar in cases and controls?	Yes No Can´t tell NA	x	
7. Statistical power			
a) Was the study power considered and sample size and power calculations reported?	Yes No Can´t tell NA	x	
b) In view of multiple tests, were by chance findings considered?	Yes No Can´t tell NA	x	
8. Statistical analysis			
a) Appropriately handled?	Yes No Can´t tell NA	x	
b) Relevant confounders adequately handled: Restriction, Stratified analysis, Multivariate modelling, Interaction tested?	Yes No Can´t tell NA	x	x
c) Ascertainment/detection bias considered (eg. cases detected due to screening)?	Yes No Can´t tell NA	x	
d) Cases/corresponding controls detected early during follow-up period removed?	Yes No Can´t tell NA	x	
9. Summary of the study quality	A B C		

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; no reporting errors; 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.

Appendix 4. NNR5 modified AMSTAR checklist for quality assessment of systematic reviews

AMSTAR checklist for quality assessment of systematic reviews

1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

9. Were the methods used to combine the findings of studies appropriate?
For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

10. Was the likelihood of publication bias assessed?
An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

11. Was the conflict of interest stated?
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.

In systematic reviews of dietary, or nutrition epidemiological, studies several aspects of dietary exposure assessment needs to be considered in addition to the general quality criteria.

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

12. Was the methodology used to assess dietary intakes described in sufficient detail?
(e.g. particulars regarding concurrent or relative validity, or the number of 24-hour recalls/diet records).

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

13. Were adequate approaches taken to control, or avoid, the influence of measurement errors and confounding factors?
The impact of measurement errors and confounding factors can be considerable (eg. mis-/underreporting, or change of food habits due to prior disease or other reasons).

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

14. Were the exposure ranges of dietary intakes adequately described?
Exposure ranges may vary considerably across populations, and thus the magnitude of a particular diet-related health problem. Such differences may also contribute to inconsistent results across studies.

☐ Yes
☐ No
☐ Can't answer
☐ Not applicable

15. Summary of the study quality *

☐ A
☐ B
☐ C

* ***Level A***
Requires Yes to all the questions
(Or Non applicable to questions 9, 12 and 14)

Level B
Requires Yes to all the questions except for 3, 4, 10 and 11
(Or Non applicable to questions 9, 12 and 14)

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; no reporting errors; 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.

Appendix 5. Quality assessment tool for retrospective case-control studies

Author:_____ Year:_____ Reference nr:_____

1. General questions and study design					Requires Yes for level A	B	C
a) Research question clearly formulated?	Yes	No	Can´t tell	NA	x	x	
b) Endpoint/outcome clearly defined?	Yes	No	Can´t tell	NA	x	x	
c) Was the study design suited to test the research hypothesis?	Yes	No	Can´t tell	NA	x	x	
2. Sampling (*Ascertainment of cases and controls)*							
a) Source population/study-base well defined?	Yes	No	Can´t tell	NA	x	x	
b) Period of recruitment/ascertainment well defined?	Yes	No	Can´t tell	NA	x	x	
c) Case status clearly ascertained and endpoint validly assessed?	Yes	No	Can´t tell	NA	x	x	
d) Control status clearly defined?	Yes	No	Can´t tell	NA	X		
e) Criteria for inclusion/exclusion clearly formulated and acceptable?	Yes	No	Can´t tell	NA	x		
f) Matching criteria clearly formulated?	Yes	No	Can´t tell	NA	X		
g) Number of non-participating controls and reasons for non-participation reported?	Yes	No	Can´t tell	NA	X		
3. Dietary exposure							
a) Type of exposure (nutrients, food groups etc) reported in sufficient detail?	Yes	No	Can´t tell	NA	x	x	
b) In retrospective assessment, is the reference (time) period clearly reported?	Yes	No	Can´t tell	NA	x		
c) Particulars of dietary assessment tool reported in sufficient detail?	Yes	No	Can´t tell	NA	x	x	
d) Food composition database reported?	Yes	No	Can´t tell	NA	X		
e) Concurrent validity (validation coefficients) of specific exposures reported?	Yes	No	Can´t tell	NA	X		
f) Measurement errors in dietary reporting considered?	Yes	No	Can´t tell	NA	x	x	
g) Energy intake at a credible level?	Yes	No	Can´t tell	NA	x	x	
h) Energy adjustment adequately done?	Yes	No	Can´t tell	NA	x		
4. Confounding							
a) Important confounders identified by authors, and ascertained?	Yes	No	Can´t tell	NA	x	x	
b) Distribution of confounders similar in cases and controls?	Yes	No	Can´t tell	NA	x	x	
c) Recall bias considered?	Yes	No	Can´t tell	NA	x	x	

5. Statistical power		
a) Was the study power considered and sample size and power calculations reported?	Yes No Can´t tell NA	x
b) In view of multiple tests, were by chance findings considered?	Yes No Can´t tell NA	x
6. Anthropometry		
a) Assessment details clearly reported and assessment adequately performed?	Yes No Can´t tell NA	x
7. Physical activity		
a) Assessment details clearly reported and assessment adequately performed?	Yes No Can´t tell NA	x
8. Analysis		
a) Conditional analysis? Or unconditional with matching variables in the models?	Yes No Can´t tell NA	x x
b) Relevant confounders adequately handled: Restriction, Stratified analysis, Multivariate modelling, Interaction tested?	Yes No Can´t tell NA	x x
9. Summary of the study quality	A B C	

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; no reporting errors; 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.

Appendix 6. Quality assessment tool for cross-sectional studies

Author: _____ Year:_____ Reference number: _____

1. General questions and study design					Requires Yes for level A B C
a) Research question clearly formulated?	Yes	No	Can´t tell	NA	x x
b) Outcome clearly defined?	Yes	No	Can´t tell	NA	x x
2. Recruitment/Participation					
a) Source population well defined and recruitment done in an acceptable way?	Yes	No	Can´t tell	NA	x
b) Participation rate acceptable (> 50%)?	Yes	No	Can´t tell	NA	x x
c) Criteria for inclusion/exclusion clearly formulated and acceptable?	Yes	No	Can´t tell	NA	x
d) Were the participants with primary outcome adequately identified/diagnosed?	Yes	No	Can´t tell	NA	x
e) Are the differences in outcome between groups relevant?	Yes	No	Can´t tell	NA	x
f) Are the participants comparable with relevant (target) Nordic population?*	Yes	No	Can´t tell	NA	x x
3. Dietary assessment					
a) Method used for dietary assessment adequate and valid?	Yes	No	Can´t tell	NA	x x
b) Diets/nutrients studied clearly defined and characterised?	Yes	No	Can´t tell	NA	x
c) Energy-intake at a credible level?	Yes	No	Can´t tell	NA	x x
d) Energy adjustment adequately done?	Yes	No	Can´t tell	NA	x
e) Use of biomarkers adequate?	Yes	No	Can´t tell	NA	x if relevant
f) Results adjusted for mis/underreporting?	Yes	No	Can´t tell	NA	x x
g) Possible drug usage taken into account?	Yes	No	Can´t tell	NA	x
d) Food composition database reported?	Yes	No	Can´t tell	NA	x
4. Confounding					
a) Were important confounders identified/considered by authors?	Yes	No	Can´t tell	NA	x x
b) Relevant confounders adequately handled: restriction, stratified analyses, multivariate modelling, interaction tested?	Yes	No	Can´t tell	NA	x x

5. Anthropometry					
a) Assessment details clearly reported and assessment adequately performed?	Yes	No	Can´t tell	NA	x if relevant
6. Physical activity					
a) Assessment details clearly reported and assessment adequately performed?	Yes	No	Can´t tell	NA	x if relevant
7. Statistical power					
a) Was the study power considered and sample size and power calculations reported?	Yes	No	Can´t tell	NA	x
8. Analysis					
a) Was the statistical method adequate?	Yes	No	Can´t tell	NA	x x
b) No possible conflicts of interests affecting the study quality?	Yes	No	Can´t tell	NA	x
9. Summary of the study quality	A	B	C		

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; no reporting errors; 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.

Appendix 7. Proposed structure of SLR reports

Proposed structure of SLR reports

Based on Cochrane, SBU and AHRQ

Abstract

(Plain language summary - used in Cochrane reports)

Introduction

- Background
- Objectives
- Key questions

Methods

- Definitions
    - Indicators of exposure
    - Outcome measures
    - Life stages
- Search methods and terms
- Selection of articles/studies
    - Abstract screening
    - Full text article eligibility criteria
        - Types of studies, participants, exposure
- Quality assessment of studies
- Data extraction and analysis
- (Meta-analysis)
- Assessment of systematic reviews
- Assessment and grading of evidence
- Reporting of evidence

Results

- Description of studies
    - Results of search
        - No. of hits,
        - No. of papers identified for further consideration
        - No. of papers meeting inclusion criteria
    - Included studies
    - Excluded studies
- Risk of bias in included studies
- Effects of exposure on outcome measures (separately for each outcome)
- Study quality
- Publication bias
- Reporting and summarizing the evidence
    - Evidence and summary tables

Discussion

- Dose-response assessment incl. exposure range
- Study duration

- Heterogeneity
- Other evidence

Authors' conclusions
- Implications for the Nordic setting
- Implications for research

Acknowledgements

References
- References to studies included in this review
- References to studies excluded from this review
- Additional references

Abbreviations and glossary

Contributions of authors

Declarations of interest

Sources of support
- Internal sources
- External sources

Appendices
1. Search strategies
    a. Index terms
    b. Medical Subject Headings (MeSH)
    c. MeSH check words
2. Data extraction and quality assessment checklists
3. Characteristics of studies
    - Characteristics of included studies
    - Characteristics of excluded studies