Second expert report

Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective

Systematic Literature Review Specification Manual

Preface

WCRF International has devised this specification manual, after detailed expert consultation, for the conduct of systematic literature reviews relevant to food, nutrition, physical activity and the aetiology of cancer worldwide.

In 1997 the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) jointly published *Food, Nutrition and the Prevention of Cancer: a global perspective*. This report remains current as the leader in its field.

The World Cancer Research Fund global network, which now incorporates AICR, decided in 2001 to commission a second report. A great deal of new evidence has accumulated in the field of food, nutrition, physical activity and cancer since 1997 and it is essential that a new report is published, firmly based on current knowledge. The process for developing the second report is scheduled to take five years.

For the second report, WCRF International, guided by a specially convened Methodology Task Force of scientists in relevant fields, has devised a new methodology by which the relevant literature can be reviewed systematically. This methodology is specified in this manual.

Existing systematic methodologies, of which those devised by the Cochrane Collaboration are perhaps the best known, are principally devised to address questions related to the efficacy of interventions, for instance the treatment of disease, rather than causation.

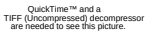
Therefore this manual, while drawing on the accumulated knowledge and success of the Cochrane Collaborating Centres and other centres of excellence, has many important differences from existing methodologies, in particular in not employing a strict hierarchy of evidence in reviewing the literature.

The immediate purpose of this manual is as a set of instructions and guidance for the systematic literature review (SLR) centres, being commissioned to carry out SLRs by WCRF International. The manual is also designed to guide the work of the independent external peer reviewers engaged in the process.

WCRF International gratefully acknowledges the guidance and support given in preparation of this manual by the Methodology Task Force (see **Appendix A**). The manual in its final form as a working document has been submitted to and approved by the expert Panel responsible for the second report (see **Appendix B**), chaired at the time by Professor Robert Beaglehole. A separate business plan has also been prepared by WCRF International.

The Board, the executives and the staff of the WCRF International global network are proud of the first report and also proud of the work done so far in preparation of the second report, due to be published in 2006. We also gratefully acknowledge the

support of members of the new Panel, and the observers from relevant UN and other international organisations, for their commitment to this major new project.



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based on advice from the Methodology Task Force (see **Appendix A**). As leaders of the test SLR centres, David Forman, Janet Cade, Larry Kushi and Elisa Bandera and their teams have also had special input. Marcel Zwahlen, Genevieve Chene, Christoph Minder, Mathias Egger, Roger Harbord, George Davey Smith and Jonathan Sterne have drafted a large proportion of section 16 of this manual. Lisa Mathers of the Centre for Research and Dissemination has provided the standardised search strategy and James Thomas has developed the database provided for data extraction. The manual has also been endorsed by the Panel and observers for the second report, listed in **Appendix B**.

Contents

Part 1
Background

1 Introduction

In 1997, the World Cancer Research Fund (WCRF) and its affiliate the American Institute for Cancer Research (AICR) published the expert report *"Food, nutrition and the Prevention of Cancer: a global perspective"*. This report became a landmark publication around the world and remains generally perceived as the most comprehensive statement on the evidence linking food and nutrition to the prevention of cancer.

Since publication of the 1997 report further evidence has been published and there have been developments in techniques of synthesising research evidence. WCRF has therefore decided to publish a new report, and will be using a formal and transparent process, described in detail in **Section 4**, based on systematic reviews of the relevant literature.

In brief the process has three main components

- The development of a convention for conducting systematic reviews, and its incorporation into a manual
- The systematic literature reviews (SLRs) themselves, conducted according to the specifications in the manual
- The interpretation of the evidence and judgements and recommendations from these SLRs and other evidence.

This manual represents the completion of the first component of the process, i.e. the development for a manual for the conduct of the SLRs. This has the aim of ensuring:

- Consistency of approach to the evidence
- Comprehensiveness of the SLRs
- Common approach to analysis
- Common format for displaying the evidence
- Common use of terminology

This manual has been developed by WCRF International with guidance from a group of independent experts, the Methodology Task Force (listed in **Appendix A**), and is the starting point for the second component of the process – the systematic literature reviews themselves. The process owes much to the conventional systematic review

methodology used by the Cochrane Collaboration and the NHS Centre for Reviews and Dissemination (NHS CRD) [1], in the UK. However in some important ways this process needs to be different.

For the reviews usually addressed by Cochrane [2] and NHS CRD[1], the question is generally of efficacy of interventions. In this context the currently generally accepted hierarchy of evidence is used, which places randomised controlled trials above observational evidence because they are less open to bias. This is entirely appropriate.

However the questions at the heart of the systematic reviews to be commissioned by WCRF International are aetiological – that is they are seeking to identify causes of cancer. For aetiological questions, the inference of causation must be based upon evidence of different types and drawn from different sources – observational, intervention, clinical and laboratory, in order to provide a basis for considering the conceptual frameworks of Bradford Hill [3] and others [4].

Thus the process outlined in this manual aims to conduct a comprehensive review of all types of evidence relating to the question of relevance – using an inclusive approach rather than a hierarchy to access the data.

It is important to note that the purpose of these SLRs is to simply display the evidence – the Panel (listed in **Appendix B**) will be responsible for drawing conclusions and making recommendations.

The SLRs will be carried out in a number of different centres. In order to facilitate consistency through the application of this specification manual, the process involves a Review Coordinator. This role is explained in more detail in **Section 10**. The review teams will be expected to work with the Review Coordinator to fulfil WCRF International's requirements.

2 The first report

The report '*Food, Nutrition and the Prevention of Cancer: a global perspective*' was published in late 1997, by the World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR), now part of the WCRF global network.

The vision of WCRF International is:

To prevent cancer worldwide

and its missions are:

To raise awareness that the risk of cancer is reduced
by healthy food and associated lifestyles

To develop and strengthen scientific knowledge
on food, nutrition and the prevention of cancer

This first WCRF report is used by national governments and by United Nations and other international agencies throughout the world, to help shape international and national policies on the prevention and control of cancer. It is also used by research scientists to guide their work; by teachers in universities and research centres; by expert organisations concerned with the prevention of chronic diseases including cancer; by health professionals; and by community groups, families and individuals, and the media. It is widely cited in the academic and professional literature and at international scientific conferences, and its research recommendations have influenced research science priorities.

The report is also used as the basis of the education programmes of the WCRF global network in the USA, the UK, Germany, the Netherlands, China (Hong Kong), and France, and of the research grant programmes of WCRF International. The report or its summary have been translated or adapted by authoritative external organisations for a number of regions and countries, including Latin America (by the Pan American Health Organization), China (by the official Chinese agencies) and in Japan, India, Germany, France, and the Asia-Pacific region.

This first report continues to set the agenda in its field. Thus, the 2003 WHO technical report series 916: '*Diet, nutrition and the prevention of chronic diseases: report of a joint World Health Organization (WHO)/Food and Agriculture Organization (FAO) consultation* [5] uses methods pioneered by WCRF/AICR to classify the strength of scientific evidence and to display evidence-based conclusions and recommendations.

3 The second report

WCRF International has now begun the process of creating, publishing and disseminating a second report. Following the first report, its mission is:

- To publish the most authoritative current global report on food, nutrition, physical activity and the prevention of cancer

- To enable governments, officials, scientists, professionals and all people worldwide, to use the report and its recommendations effectively

- To develop and promote a new assessment of the nature of evidence needed to ascertain the causes of cancer and other diseases

It is usual to produce new editions of major reports on subjects of public concern and interest. This is especially important when, as in this case, these are designed to encourage international agencies, governments, other public policy-makers, professionals in the field, and also non-governmental organisations, consumer groups, communities, families and individuals, and the media, to act in ways that are firmly based on current knowledge.

In the case of the new WCRF International report, there are a number of other key reasons:

- In the last decade, a great deal of new evidence has accumulated.
- New methods of reviewing and assessing the science have been developed.
- The electronic revolution now enables new methods of publication and review.
- There is more evidence on the role of food and nutrition for cancer survivors.
- There is more evidence on physical activity and cancer.
- Cancer remains a leading cause of death worldwide.
- The need for current evidence-based public policy is as great as ever.

WCRF International has decided that for the second report, a crucial part of the process is not only to review the literature systematically, according to best practice as developed since the late 1990s, but also, in order to ensure transparency and independence, to separate the process of review of the literature from judgements based on the evidence.

4 Overall process

The process for producing the new report takes place in three overlapping stages. The first stage has been to develop an appropriate method for systematic reviewing of the voluminous scientific literature, in the light of increasingly high standards expected from such reports – as evident in this manual. The second stage is to outsource the systematic literature reviews, based on the methodology developed in stage one. In the third stage, a panel of experts will consider the evidence, formulate judgements, draw conclusions and make recommendations.

Stage 1 – Methodology

The first stage in producing the report has been the development of a systematic methodology to review the scientific evidence. Although this has been done for questions of clinical efficacy of treatments, no well-established methodology exists for assessing data in the context of causation of disease in the field of nutrition and cancer.

In this stage, a Task Force of experts in nutrition, cancer, methodology, statistics, and epidemiology has helped the Secretariat develop this SLR specification manual. This manual will be used by independent institutions to conduct site-specific SLRs of the literature relevant to food, nutrition, physical activity and cancer, and by peer reviewers of the SLRs.

Stage 2 - Systematic literature reviews

The second stage of the process involves conducting the systematic reviews of the literature. This task is outsourced to a number of independent institutions that produce reports on all the evidence, following the methodology developed as stage 1. The reports of the systematic literature reviews display the required information from the literature in a standard format but will not interpret the evidence or draw aetiological or policy conclusions or make recommendations.

Stage 3 - Conclusions and recommendations

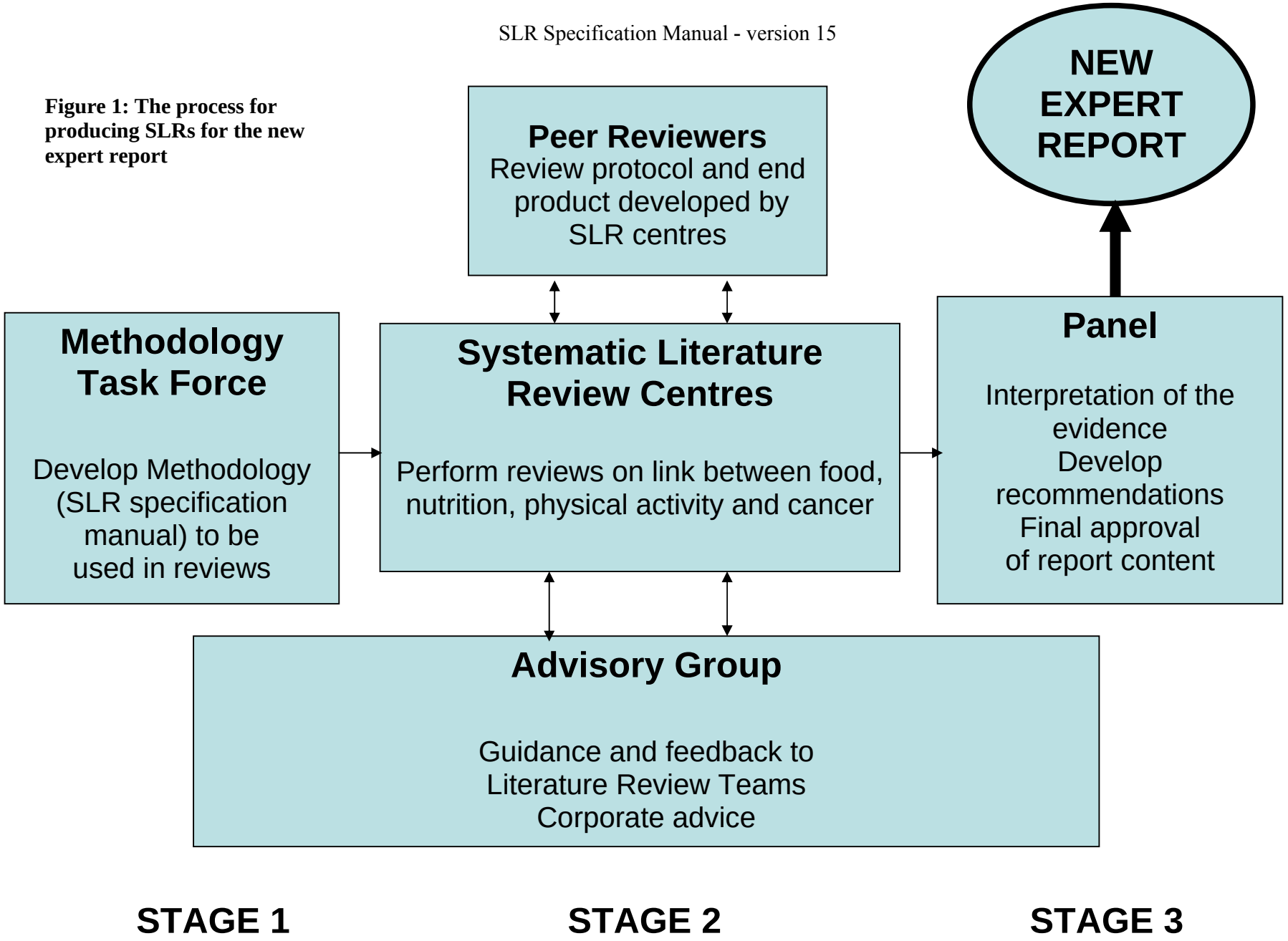
The third and final stage of assessing the evidence from the independent SLRs and other sources of evidence, making judgements, drawing conclusions and formulating recommendations is performed by an independent panel of 21 experts, who carry responsibility for the substance of the report. The Panel is globally representative and includes members of the 1997 Panel, members of the Methodology Task Force and experts from relevant disciplines. Six observers from United Nations and other relevant international organisations also participate. The Secretariat coordinates the drafting of the report, as well as the printing, launch and distribution.

A peer review process is also necessary to ensure that the SLRs are carried out to the highest standard. External peer reviewers will review the SLR protocols and the SLR reports. A detailed explanation of the peer review process is in Part 5.

The project is expected to take five years, starting with stage one in 2001 and concluding with the launch and distribution of the report in 2006.

Various bodies are involved in the development of the second report. The members of each body are listed in **Appendices B, C, D and E**. The relationships between the various bodies and their role in the new report process are illustrated in **Figure 1**:

Figure 1: The process for producing SLRs for the new expert report



5 Methodology Task Force

As the first step in producing the second report, WCRF International agreed to develop a methodology appropriate for systematic review of the literature. As already mentioned, it was apparent that existing methodologies such as those for the Cochrane reviews, while sharing common principles, could not be applied in practice because of the different nature of the questions addressed (those of efficacy of interventions rather than those of causation).

Therefore, in 2001 WCRF International convened an independent Methodology Task Force of 18 scientists with expertise in the relevant fields, supported by representatives of relevant UN agencies, to seek guidance and advice. The Task Force, met three times for 1-2 day meetings, between November 2001 and October 2002. During and between these meetings, the Secretariat developed drafts of a series of working papers. These have formed the basis of this document developed by WCRF International, with the guidance of the Task Force. The SLRs, to be used as a basis for the second report, will be conducted using the standardised methodology that this document embodies.

At the end of the third meeting in October 2002, the Task Force's main work was completed, and a Review Coordinator has been appointed as a member of the WCRF International Secretariat, to support the SLR centres and to ensure quality, consistency and uniformity of the SLRs. Several members of the Task Force are on the central Advisory Group set up to support the process of developing the second report until publication in late 2006.

6 Systematic review

In recent years the term 'systematic review' has become increasingly current. For some the term denotes a relatively rigid approach to reviewing evidence in the field of clinical efficacy [2] though there are some examples of a broader context [6]. At the root of this discipline is the need to identify and analyse the best evidence in relation to a particular question. The overall evidence base relating to a question will comprise several lines, and each line may have a greater or lesser relevance to the question posed. In addition, each line of evidence will be subject to methodological errors of various kinds, both systematic (bias) and random (e.g. imprecision in measurement). Combining the results of several studies that address comparable exposures (or interventions) and outcomes has the advantage of increasing precision. However if systematic biases are present, combining their results will not reduce bias.

Systematic review follows a number of principles. First, the process of the review should be conducted according to a pre-specified method. Second, the proposed method should be open to public scrutiny. Third, the proposed method should be subject to peer review,

as should the resulting review. Finally the review should be comprehensive within its pre-specified criteria.

The prime purpose of the SLRs covered by this manual is to provide a comprehensive display of evidence in a common format. This display will be subject to interpretation by the Panel, separate from the SLR teams, in order to produce a state of the art document that will include recommendations aimed at reducing the incidence of cancer, and also research recommendations. Both will be designed as a basis for international, national and community public health policy, and for teaching. The need for consistency in approach for this is obvious.

A systematic approach to analysing such evidence offers advantages in reducing observer bias (where for instance inclusion or exclusion of studies may be influenced by preconceived ideas of the investigators). It cannot of course improve the intrinsic quality of data, but a good review will provide details of the characteristics of studies, which may allow a qualitative interpretation of their value and relevance to the question posed. In addition, although a review cannot remove biases inherent in the original data, an exploration and analysis of such biases can aid interpretation.

The driving force behind the movement for systematic reviews has been in relation to evidence-based medicine. The principal questions asked in this context are to do with the efficacy of clinical interventions. For such a purpose, certain types of study offer clear advantages, and the wide acceptance of a hierarchy of evidence (see **Box 1**) has followed from this.

Box 1: Current conventional hierarchy of study designs, based on that used by the NHS Centre for Reviews and Dissemination (University of York) [1]

Experimental (intervention studies)

- Meta-analysis of randomised controlled trials
- Randomised controlled trial
- Quasi-experimental (non-randomised trial)

Observational

- Cohort study
- Case-control study
- Cross-sectional study
- Ecologic studies
- Before-and-after study
- Case series

The basis for this hierarchy is the primacy of randomised controlled trials (RCTs). Randomisation in intervention studies offers an opportunity to avoid bias from confounding, as any good RCT should ensure that the only difference between the intervention and control groups is the intervention itself. This is an important advantage. On the other hand there are both inherent and practical problems with conducting RCTs, and they are not the best source of evidence to answer all types of biological question.

In the context of this SLR there are three principal problems with randomised controlled trials, which are interrelated but separate. Firstly the development of cancers appears to be a process taking two or more decades. The accumulation of sufficient unrepaired DNA damage need not be a sequential linear process, and it is difficult to conceive of a practical trial that could last for sufficient time to cover more than just a small part of this timescale. Secondly, the dietary, nutritional and physical activity exposures involved are complex and interrelated, and difficult to influence in the medium to long term. The usual solution to this is to give micronutrient supplements, but clearly this relies on the assumption of a simple linear model of causation, which may not be the case and supplements may not be a guide to food as normally consumed. Finally, the outcome of a trial is to show efficacy (or lack of efficacy). The nature of a trial involves an intervention, which may result in different outcomes between intervention and control groups. Whether or not such a difference follows should not necessarily be taken as an indication that the intervention is, outside the experimental setting, a usual cause of the outcome of interest. The efficacy of pharmacological interventions is tested in this way, but does not have direct implications for causation, which must be inferred from the whole body of evidence. For instance, though high doses of nicotinic acid may reduce blood cholesterol, it cannot be inferred that prevalent high blood cholesterol in the population is a function of poor nicotinic acid status.

These factors do not mean that RCTs are not an important component of the evidence, but they do not produce evidence that overrides that from other types of study.

For the purposes of the SLRs to be commissioned by WCRF International, the hierarchy of evidence that gives supreme value to randomised controlled trials will not be used. It may be appropriate in clinical contexts to ignore other evidence when good clinical trials exist, but in investigation of causation and prevention all types of evidence need to be considered. Thus instead of a hierarchy of evidence where one type is taken to be inherently better than another, the WCRF International process involves using a inclusive approach, where all types of evidence are relevant.

It has been recognised for some time that the inference of causation of chronic disease requires a comprehensive view of the evidence base, in a broad biological context. These considerations have been set out clearly by Bradford Hill [3], Rothman[4] and others. The following factors represent the characteristics of a relationship between exposure and outcome which, using and adapting the work by Bradford Hill, together help infer the likelihood, or otherwise, of a causal connection:

- **Strength:** Essentially this relates to the size of the effect, as exemplified by relative risk and odds ratios.
- **Consistency:** That is the degree that studies, for instance at different times, in different populations, or of different designs, produce similar results. This can be quantified by tests of heterogeneity.
- **Timing:** A critical issue is to ensure that the measured exposure precedes the outcome of interest. In interventions, and prospective studies this is not an issue, but for case control studies, recall bias may confound this relation.
- **Dose response:** The presence of a detectable biological gradient in the relation between exposure and outcome lends weight to a causal inference, though absence does not rule it out.
- **Experiment:** Experimental designs whether in clinical, or laboratory settings can provide useful information especially on mechanisms that might underlie any observed association. Positive results from RCTs for instance may be telling, though interpretation of negative results needs to be taken in context.
- **Plausibility:** An observed association between exposure and outcome without evidence of a plausible biological explanation must remain only speculative. The relevance here of experimental laboratory data in humans and animals as supporting evidence for causality is important.
- **Specificity:** Specificity of the association or specificity of the magnitude of the association may aid the inference of causation. However, in the presence of

multifactorial causation, which is likely in the context of these SLRs, this aspect should not be over-emphasised.

These characteristics are important to consider when inferring causation but are not designed to be rigid criteria. They are not absolute requirements, and furthermore none of them has to apply in all cases. Each of these characteristics, to a greater or lesser extent, help to inform a judgement of cause and effect. While the principles set out by Bradford Hill in 1965 still apply, there are other factors that are now also used in practice and some modification in which the way these principles are used may be necessary. For example, the exclusion of possible causes other than those being considered is particularly important component in the inference of causation, and the use of specificity is a questionable criterion for inferring the causation of a multifactorial disease.

Other models of causation, characterising sufficient and necessary causes of outcomes, have also been proposed and offer valuable complementary approaches to making the judgement of causality[4].

To summarise, WCRF International require SLR centres to review data from observational epidemiological designs of all types, including classic ecologic studies, prospective cohorts and case control studies; data from intervention studies using foods, diets or food components in various forms; data from laboratory studies in humans, and to a lesser extent in animals. This manual also stipulates a common approach to analysing and displaying the data, in order to be able to explore the data with a view to addressing the criteria above.

The purpose of this manual is to ensure that the data are explored, analysed and displayed in a common format, in order to make their assessment and judgements based on this assessment, as reliable as possible. The model developed here may also be useful for future reports that examine questions or causation or prevention of disease in other or broader contexts.

Part 2
The systematic literature review (SLR) process

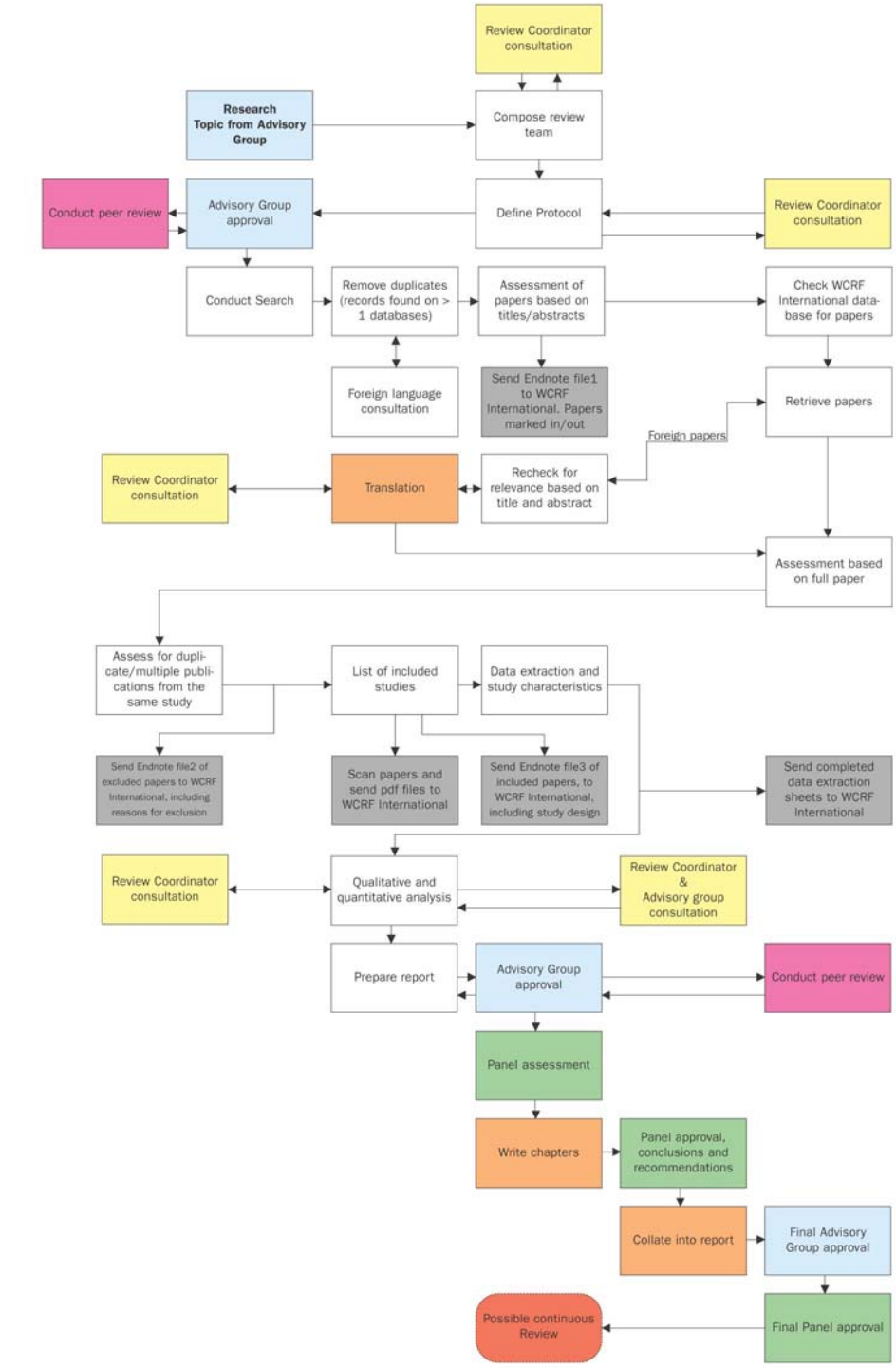
7 The process flowsheet

The process flowsheet is a graphical representation of the individual steps that will be followed in conducting the SLR and submitting the results to the Panel. It indicates the flow of information and the roles and responsibilities of the different groups. The following groups have been colour coded according to the following key:

SLR centres	White
Advisory Group	Blue
Panel	Green
Review Coordinator	Yellow
Secretariat	Orange
Peer reviewers	Pink
Files to be sent to WCRF International	Grey

The flowsheet should not be seen as a stepwise process, as some of the stages will occur simultaneously. There will also be constant contact between the Secretariat, the Review Coordinator and the SLR centres. The details of the EndNote files to be sent to WCRF International are available in **Section 13.11.2**.

PROCESS FLOWSHEET
(V. 6)



8 The SLR centres

A total of 18 SLRs will be conducted across 6 SLR centres. The list of cancer sites and their groupings are shown in **Table 1**.

Within each of the groups A to G, each SLR centre is asked to complete an SLR with the specified cancer sites as the outcomes. In addition, any studies reporting imprecise anatomical definitions of cancer site (such as "upper gastrointestinal tract"), but which includes the cancer site of interest (e.g. oesophagus, stomach) should be included for each relevant cancer site.

In addition, two SLR centres will carry out a SLR on endometrial cancer, as a testing process.

Table 1: List of cancer sites to be reviewed, and groupings across SLR centres

Group	Topics
A	Mouth, larynx & pharynx
	Oesophagus
B	Lung
	Nasopharynx
C	Colon & rectum
	Liver
	Gallbladder
D	Pancreas
	Stomach
E	Bladder
	Prostate
	Kidney
	Other*
F	Breast
	Ovary
	Cervix

*Cancers of the skin, nervous tissue, testes, thyroid, bone and haematological/lymphatic.

To ensure that the final report (due to be published in 2006) is based on the latest research, SLR centres are required to update the SLRs in March 2006.

Within each SLR centre, a SLR team will be assembled for each cancer site. The expertise required for each SLR team is specified in **Section 9**.

9 The SLR teams

In order to conduct a high quality scientific SLR, a multidisciplinary team is needed. Each SLR requires expertise in various components. SLRs will all need a common core of some expertises, but some SLRs may need particular skills in addition, which may not be needed for other SLRs.

Each SLR team should comprise a minimum of five people, of whom at least two should act as principal reviewers.

A common core of skills should include:

- Project manager
- Epidemiologist
- Specialist in cancer biology/mechanisms of the specified cancer site
- Specialist in nutrition
- Information specialist/research librarian
- Statistician with experience in meta-analysis and systematic reviews.

The SLR leader has overall responsibility for the SLR process at each centre, including the meeting of deadlines and quality of work. It is crucial that the SLR process is well managed, so time needs to be allocated to this specific task and one individual identified to act as the project manager. Administrative support is also required for this work, particularly for the retrieval and ordering of papers. The following table details the expertise required for key tasks within the SLR process:

Table 2: Expertise required for SLR tasks

Task	Expertise required
Development of the protocol	All
Development of the search strategy	Information specialist / research librarian
Assessment of papers, including relevance and study design	Epidemiology Nutrition
Data extraction	Epidemiology Nutrition
Overview of mechanisms	Cancer biology / mechanisms of the specified cancer site
Data analysis	Statistics
Final SLR report	Epidemiology Nutrition Statistics Cancer biology/mechanisms
SLR update	All

It is not necessary for each skill to be represented by a different person – an individual might bring more than one such skill. However, experience has shown that it is important that sufficient resource, both time and personnel, be given to specifically and explicitly to management of the project.

For the group of 'other' cancers it is necessary either to have access to cancer specialists in each of the sites, or to have one cancer specialist on the team with a broad area of cancer expertise.

The composition of each SLR team should be agreed between the team and the Review Coordinator.

In centres where more than one SLR is carried out, there should be a stated team for each SLR. Such teams may have a greater or lesser degree of overlap, but must be separately specified.

10 The Review Coordinator

WCRF International will use a Review Coordinator to help attain consistency of approach and execution between the various SLR centres and teams. The Review Coordinator will be experienced in systematic review, and will engage with SLR team leaders to achieve the above goal.

The Review Coordinator has responsibility for the following:

- Provide expert input into the coordination of the SLRs between and within SLR centres, and between SLR centres and WCRF International
- Assist WCRF International to develop, manage and evaluate the test of the SLR specification manual (this document).
- Report regularly to WCRF International on progress and issues relating to SLRs for the new report
- Take responsibility with SLR team leaders for obtaining relevant information common to several SLRs
- Ensure a common approach is taken to the handling of information common to several SLRs
- Help avoid incorporation of duplicate publications in SLRs
- Ensure common use of terminology in SLRs
- Ensure common approaches to SLR structure and contents, and data display, text format and presentation within SLRs
- Recommend when there is already a published review of suitable quality which addresses directly a topic which would otherwise be covered by an SLR commissioned by WCRF International; and therefore need not be commissioned
- Coordinate necessary translations of titles, abstracts and papers

- Work with SLR team managers to ensure a common approach to developing SLR protocols including
    - Search strategy
    - Data extraction
    - Analysis
    - Display of evidence
- Ensure SLRs are produced ready for electronic format
- Ensure with SLR team managers and WCRF International and Advisory Group that the process of peer review works efficiently
- Make, as necessary, regular reports to WCRF International, and visits to SLR centres
- Bear in mind the objectives of WCRF and to suggest possible improvements to the process

Part 3
Specifications for the SLR

11 Protocol and protocol checklist

11.1 Overview

A first and critical component of each SLR will be the writing of a protocol. Please note that the protocol should follow all the specifications set out in this manual, unless otherwise agreed with the Review Coordinator. The protocol needs to describe fully the process by which the SLR will be conducted. The essential components are described below, but there may be different additional components depending on the scientific question addressed.

The protocol will be subject to peer review and once finalised will be placed on the WCRF International website so it can be in the public domain.

The protocol will represent the agreed plan for the SLR. Should departure from the agreed plan be considered necessary at a later stage, this must be agreed with the Review Coordinator and possibly the Advisory Group, and the reasons documented. These reasons will be necessary for the peer review process at the end of the SLR.

11.2 Developing the protocol

The protocol for conducting the SLR in relation to a particular question is the responsibility of the review team. The protocol will be peer reviewed by WCRF International to ensure it complies with the specification in this manual, and by external peer reviewers with regard to content. Checklists (**Appendix G**) are provided for this purpose.

The protocol should include the following:

1 Research question

2 Review team

This should include the proposed contributions and expertise of each member of the review team

3 Timeline

SLR teams are required to provide a timeline for the SLR process, including a plan to meet certain milestones at certain times (see below).

The SLR centres will be required to include in their protocols, a timeline for their process. As part of this, the SLR centres need to indicate provisional milestones for when they plan to have achieved the following:

- A preliminary output from the search strategy
- Design of the data extraction sheets
- A list of all relevant papers included in the review
- The results of the preliminary analyses

These preliminary outputs, together with a short covering note summarising progress, must be sent to WCRF International at the time indicated by the SLR centres in the protocol and will serve as progress reports. The Review Coordinator will request additional progress reports as required for monitoring progress.

4 Background

A brief background is required, including the results from the first expert report.

5 Search strategy

Include the details of the search strategy and an explanation of the rationale behind the approach used.

6 Study selection criteria

Include an explanation of the process to be used for including/excluding studies.

7 Data extraction

Describe the processes to be used in data extraction.

8 Data analysis

Describe the details of the data analysis to be used, including the variables to be considered as sources of heterogeneity and the hypotheses/questions to be answered in the meta-analysis

9 References

Please refer to **Section 23** for guidelines on style, when writing the protocol.

11.3 Changes to the protocol

Any changes to the agreed protocol must be approved by the Review Coordinator and if necessary the Advisory Group. These changes must be described under the heading 'Changes to the agreed protocol' in the SLR report.

12 Research topic

The research topic is:

The associations between food, nutrition and physical activity and the risk of [site] cancer and underlying mechanisms.

The SLRs are to cover exposures related to food, diet, nutrition status and physical activity. The SLR team will expand the research topic into a clear question, which identifies the topic and scope for the SLR. The question will be approved by the Advisory Group as part of the protocol. The online searcher within the review team should then be provided with the research question.

13 Search strategy

The search strategy will be required to identify relevant research, specifying the databases and other sources that will be searched together with the search terms. The construction of a search strategy should be based on the components of the review question; i.e. minimum set of exposures (**Section 21**), additional site specific exposures not listed in **Section 21**, relevant lifecourse events, and outcomes along with types of study being considered. An explanation of the rationale behind the chosen search strategy must be presented in the protocol.

13.1 Principles and rationale

The search strategy for this exercise needs to take account of the underlying purpose of the SLR. The questions posed will all be aetiological, that is directed to evidence for dietary, nutritional or physical activity causes of cancer.

The conventional hierarchy of study designs (see **Box 1**) is appropriate to answer questions of efficacy in clinical contexts, but is inappropriate for questions of aetiology, and so will not be used for this exercise.

While recognising that different study designs have different advantages and disadvantages, it is not the purpose of these SLRs to take account of this. Such matters of

judgement are for the Panel to incorporate in their overall judgements based on the evidence.

In summary, it is essential for each SLR to search for all types of evidence relevant to the question – trials, observational, ecological, and mechanistic. In addition SLR centres should not exclude studies simply on the basis of perceived quality, but should define study characteristics that may influence results. Specific instructions are necessary for the inclusion of experimental studies (see **Section 13.8)**. As already mentioned, it is not the purpose of these SLRs to interpret these data, but only to display them. The interpretation of the data, with inference or otherwise of causality, will be the role of the Panel.

13.2 Developing the search strategy

The search strategy should initially be developed using Medline. There are a number of interfaces that can be used to search Medline. The PubMed interface, which uses the Entrez search engine should be used. This is widely available on the internet from the National Library of Medicine website. Do not use the option of searching PubMed from Endnote as this method may yield different results. In PubMed a text-based search is developed and if no truncation terms are included it automatically includes MeSH (Medical Subject Heading) terms below it in the hierarchy of MeSH terms catalogued by the National Library of Medicine. It will also search for synonyms of that term and corresponding MeSH terms.

A minimum search strategy for PubMed has been developed (see **Appendix F**, available mid-January 2004). This strategy is recommended; if you would prefer to use another method please contact the Review Coordinator for advice. The PubMed search strategy is based on the exposures listed in **Section 21** and is a required minimum. The SLR centres are responsible for further developing this search strategy to include any other possible relevant site-specific terms (e.g. menarche) and the outcome of interest.

Once the search strategy for PubMed has been developed, the information specialist is responsible for translating this for use in other databases (see **Section 13.4**).

SLR centres should not to use a study design filter when running the PubMed search. If there is a huge amount of literature received from the initial search, other methods for limiting the search can be considered and should be discussed with the Review Coordinator. However, checks are required to ensure that relevant papers are not excluded. Study design filters can be used for other databases.

The search strategy described above is designed for searching the epidemiological literature. A separate search strategy is required for identifying relevant experimental data. However, if experimental studies are identified in the search for epidemiological studies these should be passed onto the cancer biologist in the SLR team for the work on mechanisms. The scope of the experimental data to be searched will be largely defined by the mechanisms working group (see **Section 13.8**).

13.3 Comprehensiveness of the search

Studies should only be excluded if they are unrelated to the topic and are therefore not covered by the research question. Studies must not be excluded on the basis of study design or perceived quality of studies. It is the responsibility of the Panel to judge the quality of the studies in the context of different study designs, as part of the interpretation of the results.

- All types of evidence are to be included in the search strategy – Include trials, observational, mechanistic and ecological studies. Specific instructions for searching experimental studies are available in **Section 13.8**.
- Date range - Searching must go back to the date of inception of the database
- Only published and peer reviewed literature to be searched. In-press cohort studies and randomised controlled trials to be included in the SLR update (see **Section 13.5**).
- Published abstracts – not included
- Languages – Include all languages in searches
- Exposures – A minimum set of exposures must be investigated. See **Section 21.**
- The search needs to include any studies reporting imprecise anatomical definitions of cancer site (such as "upper gastrointestinal tract"), but which includes the cancer site of interest (e.g. oesophagus, stomach).

13.3.1 Exposures

To clarify the scope of the SLR a list of exposures has been developed. These are listed in **Section 21**. The exposure list has been used as a basis of the standardised PubMed search strategy.

13.3.2 Outcome

SLR centres are responsible for identifying the appropriate outcomes for their particular SLRs. Cancer and premalignant outcomes should be included as outcomes. For the purpose of the SLRs pre-malignant cancer is defined as a lesion that is truly pre-malignant, for example, an early stage of cancer and is not just a state of increased risk. These include: comparisons between normal/healthy populations and those with premalignant conditions (such as colorectal adenomas); studies investigating the recurrence of premalignant conditions (eg recurrence of colorectal adenomas); and studies investigating the progression of premalignant conditions to cancer.

13.4 Databases

Multi-database searching is necessary to ensure comprehensive retrieval. Each database will have a list of journals that have been included. Databases should be selected such that overall they will include as many journals as possible. A search strategy for Medline

(on PubMed) will be provided by WCRF International. The information scientist and the librarian must be familiar with the major medical and science databases and will translate this search strategy into a suitable strategy for the other databases depending on the unique syntax (indexing) used for each database.

The recommended minimum set of databases is:

- Medline (includes coverage from 70 countries)
- Embase (3,300 journals from 70 countries)
- ISI Web of Science
- BIOSIS (Previews) – information from more than 5,000 international serial sources
- SciSearch – includes non-English Journals
- Pascal (French, English, Russian, German and other languages)
- Meta-register
- LILACS (Latin American and Caribbean Center on Health Sciences Information)
- CAB abstracts
- Cochrane Library incorporating
    - DARE database
    - Systematic review database
    - HTA

Other databases can be added to the list, as advised by the information specialist. The following databases may also prove useful in certain circumstances, for example to search for studies not published in English. Advice should be sought from the Review Coordinator when considering using these databases.

- CINAHL
- ExtraMed
- Allied and Complimentary Medicine (Amed)
- IMSEAR (Index Medicus for the South East Asian Region)
- IMEMR (Index Medicus for the WHO Eastern Mediterranean Region)
- AIM (African Index Medicus)
- AMI (Australasian Medical Index)

13.5 In-press articles

In-press articles from a predefined list of cohorts/RCTs must be included in the SLR at the update stage. The Panel has identified a list of major cohort studies and randomised controlled trials that will also be placed on the WCRF International website for comment. The Secretariat will make contact with the principal investigators of the studies on the final list and seek any in-press papers from these studies. The in-press papers will be passed on to the SLR centres for inclusion in their SLR updates.

13.6 Abstracts

Abstracts should not be included in the SLR. Therefore abstracts should be excluded when assessing the paper for relevance if a full paper is not available.

13.7 Foreign language papers

No language should be excluded when searching. Therefore several papers will be retrieved in languages other than English. A preliminary search indicated that papers might be found in the following languages:

- Japanese
- German
- Spanish
- French
- Chinese
- Italian
- Russian
- Dutch
- Polish
- Czech
- Danish
- Portuguese
- Norwegian
- Hebrew
- Hungarian

When non-English language titles and abstracts are retrieved the first stage is to identify whether the study is relevant. In some cases, the abstract is presented in English. Otherwise, SLR centres should use language resources available within the study centre as a first option, to assess the relevance. If the study is relevant the SLR team should then contact the Review Coordinator who will arrange for a full translation to be made. If the basic language skills appropriate to identify whether a study is relevant or not are not available at the SLR centre, then the SLR team should consult the Review Coordinator. The Review Coordinator will then use other resources, including those at other SLR centres, to ascertain the relevance of the paper, and arrange a full translation where necessary. Translated papers will then be returned to the SLR centre for use in the SLR.

13.8 Experimental studies

Experimental data are an important component of the evidence required to infer causation, and therefore mechanistic studies need to be included in the SLRs on a

selective basis. The demonstration of mechanisms actually operating in humans or in relevant models can add weight to epidemiological associations in inferring causation, though the absence of such evidence is not evidence of a non-causal association. However, the experimental literature is voluminous and many types of studies are not directly relevant to the question of causation of cancers in humans. It is therefore necessary to develop a set of guidelines for the inclusion of relevant data. SLR centres are required to supply a comprehensive narrative of the mechanisms operating for each cancer site, rather than conduct a full systematic literature review of mechanistic data.

A cancer biologist/mechanisms expert is required on each of the SLR teams. This person is responsible for a comprehensive narrative review of the experimental data and key mechanisms for that particular cancer site. The narrative review should be incorporated into the final SLR report as described in **Section 19**. The SLR centre leader is responsible for ensuring that the narrative reviews of the experimental and mechanistic data is prepared within the SLR deadlines.

The cancer biologists/mechanistic experts will together form a working group that will coordinate approaches and provide expert opinion. This "Mechanisms Working Group", will be chaired by Dr John Milner from the National Cancer Institute (NCI) in the USA. The cancer biologist/mechanism expert for each cancer site will be a representative on this working group, although one person from an SLR centre may cover more than one cancer site. The purpose of the mechanisms working group is to ensure a comprehensive perspective of mechanisms within and across cancer sites. Each member of the working group will assess the experimental data on general food, nutrition and physical activity-cancer mechanisms for their assigned cancer sites. The Mechanisms Working Group will also contribute to a section of the second report on the cancer process. Crucially, the working group will decide how best to deal with mechanisms that are common to different cancer sites, with a view to avoiding duplication of effort. The working group will work primarily via email (mwg@wcrf.org) but may need to meet once/twice during the project.

The process for identifying appropriate experimental data to review is as follows:

1) SLR centres first look for recent reviews, and any papers published since. The review should meet the following standards:

   - **The exposures must be well defined**: attention is paid to characterising specific exposure(s) e.g. food or dietary component, physical activity.

   - **It must be relevant**: exposures should be relevant to usual human exposures. Reviews or studies using extreme or unusual exposures (for instance in dose or method of administration) should not be included.

   - **There must be defined end-point(s)**: a specific endpoint e.g. colorectal cancer or colorectal adenoma relevant to human cancer in a relevant model.

2) If there is no review available, SLR centres must search for primary data using the exposures, intermediary factors and outcomes agreed by the mechanisms working group.

In order to provide guidance on the use of primary data, a hierarchy has been developed (see **Box 2**). The complete hierarchy is included for information, but only the data from class 1 studies need to be included. Studies that report both relevant exposures (food, nutrition and physical activity) and outcomes (cancer) need to be included in the review. In addition, with necessary help from the mechanisms working group, each cancer biologist/mechanisms expert will identify a small number of key intermediary factors for their specific cancer sites. Studies that investigate the dietary/physical activity determinants of these intermediary factors, and also the relationship between intermediary factors (as exposures) and outcomes, should be included in the review. Important mechanisms involving interactions between dietary and non-dietary factors should also be covered. Mechanistic studies nested within trials or observational studies with relevant cancer end points are particularly valuable and should be included in the mechanistic narrative review.

Box 2

A hierarchy of robustness has been developed in order to determine which types of studies are more applicable to human cancer and to provide a screen for relevant studies. This hierarchy is split up into 3 classes of evidence, of which only class 1 evidence needs to be reviewed.

(i) ***In vivo*** **studies in human volunteers.**

(ii) ***In vivo*** **data in transgenic animal models highly germane to human cancer (e.g. knockout mouse models).**

(iii) ***In vivo*** **data in rodent cancer models to study modifiers of the cancer process.**

(iv) *In vitro* data in human cells validated with an *in vivo* model e.g. transgenic model.

(v) *In vitro* data in primary human cells.

(vi) *In vitro* data in human cell lines.

(vii) *In vitro* data in animal cells.

(viii) Data from mechanistic test systems e.g. isolated enzymes, isolated gene.

(ix) Studies using bacterial systems.

Class 1 evidence (i – iii)

More weight should be given to human mechanistic studies, when considering both primary data and reviews.

Class 2 evidence (iv – vi)

A second class of evidence looking at studies in categories (iv – vi). Class 2 evidence should not be reviewed.

Class 3 evidence (vii – ix)

A third class looking at studies in categories (vii – ix). Class 3 evidence should not be reviewed.

13.9 Hand searching for cited references

The term 'hand searching' is used to describe the work of carefully searching through publications for relevant articles. The main reason for hand searching is to check on completeness of initial electronic searches. Hand searching may identify missed articles, or relevant journals not picked up by routine databases.

Hand searching of journals not included in the electronic databases should not be routinely conducted. However, if a journal consistently shows up in citation lists from papers identified by the search and is not included in the electronic databases, then it should be hand searched. Hand searching of the reference lists of key papers is therefore important.

13.10 Study selection procedures

The aim of the study selection is to identify those articles that help to answer the review question. Therefore, selection criteria (both inclusion and exclusion) should follow logically from the questions and should be defined in terms of population, exposure, outcomes and types of study. **Section 13.8** gives instructions for the inclusion of experiemental studies. The study selection procedure usually consists of several stages; these are summarised in the process flowsheet (**Section 7**). An initial search will identify a number of papers. The results of this search should be sent to WCRF International (EndNote file 1). At this first stage study selection criteria are applied to the titles and abstracts generated from the literature search. The full papers of any study that cannot be excluded at this point should be sought. Once these copies are obtained the inclusion/exclusion criteria are applied and decisions about each paper made. At this stage the decision for inclusion of a paper should be performed in duplicate. The reasons for exclusion of papers should be recorded in EndNote file 2. The study design of included papers should be recorded in EndNote file 3. Any disparity between the duplicate data entries should be resolved initially within the team, then with the Review Coordinator, and only after that with the Advisory Group. The study selection procedures to be used by each SLR team must be presented in the protocol.

13.11 Retrieving papers

The search is conducted once the Review Coordinator has approved the search strategy. The SLR centres must send the complete set of search results (references and abstracts where available), once they have been checked for duplicates (the same paper retrieved from more than one database), to the Secretariat and the Review Coordinator. The name of the file should reflect the name of the cancer site being reviewed.

SLR centres are expected to use resources at their own institutions to retrieve the papers identified as satisfying the inclusion criteria. It is also now common to be able to download electronic versions of papers from the Internet.

If a SLR centre retrieves a paper that reports an outcome for more than one site, it is useful to send this paper on to the Review Coordinator. For example, if the SLR centre covering stomach cancer retrieves a paper that covers both stomach and oesophageal cancers, this should be passed on to the Review Coordinator who can in turn check that this paper has been included by the group conducting the SLR on oesophageal cancer.

13.11.1 Labelling of references

It is strongly recommended that all references used in the SLR be entered into an EndNote database. If a SLR centre intends to use an alternative reference manager package then advice should be sought from the Review Coordinator. In any event, the package used must be compatible with EndNote.

One of the fields in EndNote is called 'Label'. This field should contain a unique identifier for that particular reference. This should be constructed using a 3-letter code to represent the cancer site, followed by a 5-digit number that can be allocated in sequence.

Table 3: Allocation of study identifiers

Cancer site	Code	Example Study identifier
Mouth, larynx and pharynx	MOU	MOU00011
Oesophagus	OES	OES00256
Lung	LUN	LUN00962
Nasopharynx	NAS	NAS00063
Colon and rectum	COL	COL01596
Liver	LIV	LIV00999
Gallbladder	GAL	GAL00257
Pancreas	PAN	PAN00258
Stomach	STM	STM01002
Bladder	BLA	BLA00584
Prostate	PRS	PRS01021
Kidney	KID	KID00052
Other	OTH	OTH00086
Breast	BRE	BRE02004
Ovary	OVA	OVA00009
Cervix	CER	CER00002

This 'label' should be clearly indicated on the hard copy of the paper (if you are working from a hard copy)

At the end of the SLR, all original sources of data (i.e. all references) should be sent to WCRF International, together with the EndNote database.

For any one SLR, a particular study may have a number of publications that satisfy the inclusion criteria (for example the EPIC study). This is useful information that Secretariat would like to have easily available. When more than paper is derived from a particular study, SLR centres are asked to identify these papers and present them in a table as follows:

Table 4: Identification of papers from the same study

Study name and Institution	Number of papers included	Study identifiers
Nurses Health Study, Harvard	3	OVA00108 OVA00158 OVA00009
EPIC Norfolk IARC	2	OVA00222 OVA00006

This table should form an appendix to the SLR report.

13.11.2 EndNote files

The process flowsheet (see page 16) indicates that three EndNote files need to be sent to WCRF International for each SLR conducted.

1) A file containing the results of the initial search. The study identifier should be entered under the field titled 'label', as described in **Table 3**. Name one of the customised fields (custom 1) 'inclusion' and this field should be marked 'in' or 'out' for each paper, thereby indicating which papers were deemed potentially relevant based on an assessment of the title and abstract. Name this file according to the cancer site e.g. Ovary search.

2) A file containing the excluded papers. The study identifier should be entered under the field titled 'label'. Name one of the customised fields (custom 1) 'reasons' and this field should include the reason for exclusion for each paper. Name this file according to the cancer site e.g. Ovary excluded.

3) A file containing the included papers. The study identifier should be entered under the field titled 'label'. Name one of the customised fields "study design" and this field should include a letter (A-Q) representing the study design of each paper, allocated using the study design algorithm in **Appendix J**. Name this file according to the cancer site, e.g. Ovary included.

As an additional check of the search strategy, the Secretariat will send the list of included papers (Endnote file 3) to a list of Panel members and principal investigators (PIs) of major cohort studies. The Review Coordinator will then alert the SLR centres to any papers that may have been missed by the search.

14 Data extraction

The SLR centres are requested to use a database for data extraction. WCRF International has provided an Access database for data extraction. This contains a set of fields recommended for each study design, including quality characteristics and results. SLR centres are expected to further develop the data extraction database for their individual requirements. It is therefore necessary for a member of the review team to be able to add and change fields in Access.

The exposure list (**Section 21**) is programmed into the Access database. When additional exposures are identified these can be handled by adding sub-categories to exposures; it is important to utilise this capability for a number of exposures that need to be kept separate. A separate Access database should be used for each cancer site SLR.

If the SLR centres choose not to use the Access database provided, then they must ensure that the required minimum data are captured. Please refer to the fields listed in **Appendix L**, as a starting point. These fields are a required minimum. Most of these fields are purposely designed to be expanded e.g. 'anthropometry details' would be expanded by the SLR centre to include BMI, weight, height, weight gain and details of the assessment method if thought appropriate. If an alternative to the Access database is used, this must be discussed with the Review Coordinator before data extraction starts.

Ideally, data extraction should be performed in duplicate for all papers. Studies with prospective dietary assessment (i.e. cohort and nested case-control studies) are particularly liable to effect the interpretation of the evidence by the Panel. There may only be evidence from few of these studies and hence the impact of any errors in the data extraction on conclusions made by the Panel may be serious. Therefore, duplicate data extraction should be performed on ALL papers from studies with prospective dietary assessment. For all other studies, if full data extraction is not feasible within the SLR deadlines the following process can be used, subject to agreement with the Review Coordinator:

a) Carry out duplicate data extraction for the first ten papers, compare the entries and then discuss to come to an agreed position on all differences.
b) Carry out a further duplicate data extraction for the next ten papers and compare and discuss the entries as above.
c) For the remainder of papers one reviewer to enter the data and another reviewer to check the entries against the original paper; any differences to be discussed and agreed.

The completed access database (or data extraction sheets if an alternative method is agreed) should be sent to the Review Coordinator when the data extraction process is complete for any one SLR.

14.1 Requirements for data analysis

It is important to take into account the requirements for data analysis when designing the data extraction database. When results are reported for different exposure levels, the data extraction needs to be separated into two parts. For each study included in the review, the first part should collect information on the study and the reported analysis as a whole, the second part the exposure level specific information.

Important overall aspects of the study that need attention are the strategy of analysis, the variables for which the exposure – disease association was adjusted for, the information given on the validity of the measurements and whether analyses were performed that attempted to correct for the likely effect of measurement error in the exposure variable. In addition, in relation to effect modification please report whether interaction terms were included in models and extract the results, in particular any statistical tests of heterogeneity across strata.

Note, that more than one effect measure and its standard error (or confidence interval) will need to be abstracted. In order to calculate covariance adjusted standard errors of study specific dose-response slopes according to Greenland's or Chêne and Thompson's method [14,15], the number of cases and controls need to be abstracted for each exposure level (and their overall study totals).

Minimally adjusted and maximally adjusted effect measures should always be abstracted. In addition the model considered by the SLR centre most appropriate for inclusion in the forest plot and meta-analysis should also be extracted. If the most appropriate model for inclusion in the forest plot is the maximally or minimally adjusted model then only two models are required. The variables adjusted for, in each model, should be recorded in the data extraction database, as well as in the forest plot and results tables (see **Sections 16.1.1. and 16.1.2**). There is a conceptual difference between nutritional (including body mass etc) and non-nutritional confounders (eg socioeconomic status, sex). Where the literature allows, adjustment for nutritional and non-nutritional confounders, should be reported separately.

Data should be abstracted for sub-groups corresponding to the list of effect modifiers agreed in the protocol. Where the data permit, the following sub-groups must be reported (if they are stated as having been considered, and also any quantified information):

- smoking
- age
- sex

- body mass index
- pre/post menopausal for women.

14.2 Study design algorithm

A study design algorithm has been devised for use when allocating study designs to papers (see **Appendix J**). It is essential that this algorithm is used in order to ensure consistency in approach across the 6 SLR centres. A set of study design definitions is available in **Appendix K** for extra guidance. Assignment of study designs to papers should be done in duplicate. When assigning study designs to papers it is important to read the full details in the methods section of papers. In some cases, the definition of a study design used in the paper itself will differ to that allocated using the algorithm. The algorithm should be followed. In some cases it will be appropriate to assign more than one design to a particular paper because the methods for assessment of different exposures may vary e.g. BMI may be measured retrospectively, but fruit and vegetable intake measured prospectively in the same paper. It is therefore important to report the study design relative to that particular exposure in the results tables.

14.3 Qualitative study characteristics

Qualitative characteristics of primary studies can be used at various stages in the review process, from study selection to generation of recommendations for practice and research. Formal quality grading should not be performed on an individual study basis. Instead, study characteristics (such as aspects of study design, methods of exposure assessment etc.) will be used to explore potential sources of bias and the robustness of conclusions. This approach has the following uses:

1) To explore the reasons for heterogeneity in study results
2) To guide interpretation of findings and to aid determining the strength of inferences
3) To guide recommendations for future research

A comprehensive approach to extracting data is important. In particular, it is imperative that study characteristics related to quality are included in the data extraction. The Access data extraction database provided by WCRF International includes fields for a minimum set of quality characteristics. SLR centres may choose to record further study quality characteristics if they feel this is appropriate.

14.4 Case series

A test of the SLR process has shown that there are likely to be numerous case series papers in the literature on food, nutrition, physical activity and cancer. The information available from the case series is not likely to warrant the amount of work involved in retrieving the papers and completing the data extraction. Case series cannot contribute to

the principal purpose of the SLR i.e. to help infer causation in observed associations, so it is reasonable not to extract data for this category of study.

Case series identified by the search should be recorded but no data extraction is required unless this study design is the only one available for a particular SLR.

14.5 Gene-nutrient interactions

The study of interactions between nutritional and genetic factors is a relatively new and important area of research. Gene-environment interactions arise when the response of individuals to environmental changes is modulated by the genotype of the individual, or equally, when environmental factors influence gene expression. Gene-nutrient interactions are likely to contribute to inter-individual variations in cancer risk in response to exposure to nutritional factors. It is essential that results related to gene-nutrient interactions available in the epidemiological data are extracted and reported in the SLR report. These results will be used by the Panel for interpretation and evaluation of the results.

It is becoming more common for epidemiological studies to characterise the genotypes of subjects in order to investigate possible gene-nutrient interactions, and the relationship with disease outcomes (e.g. some large cohorts collect genetic information on subjects). In cases where such information has been used to investigate gene-nutrient interactions, SLR teams are required to extract the relevant data and report the results. For example, when an association between a particular exposure and cancer development is limited to individuals with a particular genetic polymorphism, this information should be extracted from the papers and reported.

14.6 The lifecourse approach

A lifecourse approach assesses the biological and social factors at each stage of life that affect contemporaneous and later health outcomes. Cancer typically takes decades to develop from the first stage in the cancer process, to clinically evident cancer. Different cancers can develop at different rates and different environmental insults can act at different times throughout the lifespan. The static and dynamic biological state at the time of exposure to an environmental (including nutritional) insult can determine the nature of the impacts on structure and function, some of which may have lasting effects. The possibility that exposures at particular times during growth and development might have lasting impact on the likelihood of development of cancers needs to be explored in the report, and hence in the SLRs.

Both exposure and outcome are important in the context of a lifecourse approach to assessing the evidence. Studies on the lifecourse approach often place emphasis on events in early life, including fetal life. However, age and aging should also be considered as

modifying factors. Breast feeding for the infant and lactation for the mother are both included in the exposure list.

Study results related to the lifecourse approach need to be included in the SLR report. It is therefore imperative that relevant variables are included in the data extraction. The following list gives some examples of important variables that should be extracted for relevant cancer sites. It is the responsibility of the SLR centre to ensure that all relevant data are extracted. The list below is designed to give some guidance but is not comprehensive. Variables that are not clearly nutritionally related e.g. parity should be included (as potential confounders) as well as those that may be nutritionally relevant themselves e.g. menarche.

- Birth weight
- Weight at one year
- Age at menarche
- Pubertal status
- Age at first birth
- Parity
- Age of menopause

15 Potential sources of bias

15.1 Publication and citation bias

Publication bias is caused by the tendency of authors to write and submit, and peer reviewers and editors to accept and publish research, depending on the strength and direction of the results.

It is important to consider whether the SLRs might have been affected by publication bias. Studies that demonstrate statistically significant differences are published more frequently and are more easily published than studies that do not demonstrate statistically significant differences. Studies with a positive result are also cited more frequently and thus are more easily identified than studies with a negative result.
For RCTs, time lag bias occurs when the speed of publication depends on the direction of the trial results. In some cases, trials with negative results take twice as long to be published as positive results [7], meaning that new interventions may be accepted as effective in the absence of evidence to the contrary, although that evidence may already have been gathered.

In order to assess the degree of publication bias there are various graphical and statistical techniques. The most common graphical technique is the funnel plot [8] and for the WCRF International SLRs, publication and other bias should be assessed using this method.

The funnel plot is a tool to examine whether the size of the association observed in a study is associated with the size of the study. It is a scatter plot of effect size (log odds

ratio) versus study size, measured by the standard error of the log OR, with each data point on the plot representing one study. If there is bias, for example because smaller studies showing no statistically significant effects remain unpublished, then the funnel plot will appear asymmetrical. However it is important to realise that there are causes of funnel plot asymmetry other than publication bias: these are discussed in Sterne, Egger and Davey Smith (2001)[10] .In the context of observational studies of diet and cancer, reviewers should also consider the possibility that differences in the size of associations comparing smaller with larger studies may arise because in smaller studies more confounding variables were measured, or confounding variables were measured more precisely. In this case it would be the smaller rather than the larger studies that provided the more reliable results.

Funnel plots should be provided as a standard part of data presentation. The "metafunnel" command in Stata may be used to produce them.

15.2 Grey literature

Grey literature should not be included in the SLRs. The SLR teams must include only published literature from peer-reviewed journals in the SLRs. Although the exclusion of unpublished grey literature leads to the possibility of publication bias, it is difficult to draw a distinction between acceptable and unacceptable grey literature. The distinction between peer-reviewed and non-peer-reviewed literature is clear and therefore it was agreed that this is a suitable cut-off point. There are also a number of practical issues associated with including a search of grey literature. Finally, using an evidence base that includes grey literature of uncertain quality might jeopardise the credibility of the report. In-press articles from a predefined list of cohorts/RCTs should be included in the SLR at the update stage (see **Section 13.5**).

15.3 English-language bias

Negative studies are less likely to be published in English-language journals than positive studies and therefore may be published in foreign language journals. This problem should be minimised by including studies in other languages.

A proportion of important nutrition and cancer research may be missed if only English translated articles are included in the literature searches. For this reason, papers should not be excluded on the basis of language. Selection of papers should be based initially on titles and then abstracts.

15.4 Multiple publication

Duplicate publication of studies, where the same data is presented in two different journals, or in the same journal at different times, could lead to over-sampling of data

from the same research. This may arise with use of meta-analyses and other reviews. In such cases the individual papers should be used and not the meta-analyses or reviews.

Data should be extracted for each individual paper, even if there is more than one from any one study, unless the information is identical. One study might publish data in different papers, due to different outcomes, different time points etc. Each of these should be the subject of separate analyses. Of course, the extracted information should only be used once per analysis, although there can be more than one analysis on any one exposure per SLR. There might be some instances when the SLR centres suspect that identical data have been published more than once, either by the same or by different authors. The SLR centre should contact the authors to confirm or refute these suspicions. If the matter remains unresolved then the Review Coordinator should be contacted for advice. The Review Coordinator will then seek advice from the Advisory Group if necessary. True duplicate publication should be exposed, e.g. by contact with the relevant journals.

15.5 Confounding

Confounding may explain an observed association (or lack of one) due to the occurrence together of the exposure being investigated, the disease and a third factor that is associated with the exposure and independently affects the risk of developing the disease. The third factor may itself be an exposure that also needs to be investigated. There are numerous approaches to control confounding and these can be utilised both during the design of the study and in the analysis. It is important to distinguish between confounding and effect modification. A confounder is related to both the exposure and outcome variable but does not lie in the causal pathway between them. An effect modifier modifies the effect of the exposure of interest on the outcome, and therefore represents an interaction. Confounding is a bias that investigators hope to prevent or remove from the effect estimate whereas effect modification is a property of the effect under study and therefore is a finding to be reported, rather than a bias to be avoided.
The issue of controlling for confounders is addressed when assessing the quality of studies in the study characteristics forms. Failure to control for potential confounders in some studies may explain heterogeneity of results. **Tables 5** and **6** list confounders that are well known in diet-cancer studies. This list is not exhaustive but provides some of the most relevant confounders to be considered. Inclusion in these illustrative lists does not imply that the factor is outside the remit of the SLRs.

Table 5: General potential confounders in diet-cancer studies

General	Age
	Sex
	Smoking habits (current and history)
	Social class/living conditions/income
	Physical activity
	Body mass index (BMI)
	Total energy intake
	Alcohol consumption
	Ethnicity
	Supplement use
	Family history of specific cancer (1st degree relatives sufficient)
	Other components of the diet

Table 6: **Site-specific potential confounders in diet-cancer studies**

Mouth and Pharynx	Oral hygiene
	Maté drinking
	Sexual activity
Nasopharynx	Epstein-Barr virus
	Dietary intake during childhood/weaning
	Maté drinking
Larynx	Maté drinking
Oesophagus	History of reflux oesophagitis/indigestion
	Gastroesophageal reflux symptoms
	Maté drinking
Lung	Prior lung disease e.g. bronchitis, pneumonia
Stomach	Helicobacter pylori infection
	Methods of preservation
Gallbladder	Presence of gallstones
Liver	Hepatitis B or C infection
	Aflatoxin consumption
Colon/Rectum	NSAID usage, Hormone replacement therapy
Breast	Reproductive factors: age of menarche, duration of exclusive breastfeeding, weight at birth, age at first live birth, parity, age at menopause, attained adult height, menopausal status, hormone replacement therapy (HRT)
	Previous treatment for benign breast conditions
Ovary	Reproductive factors (as above)
	Hysterectomy/oophorectomy
	Oral contraceptive use
Endometrium	Reproductive factors (as above)
	Oral contraceptive use
	Number of miscarriages
	Number of induced abortions
	Menopausal oestrogen use
Cervix	Human papilloma virus
	Oral contraceptive use
Thyroid	Thyroid disease
Bladder	Occupational exposure to dye, rubber, leather, vehicle fumes

15.6 Effect modification

An effect modifier modifies the effect of the exposure of interest on the outcome and therefore represents an interaction. Therefore it is a finding to be reported, rather than a bias to be avoided. Therefore effect modifiers should not be adjusted for in the analysis; instead a stratified analysis should be presented. **Table 7** describes a list of potential effect modifiers that should be considered when analysing the data.

Table 7: **Potential effect modifiers in diet-cancer studies**

General	Age
	Sex
	Obesity
	Physical activity
	Oral contraceptive use
	Menopausal status
	Hormone replacement therapy
	Ethnicity
	Smoking

15.7 Measurement errors

Measurement errors may be defined as the difference between the observed value and the corresponding true but unknown value. These errors may occur during the measurement and collection of food and/or nutrient intake, and of physical activity. They fall into two types – random and systematic. Random errors may occur across all subjects and all days and can be minimised by extending the number of observations, though cannot be entirely eliminated. In contrast, systematic errors may exist for only certain respondents e.g. elderly, obese, health conscious, or certain interviewers, or for certain types of assessment e.g. underreporting of food and drink intake. Systematic error or bias cannot be minimised by extending the number of observations. Therefore important biases may be introduced into the results. It is important to record whether, within a study, consideration was given to dealing with these issues.

Therefore it is important to document whether studies have identified possible sources of measurement error, as well as whether, and if so what, actions were taken to deal with them. This issue forms an integral part of assessing study quality, which will be an important characteristic to examine when assessing heterogeneity of results.

16 Data analysis

The overall aim of data synthesis is to collate and summarise the results of the studies included in the SLR. Meta-analytic and narrative aspects of the data analysis complement each other. A purely statistical (meta-) analysis cannot capture and explore all the caveats and shortcomings of the research reviewed. On the other hand, a purely qualitative review will lack precision and may miss small associations of relevance to public health. This SLR of etiological studies should attempt a formal meta-analysis but SLR centres should be aware that statistical combination of studies should be performed with caution and not be the only or most prominent component of reviews of observational

studies. There are limitations associated with performing a statistical (meta-) analysis; in particular, explaining heterogeneity among study results is challenging. The first stage of the analysis is therefore to investigate whether any variations in estimates of effects exist between these studies. If sufficient homogeneity exists, an overall summary of effect should be determined. If there is significant heterogeneity, it should be characterised as clearly as possible. If possible meta-regression should be performed to investigate sources of heterogeneity. Variables to be considered as sources of heterogeneity should be pre-specified as part of the SLR protocol.

16.1 Assessment of heterogeneity

Heterogeneity should always be assessed before any attempt to perform a meta-analysis. Heterogeneity should first be assessed qualitatively; a quantitative assessment should then also be performed.

The thorough consideration of possible sources of heterogeneity between observational study results can provide more insight than the mechanistic calculation of an overall measure of effect, which can often be biased.

It is important, wherever possible, to specify in advance those characteristics to be explored as possible causes of heterogeneity. These should appear as part of the SLR protocol to be submitted for peer review. A list of study characteristics is shown in **Box 3**. For any given diet/nutrition/cancer association, other characteristics may need to be pre-specified. However, reviewers should interpret findings that particular study characteristics explain between-study heterogeneity with caution. If a considerable number of study characteristics are considered as possible explanations for heterogeneity in a meta-analysis containing only a small number of studies, then there is a high probability that one or more will be found to explain heterogeneity, even in the absence of real associations with between the study characteristics and the size of associations.

Box 3: The following characteristics of studies should be investigated as possible sources of heterogeneity in the data.

- Exposure characterisation (FFQ, recall, diary, anthropometry etc.)
- Exposure range (including correction for measurement error, length of intervention)
- Sex ratio
- Adjustment for confounders
- Age at recruitment
- Follow-up
- Geographical region
- Study design
- Outcome (e.g. right colon cancer, left colon cancer)

From this identification, it may be possible for studies to be grouped according to a particular characteristic and separate analysis performed within each sub-group.

16.1.1 Tabulation of study characteristics

Information on the characteristics (e.g. population, exposure, outcome, study design) and results of the study (e.g. direction and magnitude) should be summarised, which is best achieved by tabulation. This table should be constructed in such a way as to highlight any differences and similarities between the studies. This tabulation should allow an immediate visual impression of the data. Critical analysis of this table is the first step in assessing heterogeneity as it allows qualitative assessment of differences between the studies. A recommended format for the presentation of results is available in **Appendix M**. These tables can be automatically generated using the Access database. Within this table the studies should be ordered according to design (e.g. cohort studies, case-control studies, etc.). Analyses that have been included in the meta-analyses should be highlighted so that readers of the final SLR report can assess the impact of the studies not included in the meta-analyses.

SLR centres are required to explore quality differences as an explanation for heterogeneity in study results. Any individual quality items from the data extraction can be entered as variables in a meta-regression analysis where appropriate and possible. In addition, reviewers may use the results of quality assessment in any sensitivity analysis in whatever way they feel is appropriate.

As indicated in **Section 20.2**, SLR centres are required to include a comment on issues relating to the quality of studies in part 2 of the SLR summary. This should be done for each exposure presented in the summary. In addition, further general issues of study quality should be included in the SLR report discussion.

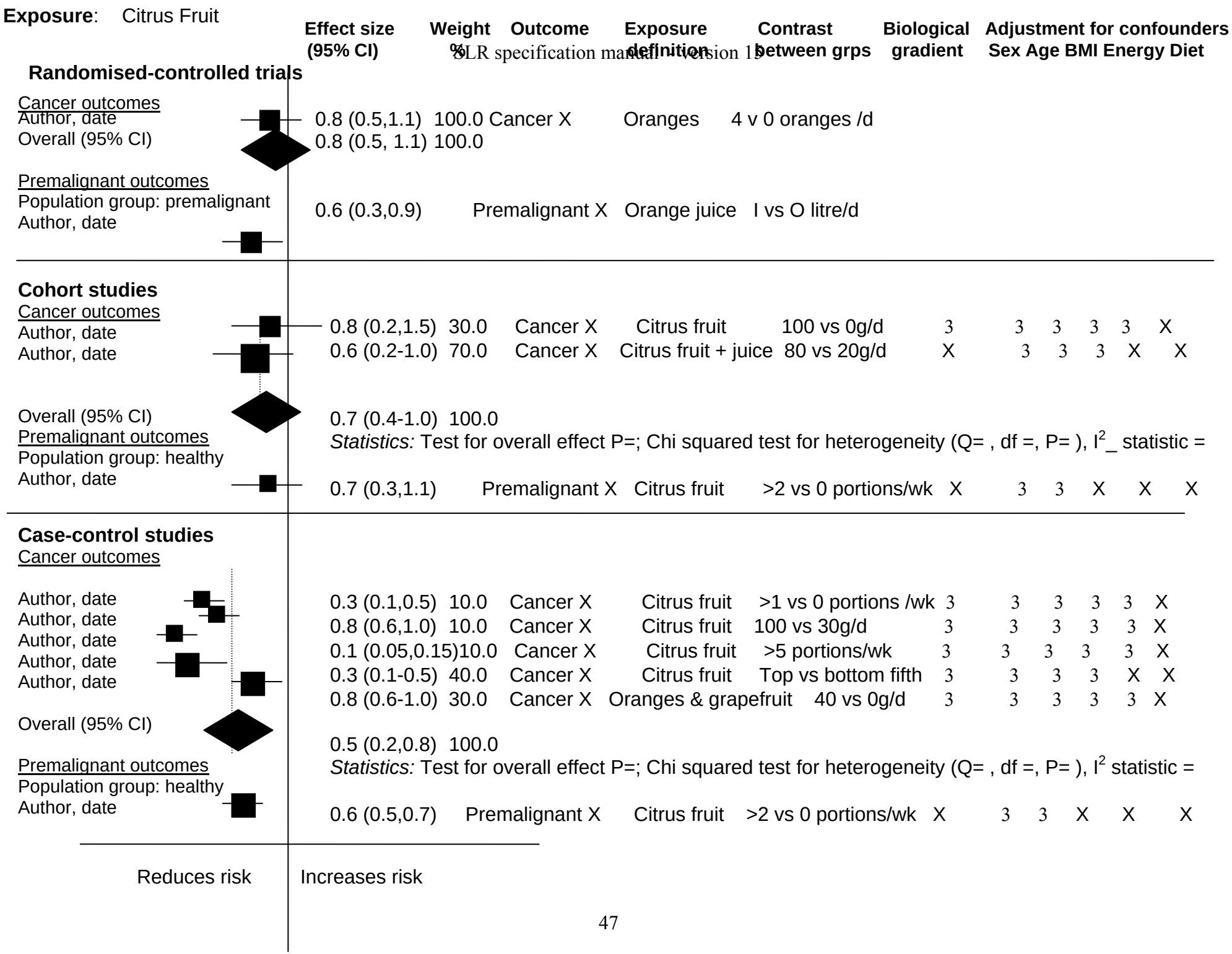
16.1.2 Forest plots

A usual method of assessing and displaying heterogeneity is to construct and examine forest plots [9]. Forest plots provide a simple visual representation of the amount of variation between the results of the individual studies. Their construction begins with plotting the observed exposure effect of each individual study, which is represented as the centre of a square. Horizontal lines run through this to show the 95% confidence interval. Different sized squares may be plotted for each of the individual studies, the size of the box increasing with the size of the study and the weight that it takes in the analysis.

The overall summary estimate of effect and its confidence interval can also be added to the bottom of this plot, if appropriate, and this is represented as a diamond. The centre of the diamond is the pooled summary estimate and the horizontal tips are the confidence intervals. Footnotes can also provide quantified information (statistical tests) on the degree of heterogeneity between the displayed studies and/or study designs.

When examining forest plots for heterogeneity, it is important to be aware of any differences in the direction of the results e.g. if the results of some studies show a positive association and others show a negative association. Differences in the magnitude of the results are also important when assessing heterogeneity of results e.g. if some studies show a strong positive association and others only a weak positive association. Therefore both direction and magnitude of estimate of effect must be considered.

Forest plots should be used to assess and display heterogeneity. These should be presented in the main body of the SLR reports and also the SLR summary. A standard format for the presentation of the forest plots is required. An example of how a forest plot should be presented is shown in **Figure 1** on the next page.


Exposure: Citrus Fruit
Effect size (95% CI)
Weight %
Outcome
Exposure definition
Contrast between grps
Biological gradient
Adjustment for confounders
Sex Age BMI Energy Diet
Randomised-controlled trials
Cancer outcomes
Author, date
0.8 (0.5,1.1) 100.0 Cancer X Oranges 4 v 0 oranges /d
Overall (95% CI)
0.8 (0.5, 1.1) 100.0
Premalignant outcomes
Population group: premalignant
Author, date
0.6 (0.3,0.9) Premalignant X Orange juice I vs O litre/d
Cohort studies
Cancer outcomes
Author, date
0.8 (0.2,1.5) 30.0 Cancer X Citrus fruit 100 vs 0g/d 3 3 3 3 3 X
Author, date
0.6 (0.2-1.0) 70.0 Cancer X Citrus fruit + juice 80 vs 20g/d X 3 3 3 X X
Overall (95% CI)
0.7 (0.4-1.0) 100.0
Premalignant outcomes
Statistics: Test for overall effect P=; Chi squared test for heterogeneity (Q= , df =, P=), I2_ statistic =
Population group: healthy
Author, date
0.7 (0.3,1.1) Premalignant X Citrus fruit >2 vs 0 portions/wk X 3 3 X X X
Case-control studies
Cancer outcomes
Author, date
0.3 (0.1,0.5) 10.0 Cancer X Citrus fruit >1 vs 0 portions /wk 3 3 3 3 3 X
Author, date
0.8 (0.6,1.0) 10.0 Cancer X Citrus fruit 100 vs 30g/d 3 3 3 3 3 X
Author, date
0.1 (0.05,0.15)10.0 Cancer X Citrus fruit >5 portions/wk 3 3 3 3 3 X
Author, date
0.3 (0.1-0.5) 40.0 Cancer X Citrus fruit Top vs bottom fifth 3 3 3 3 X X
Author, date
0.8 (0.6-1.0) 30.0 Cancer X Oranges & grapefruit 40 vs 0g/d 3 3 3 3 3 X
Overall (95% CI)
0.5 (0.2,0.8) 100.0
Premalignant outcomes
Statistics: Test for overall effect P=; Chi squared test for heterogeneity (Q= , df =, P=), I2 statistic =
Population group: healthy
Author, date
0.6 (0.5,0.7) Premalignant X Citrus fruit >2 vs 0 portions/wk X 3 3 X X X
Reduces risk
Increases risk

16.1.3 Statistical tests for heterogeneity

The presence of heterogeneity should be highlighted by visual examination of the table and the forest plot (e.g. **Figure 1)** together with statistical tests of heterogeneity. Statistical tests assess whether the observed variability in study results is compatible with that might occur by chance. SLR centres should do a formal statistical assessment of the amount heterogeneity using the I^2 statistic[11]. Where heterogeneity not explicable by chance is detected, it should be characterised as an important element of the evidence for review and this process should be followed by an investigation of possible sources of heterogeneity. It is important to consider carefully whether it is appropriate to present a combined estimate where substantial variability exists between studies, even after allowing for possible causes.

16.1.4 Meta-regression

Meta-regression allows identification of sources of heterogeneity and is increasingly used in meta-analyses [12]. It involves the statistical assessment of whether specific factors e.g. study characteristics influence the magnitude or direction of the effect estimate across the studies. It is appropriate to use meta-regression to explore heterogeneity even if the initial overall test for heterogeneity is non-significant as these tests often have low power.

Meta-regression should be conducted within particular study types. As noted in **Section 16.1**, results of meta-regression analyses should be interpreted with caution if a considerable number of study characteristics are considered as possible explanations for heterogeneity. Further, meta-regression analyses are not appropriate for examining whether characteristics of individuals, rather than studies, modify associations between diet and cancer. For example, there could be strong differences between men and women, but these would not be seen in meta-regression analyses if all studies included equal numbers of men and women.

16.2 Meta-analysis

16.2.1 Individual level data and study level meta-analyses

Where there is significant heterogeneity between study results, it is inappropriate to calculate a single summary estimate of effect size. Where studies are sufficiently homogeneous, a summary of effect can be calculated. This can be done using one of two methods:

1. Pooling or combining data relating to individual subjects – this involves extracting the raw data from studies and re-analysing it in one analysis, including indicator variables for the individual studies.
2. Meta-analysis or study level analysis – this involves combining the estimates of effect sizes from individual studies

Combining individual subject data enables analysis using the same methods, which typically vary in individual studies. It has the further advantage in that it can produce

new analyses which cannot be covered within any one study e.g. assessment of effects within sub-groups, more adequate control of confounding. Furthermore, it allows a consistent coding and categorisation process to be used as exposures are very often categorised in very different ways in individual studies. However pooling data involves a great deal of work, as it is necessary to check and recode the original data to produce a comparable data file for analysis. It also requires much support from the investigators of the original studies who need to provide the original data.

Pooling of individual level data is not required for this exercise. However, study level meta-analysis should be performed where appropriate. Access to the raw data is not required for study-level meta-analysis as the calculation of a summary effect is based solely on the published estimates of effect of the individual studies. Although this is an easier method, its main disadvantage is that any limitations or biases that were built into the original studies cannot be dealt with.

In the published literature there may be analyses of pooled individual level data in addition to reports of the studies from which those individuals are drawn. In some cases these results might be more valuable than the study level meta-analyses required. Existing published pooling studies should be mentioned in the report but not included in the meta-analyses. This should be discussed with the Review Coordinator as the need arises.

16.2.2 Selection of exposures for meta-analyses.

Quantification of effect need not be done in all cases. It is only appropriate to perform a meta-analysis when the data set is reasonably homogeneous. The selection of the most important exposures to meta-analyse is dependent upon the data available and therefore some judgement is required by the SLR centres on when meta-analyses are appropriate.

However, due to the large number of potential analyses that could be carried out for any individual SLR it is necessary to provide some guidance. It is also important that there is consistency in approach across the SLR centres.

Meta-analyses should be carried out if there were at least two cohort studies, or at least five case-control studies available with sufficient information to allow meta-analysis. SLR centres are free to perform meta-analyses on fewer than five case-control studies if they feel it is justified but the justification should be stated clearly. Furthermore, if two or more randomised controlled trials are available, these should also be meta-analysed.

Summary estimates should be prepared for each study design separately but not combined, and these should be displayed on the same forest plot. The studies should be ordered by study design: randomised controlled trials, cohort and then case-control and within these study types by effect size (in decreasing order).

SLR centres will need to choose the adjustment model most appropriate for inclusion in the forest plot and meta-analysis should also be extracted. Also see **Section 14.1** for

instructions on data extraction. The variables adjusted for in this model should be presented in the forest plot (see **Figure 1**).

Data on premalignant outcomes and data on cancer outcomes should be analysed separately, but presented in the same forest plots (see **Figure 1**).

In some cases it is appropriate to perform meta-analyses for sub-groups. Consider sub-group analyses for the following:

- smoking
- age
- sex
- body mass index
- pre/post menopausal for women.

SLR centres are required to do a preliminary meta-analysis of one key hypothesis (to be selected by the SLR centre and agreed with the Review Coordinator) early in the process. This should be sent to the Review Coordinator for review before the full set of analyses is conducted.

16.2.3 Fixed effects versus random effects models

The calculation of a summary estimate of effect in a meta-analysis can be carried out using either a fixed effects or random effects statistical model [20].

Fixed effects models assume no heterogeneity and consequently produce narrower confidence intervals. This may have the effect of providing a misleading appearance of precision in the estimate of effect. Random effects models allow for the presence of heterogeneity, and will have the effect of expanding confidence intervals. This may make the data more difficult to interpret, but may also be less likely to produce a falsely precise estimate. In cases where there is little heterogeneity, both models would provide similar findings.

There are arguments both for and against the use either of fixed or of random effects models. The SLR team should specify their proposed method with justification as part of the protocol. It is recommended that the testing of these models is conducted as part of the sensitivity analyses.

16.2.4 Software packages

There are statistical software packages available that are designed to extract data from studies and perform meta-analysis. The SLR teams should use these analysis tools for the meta-analysis. The methods for conducting a meta-analysis recommended in **Section 16.2.5**, are based on using Stata. A general guide on how to do meta-analysis in Stata is available elsewhere[13]. This can also be downloaded from ww.systematicreviews.com. All the relevant meta-analysis commands required for the techniques recommended in **Section 16.2.5** can be downloaded from within Stata,

using the instructions contained in "Systematic reviews in healthcare: meta-analysis in context" [13].

It is recommended that the files used for the statistical analysis are kept on record once the SLR report has been submitted to WCRF International. These files can then be updated when the SLR centres complete the final update in 2006.

16.2.5 Recommended methods

Studies vary in terms of exposure assessment methods, definition of unexposed individuals, choice of exposure scale (absolute measurements versus percentile distributions), choice of reference groups, and the degree of control of confounding and adjustments for measurement error in exposure variables. Furthermore, a clear distinction needs to be made between exposures that have a well-defined baseline category (e.g. teetotalers in the case of alcohol consumption) and exposures with continuous levels (e.g. levels of serum albumin).

The key feature of studies of the association between a component of diet and cancer is that the exposure measurement (diet) will be continuous (possibly with a separate category of zero consumption) but may be analysed in diverse ways. This means that summarising different studies for inclusion in a meta-analysis can be difficult. The solution to this problem is to express the results of the studies in a common form, so that they can then be meta-analysed using standard methods. Results expressed in different ways can be translated into an estimate of the *log odds ratio per unit increase in the exposure variable*, together with its standard error. Standard methods and programs for inverse-variance weighted meta-analysis can then be used to provide summary measures of the association.

The recommended method for presenting the results of the meta-analyses in terms of *log OR per unit increase in exposure* negates the need to present results from meta-analyses in terms of comparison of extreme categories. If you come across situations where it is not possible to use this recommended method please contact the Review Coordinator.

Unfortunately, reporting in published research is often incomplete. In addition to effect measures and their standard errors (or confidence intervals), key elements of adequate reporting include: (i) number of individuals with and without disease for each exposure category, (ii) exact cut-offs of exposure categories, (iii) details of the chosen statistical analysis, including (iv) confounding variables included in multivariate models.

16.2.5.1 Terminology and notation

Measures of exposure effect

In aetiological research the strength of the association is often of particular interest, and the emphasis is on effect measures on the multiplicative scale, i.e. odds ratios,

risk ratios and rate ratios. As absolute cancer risks are small, these three measures will be approximately equal in studies of diet and cancer.

Types of exposure variables

In many studies the exposure of interest does not only come in two levels (smoking or not smoking) but in several quantitative levels (never smoker, ex-smoker, current smoker) or is continuously measured (pack years). The following situations need to be distinguished:

- Exposures covering a range of intensity, starting from zero (not exposed). Examples include many lifestyle exposures such as drinking and smoking. In a study a certain proportion of study participants will not be exposed to the risk factor of interest, and this group provides a natural baseline or reference category.

- Exposure with a certain range of possible values but no naturally defined unexposed group. Here two types of exposures are common:

    - Body weight, birth weight, body mass index, dietary factors like consumed calories, physical activity, etc.
    - Blood or other tissue levels of certain compounds that can be measured in the laboratory, for example vitamin levels, certain hormone levels (estrogens, growth factors), etc.

Investigators who conduct epidemiological studies on associations of such exposures with cancer face a number of choices regarding definitions, data analysis and reporting of results. These choices will result in different ways of reporting results.

Notation

We will assume that the outcome variable D (e.g. cancer mortality, cancer registration, cancer diagnosis) is binary. The total number of occurrences of the outcome will be denoted by d (disease), and the total number of individuals who do not experience the outcome will be denoted by h (health). The total number of individuals in the study is $n=d+h$. We will assume that for each individual in the study we measure a (dietary) covariate X, and denote the measured value of X for individual i by x_i.
In many studies, information is presented on k quantiles of the distribution of X, defined by the cutpoints $c_j, j=1,\ldots,(k-1)$. We will denote the mean of X in each of these quantiles by $m_j, j=1,\ldots,k$. The focus of this manual is the conversion of analyses based on quantiles to analyses based on the overall association between X and D. We will denote the number of individuals who do and do not develop disease in quantile j as d_j and h_j respectively. Based on this, the information presented for an analysis based on quantiles will usually be a subset of the information presented in the **Table 8** below.

Table 8. Notation for analyses of the association between a dietary covariate *X* and cancer outcome *D*, when analyses are based on quantiles of the distribution of *X*.

Column 1	Column 2	Column 3	Column 4	Column 5	Column 6	Column 7
Quantile	Range	Mean of X in quantile	Number of events (cases)	Number without event (controls)	Crude OR	Adjusted OR
1	$<c_1$	m_1	d_1	h_1	1 (reference)	
2	c_1 - c_2	m_2	d_2	h_2	OR_2	OR_2^*
:						
:						
(k-1)	$c_{(k\text{-}2)}$ - $c_{(k\text{-}1)}$	$m_{(k\text{-}1)}$	$d_{(k\text{-}1)}$	$h_{(k\text{-}1)}$	$OR_{(k-1)}$	$OR_{(k-1)}^*$
K	$\geq c_{(k\text{-}1)}$	m_k	d_k	h_k	OR_k	OR_k^*

For example, **Tables 9** and **10** depict two typical patterns of how study results are reported. **Table 9** is adapted from an example used in an earlier paper on methods for summarising the risk associations of quantitative variables in epidemiological studies [14], and **Table 10** from another relevant reference on the meta-analysis of dose-response data [15]. In both situations one estimate of the exposure-outcome association needs to be derived.

Table 9: Results from the British Regional Heart Study [16] on the relation between albumin concentration and mortality.

Quantile (j)	Albumin (g/liter)	Cutpoint (c_j)	Number of events (d_j)	Number without events (h_j)	Total (n_j)	Mortality rate per 1000 per year	
						Crude	Adjusted*
1	< 40	39.5	45	142	187	26.2	20.3
2	≥40-<42	41.5	81	573	654	13.5	11.6
3	≥42-<44	43.5	191	1,524	1,715	12.1	11.4
4	≥44-<46	45.5	182	2,234	2,416	8.2	8.7
5	≥46-<48	47.5	121	1,733	1,854	7.1	7.8
6	≥48	n.a.**	35	829	864	4.4	5.0
Total			655	7,035	7,690		

* Adjusted for age, social class, town of residence, cigarette smoking status, systolic blood pressure, serum total cholesterol, and forced expiratory volume in 1 second,
** na = not applicable

Table 10: Case-control data on alcohol use and breast cancer taken from Rohan and McMichael [17]

Quantile (j)	Alcohol (g / day)	Number of events (d_j)	Number without events (h_j)	Total	Reported odds ratio (95% confidence interval)	
					Crude	Adjusted*
1	0 (abstinent)	165	172	337	1.0 (referent)	1.0 (referent)
2	< 2.5	74	93	167	0.83	0.80 (0.51, 1.27)
3	2.5-9.3	90	96	186	0.98	1.16 (0.73, 1.85)
4	> 9.3	122	90	212	1.41	1.57 (0.99, 2.51)
Total		451	451			

Odds ratio from age-matched conditional logistic regression including variables for benign breast disease, bilateral oophorectomy, smoking, education, family history of breast cancer, ages at first and last menstrual period, age at first live birth, ever use of oral contraceptives, ever use of replacement estrogens, and practice of breast self-examination.

16.2.5.2 Summary measures for subsequent meta-analysis

Odds ratio, or log odds ratio, per unit increase in X

As explained in the introduction, the aim is to estimate the increase in the log odds of the outcome D per unit increase in X (the log odds ratio per unit increase in X). Formally, we wish to estimate β, the coefficient of x in the logistic regression model:

$$\text{log odds of } D = \alpha + \beta x$$

We will denote the estimated value of β by $\log(OR_X)$, and the corresponding value of the odds ratio per unit increase in X by OR_X. **Note that we assume a linear increase in the log odds of *D* per unit increase in *X*: it should be confirmed that this assumption is reasonable.**

In analyses controlling for confounding, $\log(OR_X)$ is the estimated value of β in the extended logistic regression model

$$\text{log odds of } D = \alpha + \beta x + \gamma z,$$

where γ is a vector of regression coefficients corresponding to z, the vector of confounding variables.

The standard error of $\log(OR_X)$ will be denoted by $se_{\log(OR_X)}$. Since our aim is to estimate $\log(OR_X)$ and $se_{\log(OR_X)}$ in each study, no further analysis is required when the results of a study are presented in this format.

Often the estimated value of OR_X is reported, together with a 95% CI (L_{OR_X}, U_{OR_X}), where $L_{OR_X} = \exp(\log(OR_X) - 1.96 \times se_{\log(OR_X)})$ and

$U_{OR_X} = \exp(\log(OR_X) + 1.96 \times se_{\log(OR_X)})$. This means that both log(OR_X) and $se_{\log(OR_X)}$ may be derived from OR_X and its 95% confidence interval, since:

$$se_{\log(OR_X)} = [\log(OR_X) - \log(L_{OR_X})]/1.96 = [\log(U_{OR_X}) - \log(OR_X)]/1.96 .$$

If the two estimates of $se_{\log(OR_X)}$ based on the lower and upper confidence limits are similar, then their mean may be used as the final estimate of $se_{\log(OR_X)}$ for the study. If they are very different (e.g. if their ratio is <0.9 or >1.1) then it may be necessary to contact the authors of the study to ascertain whether there is an error in the reported results.

Standardized odds ratio, or log odds ratio

Rather than presenting OR_X or log(OR_X), some studies may present results that are standardized relative to the observed variability in X in that study. We will denote this by log(OR_X)$_{STD}$: the log odds ratio per standard deviation increase in X. If the population standard deviation of X is σ_X then:

$$\log(OR_X) = \log(OR_X)_{STD}/\sigma_X$$

and similarly $se_{\log(OR_X)} = se_{\log(OR_X)_{STD}}/\sigma_X$. It is therefore straightforward to convert standardized results to per-unit results.

Meta-analysis of log odds ratios estimated in each study

The primary outcome of each meta-analysis will be the summary estimate of log(OR_X), combined across studies. If the estimate of log(OR_X) in study i is log(OR_X)$_i$, then the inverse-variance weighted fixed-effect estimate will be denoted by log(OR_X)$_F$, where:

$$\log(OR_X)_F = \frac{\sum w_i \times \log(OR_X)_i}{\sum w_i}$$

The weight w_i for study i equals the inverse of the variance of log(OR_X)$_i$:

$$w_i = 1/(se_{\log(OR_X)})^2$$

The standard error of the summary estimate = $\sqrt{\frac{1}{\sum w_i}}$

This can be used to derive a confidence interval for log(OR_X)$_F$, and hence for (OR_X)$_F$, in the usual way.

Where possible, log(OR_X)$_F$ should be the primary outcome of the meta-analysis. This is because it has a direct interpretation as the increase in the log odds of D associated with a unit increase in X. It will of course be necessary to check for evidence of

between-study heterogeneity, and it may be necessary to consider explanations for heterogeneity, or to consider random-effects meta-analysis.

In some circumstances, investigators may also wish to report a summary estimate of $\log(OR_X)_{STD}$. This might be appropriate if they believe that the main reason that σ_X varies between studies is differing measurement procedures, rather than differing true population variability. Alternatively, it might be impossible to convert measures of X in different studies to the same units: for example if they are based on different, semi-quantitative food frequency questionnaires. In this case a meta-analysis based on $\log(OR_X)_{STD}$ may be the only option. Finally, if there is substantial between-study heterogeneity in $\log(OR_X)$ then it may be of interest to know whether the amount of between-study heterogeneity in $\log(OR_X)_{STD}$ is smaller.

In summary, we suggest that the primary meta-analysis should be based on $\log(OR_X)$, and that investigators consider reporting an additional meta-analysis based on $\log(OR_X)_{STD}$.

16.2.5.3 Estimating $\log(OR_X)$ from analyses presented in published studies

We will now consider the further possible estimates of the D-X association that may be presented in published studies. In each case we will show how they can be converted to the required common format.

Case A. Mean difference, in individuals who do and do not develop the outcome D

Here, data analysis is based on $\bar{x}_D$ and $\bar{x}_H$, the mean of X in individuals who do and do not develop cancer respectively. The standard errors of these two means will be denoted by se_D and se_H respectively. The standard error of the mean difference $\bar{x}_D - \bar{x}_H$ will be denoted by se_{DIFF}, where $se_{DIFF} \cong \sqrt{(se_D^2 + se_H^2)}$

Chêne and Thompson [14] show that the mean difference may be derived from $\log(OR_X)$ and vice versa, since:

$$\log(OR_X) = \frac{\bar{x}_D - \bar{x}_H}{\sigma_X^2}$$

where σ_X^2 is the variance of X in the population, (assumed to be the same in individuals with and without cancer). Therefore, analyses based on mean differences can be converted to analyses based on log odds ratios, and vice-versa.

For meta-analysis, we also require $se_{\log(OR_X)}$, the standard error of $\log(OR_X)$. This may be estimated from se_{DIFF}, the standard error of $\bar{x}_D - \bar{x}_H$, as:

$$se_{\log(OR_X)} = \frac{se_{DIFF}}{\sigma_X^2}$$

Example

In **Appendix N** we show that, for the data in **Table 9**, mean albumin is estimated to be 1.055g/litre lower (standard error 0.1026) in individuals who died ($\bar{x}_D - \bar{x}_H$ =-1.055, se_{DIFF} = 0.1026). The corresponding estimates of log(OR_X) and $se_{\log(OR_X)}$ are –0.1673 and 0.0163 respectively.

Analyses based on groups or quantiles of X

The problem of how to derive estimates of the overall association between *D* and *X* from analyses based on groups or quantiles has been addressed by Greenland and Longnecker [15] and Chêne and Thompson [14]. The material presented here is adapted and extended from these papers. The following data or analyses may be presented.

Case B. Numbers of individuals in each group, together with information on quantile means or ranges.

This situation is given when studies provide information as in columns 4 and 5, and columns 2 or 3 of **Table 8**. Based on Chêne and Thompson [14] pages 612 to 615 we show how to derive the overall mean and standard deviation of X in individuals with disease. (The mean and standard deviation of X in individuals without disease are derived in exactly the same manner). We define the cumulative proportion of subjects with values of X less than cutpoint c_j as:

$p_j = \sum_{i=1}^{j} d_i / d$, where $d = \sum_{i=1}^{j} d_i$ is the total number of individuals with disease.

The *normal deviates* z_j corresponding to each p_j should be derived:

$$z_j = \Phi^{-1}(p_j)$$

For example, the normal deviates corresponding to cumulative proportions of 0.025, 0.1, 0.5, 0.9 and 0.975 are -1.96, -1.28, 0.00, 1.28 and 1.96 (to two decimal places).

To derive the estimated mean and standard deviation of X, a weighted regression of the cutpoints c_j on z_j needs to be conducted, using weights w_j that are proportional to $\phi_j^2/[p_j(1-p_j)]$, where ϕ_j is the normal density with mean 0 and variance 1, corresponding to z_j. The estimated intercept in this regression corresponds to the mean of X, while the estimated regression coefficient (slope) for *z* corresponds to the standard deviation.

The estimated mean difference, together with its standard error, is derived from the number of observations, mean and standard deviation in individuals with and without disease. Alternatively, it may be derived directly by using a "parallel regression" on the quantiles. See **Appendix N** for an illustration with Stata code.

Example

In **Appendix N**, we show that, for the data in **Table 9**, mean albumin is estimated to be 43.585 (standard deviation 2.565) in individuals who died, and 44.630 (standard deviation of 2.457) in individuals who did not die. Using an unpaired t-test, mean albumin is estimated to be 1.045g/litre lower (standard error 0.101) in individuals who

died. The corresponding estimates using the "parallel regression" approach are mean difference = -1.055, standard error 0.1026.

When deriving the odds ratio per unit change in X from quantile means and the number of individuals in each group, the mean m_j of X in quantile j may be estimated by:

$$m_j = \bar{x} + \sigma_X \frac{\phi(z_{j+1}) - \phi(z_{j+1})}{\Phi(z_j) - \Phi(z_{j-1})}$$

Having estimated the mean in each group, a logistic regression model that directly estimates the log odds ratio per unit increase in X should be fitted using the total number of individuals with and without disease in each quantile.

Example

In **Appendix P** we show that for the data in **Table 9**, mean albumin is estimated to equal 38.70, 40.74, 42.58, 44.47, 46.40, 48.76 in quantiles 1 to 6 respectively. Using these values, the estimated value of $\log(OR_X)$ is –0.170, with standard error $se_{\log(OR_X)}$=0.0173.

Case C. Adjusted or unadjusted odds ratios comparing each non-baseline quantile with a baseline quantile.

This situation arises when a particular group, usually that with the lowest level of X (columns 6 and/or 7, and columns 2 or 3 in **Table 8**) is used as the reference category. As pointed out by Greenland and Longnecker [15], the use of a common reference category implies that the odds ratios for the different exposure levels are not statistically independent [15,18]. Assuming independence of the level-specific odds ratios will tend to underestimate the standard errors of study specific dose-response slopes (calculated from data as in **Table 10).** Greenland and Longnecker [15] $\log(OR_X)$ proposed a method to estimate $\log(OR_X)$ after accounting for the covariances between the log odds ratios for the different exposure groups. This relies on three assumptions: that the crude ORs approximately equal the adjusted ORs, that the correlation matrices of the crude and the adjusted ORs are approximately equal and that the usual formulas for the variances of the crude ORs may be used. Based on these assumptions, we estimate the variance-covariance matrix of the log odds ratios in the different exposure groups, and use this to estimate $\log(OR_X)$ using weighted least squares for correlated outcomes.

Details of the Stata code used to implement this method are given in **Appendix Q**, for the data in **Table 10**. After controlling for confounders, the estimated value of $\log(OR_X)$ is 0.0454, with estimated variance 0.000427 (standard error $se_{\log(OR_X)}$=0.0207)

Case D. Odds ratio comparing top and bottom quantile groups, or top quantile group to everyone else

There may be situations where the only information available is the odds ratio OR_k comparing the top quantile group to the bottom quantile group, or the odds ratio comparing the top quantile group to the remainder of the population. In such cases it is possible to calculate an approximation to $\log(OR_X)$ if the standard deviation of X (σ_X) is reported. (If σ_X is not reported, it may be considered reasonable to use the s.d. from other studies, perhaps the larger ones)[19]. However to do so it is necessary to assume that X has a normal distribution, which is not assumed in the method proposed by Greenland and Longnecker (see Case C above) providing that the quantile means are reported. Estimating $\log(OR_X)$ from a single odds ratio makes no use of the ORs for intermediate categories of X if these are given, thereby ignoring some information. It has been used in a meta-analysis[19], and is also briefly mentioned in the discussion section of Chêne and Thompson [14].

The approximation is based on the difference between the means in the top and bottom quantile groups of a standard normal distribution. In general, this can be shown to be $d_k = 2k\phi\left(\Phi^{-1}(1/k)\right)$, where φ and Φ are the standard normal density and distribution functions respectively. It follows that the log odds ratio per standard deviation increase in X, ($\log(OR_X)_{STD}$: see **Section 16.2.5.2**) is given by $\log(OR_X)_{STD} = \log(OR_k)/d_k$. The per-unit log odds ratio, $\log(OR_X)$, can then be calculated from the standardized version as described in **Section 16.2.5.2**. An estimate of $se_{\log(OR_X)}$ can be calculated by first converting the upper and lower limits of the confidence interval by following the same procedure, then calculating the standard error from this confidence interval as in **Section 16.2.5.2**.

An analogous procedure can be used if an odds ratio is given for comparing the top quantile group to the entire remainder of the population. The divisor is then the difference between the mean in the top quantile group and the mean in the remainder of a standard normal distribution,

$$d'_k = \left(\frac{k^2}{k-1}\right)\phi\left(\Phi^{-1}(1/k)\right).$$

For convenience the two divisors are tabulated below for some common values of k:

Number of quantile groups, k	2	3	4	5	10
d_k	1.596	2.182	2.542	2.800	3.510
d'_k	1.596	1.636	1.695	1.750	1.950

Note that the two formulae give the same result for k=2, when both give the divisor for converting the log odds ratio comparing subjects with values of X above and below the median to $\log(OR_X)_{STD}$, the log odds ratio for a one standard deviation increase in X.

OR for an arbitrary dichotomization

A similar approximation may occasionally be useful for the situation where the reported OR compares subjects with values of X above and below an arbitrary cut-off x_0. Again we assume that X has a normal distribution, and we now need to know the

population mean $\bar{x}$ as well as the standard deviation σ_X. First calculate the standard normal deviate z_0 corresponding to the cut-off x_0:

$$z_0 = (x_0 - \bar{x})/\sigma_X$$

Then to convert the log*OR* comparing subjects with *X* above and below x_0 to a standardized log(OR_X), divide by the difference in the mean values of a standard normal distribution above and below z_0, which is $\frac{\phi(z_0)}{\Phi(z_0)\{1-\Phi(z_0)\}}$

16.2.5.4 Summary and choice of methods

Table 11 shows our suggested priority order for choice of possible methods to derive log(OR_X) and its standard error. This is based on the desire to avoid the assumption that X has a normal distribution, if this is possible. Providing that group means are reported, the method of Greenland and Longnecker [15] allows estimation of log(OR_X) without such a normality assumption.

Table 11. Suggested priority order for choice of method to estimate log(OR_X)

Priority	Crude association	Association controlled for confounding variables
1	log(OR_X) and its standard error, or OR_X and the corresponding 95% CI, reported in paper	log(OR_X) and its standard error, or OR_X and the corresponding 95% CI, reported in paper
2	Derive log(OR_X) directly from numbers with and without disease and group means, reported in paper	Derive log(OR_X) using the method of Greenland and Longnecker, using group means reported in the paper and adjusted odds ratios related to a reference category
3	Derive log(OR_X) using the method of Greenland and Longnecker, using group means reported in the paper related to a reference category	Derive log(OR_X) from adjusted difference in means, using the method of Chêne and Thompson
4	Derive log(OR_X) from numbers with and without disease and group means estimated using the method of Chêne and Thompson	Derive log(OR_X) from reported comparison of two groups (Case D)
5	Derive log(OR_X) from overall group means, using the method of Chêne and Thompson	
6	Derive log(OR_X) from reported comparison of two groups (Case D)	

The methods proposed by Chêne & Thompson [14] and by Greenland and Longnecker [15] differ in several respects, including assumptions (**Table 12**).

Table 12: Characteristics of methods proposed for calculating dose-response slopes

	Greenland's method [15]	Chêne & Thompson's method [14]
Effect measure	Odds ratio or risk ratio (per exposure category)	Crude or adjusted event rates (per exposure category) Mean exposure difference between cases and controls
Comparison group	Baseline exposure or lowest exposure group	
Prototype situation	Exposure is questionnaire based, comes in categories and has well defined baseline category (e.g. alcohol consumption).	Exposure is a normally distributed laboratory measurement (e.g. serum albumin)
Assumptions	Covariance among unadjusted odds ratios is equal to covariance of adjusted results Unmatched design (in case-control studies) Log - linear risk association	Exposure variable has normal distribution Variance in cases and controls are equal Log - linear risk association
Dose-response effect measure	Dose - response slope, typically from logistic regression analysis, and its standard error	
Issues of concern	Assignment of numeric exposure level to exposure intervals (e.g. midpoint) Exposure assignment problematic for unbounded categories (e.g. ≥9.3 g alcohol per day in **Table 10**). This is addressed by Chêne and Thompson's method. Model assumptions Role of confounder variable adjustment, residual confounding and measurement error in original studies Case - definitions used in individual studies	

16.2.6 Dose-response

Dose-response graphs must, wherever possible, be derived as a means of summarising the combined quantitative results derived from meta-analyses. Examples are shown in **Figure 2** and **Figure 3** using absolute levels of intake and quantiles respectively. A minimum of three points on the dose-response graph must be plotted. These plots not only show the direction of the association, but also allow estimations of levels of exposure that may reduce risk. In addition the presence of a biological gradient may add weight to an inference of causality. This may be particularly important when developing and quantifying public health recommendations.

Figure 2: This is a hypothetical example of a dose-response graph based on absolute levels of intake.

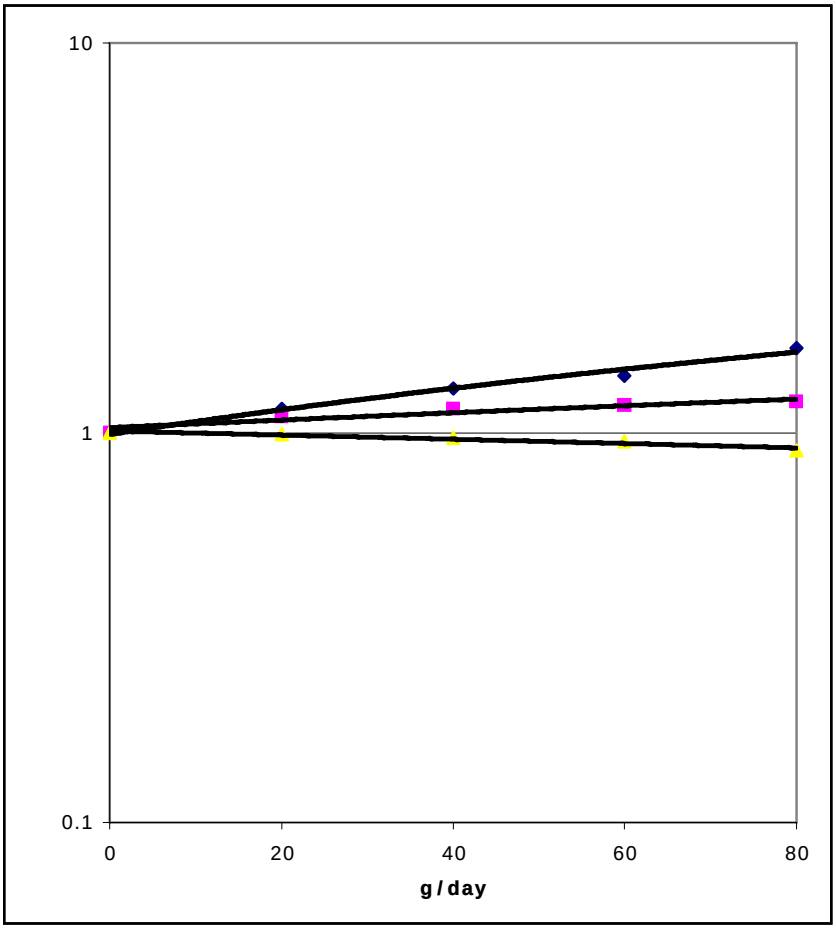
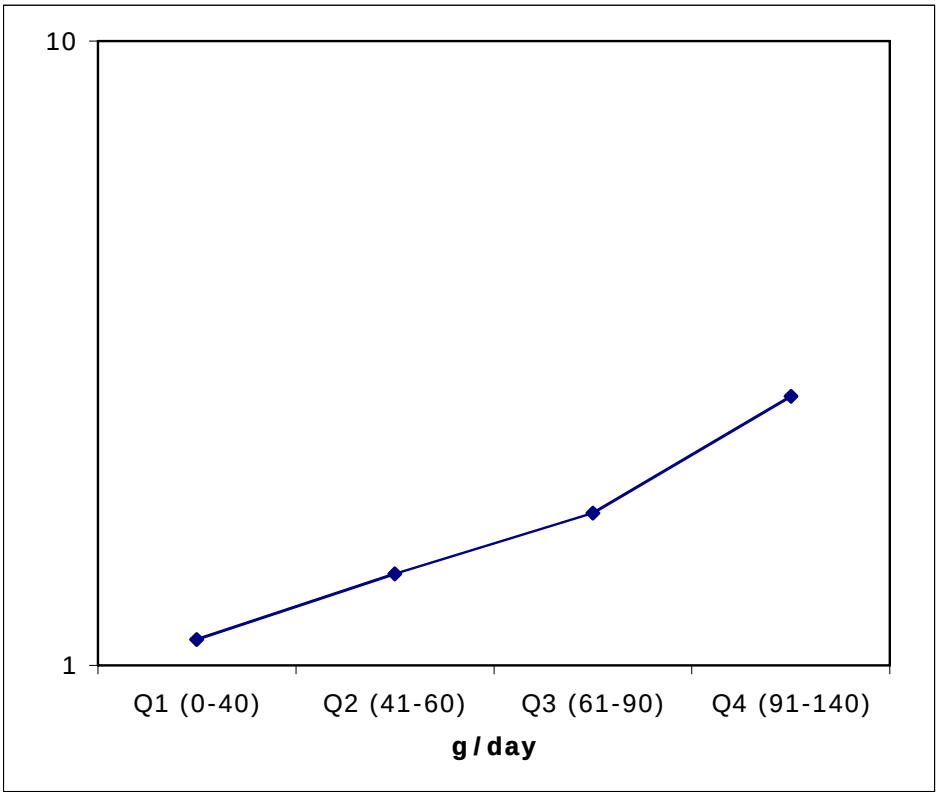


Figure 3: This is a hypothetical example of a dose-response graph based on quartiles of intake.



If it is not possible to present the results using dose-response curves, the Review Coordinator should be contacted to provide consistent guidance to each of the SLR teams and suggest possible alternatives for displaying the data.

16.2.7 Interaction analyses:

A narrative description of the results on any interactions (between exposures) identified in the literature is required (qualitative analysis). However, it is important to take a comprehensive approach to data extraction so that the qualitative analyses can be supplemented with quantitative analyses if required by the Panel at the update stage.

16.3 Sensitivity analyses

Sensitivity analyses are carried out to investigate how robust the overall findings of the SLR are relative to key decisions and assumptions that were made in the process of conducting the SLR. Each SLR team should identify how the key decisions and assumptions might conceivably have affected the results of the SLR. Redoing the analysis whilst changing each option will indicate how robust the SLR's results are to these uncertainties.

Sensitivity analyses could include:

- Changing the inclusion criteria for the types of study (e.g. using different methodological cut-points), participants, exposures or outcome measures.
- Including and excluding studies where there is some ambiguity as to whether they meet the inclusion criteria.
- Reanalysing the data using a reasonable range of results for studies where there may be some uncertainty about the results (e.g. because of inconsistencies in how the results are reported that cannot be resolved by contacting the investigators, or because of differences in how outcomes are defined or measured).
- Reanalysing the data by substituting missing data with the least favourable and most favourable outcomes to assess best case and worst-case scenarios.
- Reanalysing the data excluding one or more large studies that tend to dominate the results.

If the sensitivity analyses that are done do not materially change the results, it strengthens the confidence that can be placed in the results. If results do change in a way that might lead to different conclusions, this indicates a need for greater caution in interpreting the results.

17 SLR updates

To ensure that the evidence reviewed for the second report is as up to date as possible at the time of publication, all SLRs need to be updated in early 2006. The earliest 'final search' of the literature must be the 31st December 2005 to allow sufficient time for retrieval of papers before the final Panel meeting. At this time, the SLR centres will also be provided with any in-press papers identified by the Secretariat. When new papers are identified as relevant, the data from these papers should be extracted and the analyses re-run for the particular exposures covered by the new papers.

The SLR centres will need to provide a summary table for the new papers, indicating whether their addition alters the results from the analyses. If the results from the meta-analyses change for any particular exposure, the results sections of the SLR report will need to be redone for these exposures. There is no need to issue a fully revised SLR report.

Part 4
Presentation of results

18 Systematic literature review (SLR) reports

In general, reviews should be comprehensive without attempting the impossible task of being exhaustive. Guidance has already been given in **Part 3** of this manual regarding the use of a inclusive approach to the different types of study, and the depth to go into the discovery of relevant data. While there is a need to be comprehensive in displaying and describing the evidence reviewed, SLR centres should not make causal inferences from the data. This will be the responsibility of the Panel.

It is not necessary to present background and methodology sections in the SLR report, as this information is available from the agreed protocols. The final SLR report needs to include the following format described in **Section 19**.

19 Structure of SLR reports

It is important that certain key pieces of information are set out in the SLR report in a common format and sequence. The following represents the minimal set of information needed and the structure required for results by exposure. The SLR report should be presented in the following format:

Title page
Include title of report (question), review team members and date completed

1. Introduction

2. Changes to the agreed protocol
   Please justify any changes to the agreed protocol. If no changes have been made state 'No changes were made to the agreed protocol'. Also provide further information on methodologies used if not detailed sufficiently in the protocol.

3. Results of the search
   Provide information on the databases searched and number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of included relevant papers. The reasons for excluding papers should also be described.

4. Description of studies
   4.1 Amount of data and study types (i.e. numbers of different types of studies)
   4.2 Populations studied

4.3 Exposures identified and the timing of exposures within the lifespan.
4.4 Outcomes identified (including grouped cancers that include the site of interest)
4.5 Length of follow up
4.6 Methodological issues for ascertaining exposure and outcome

5. Results by exposures

Exposures should appear in the order specified in **Section 21**. This order corresponds to the proposed structure of Part 2 in the new report, and it is essential that the SLRs also follow this structure. Where a heading is not relevant to a particular cancer, please state 'no results found'.

Follow the instructions and numbering given in **Section 21** of this manual.

For each exposure enter details under the following sections:

A. Study design

Each study design should be presented in a separate table. Use the results tables generated from the Access database. These should look like the tables in Appendix M. Results used in meta-analyses should be highlighted. Tables and text should then follow the order below:

A1 Intervention studies
A2 Cohort studies
A3 Case control studies
A4 Cross sectional studies
A5 Ecological studies

B Detailed analyses

B1 Issues related to the timing of exposure
B2 Size of effect
B3 Biological gradient
B4 Internal consistency/heterogeneity e.g. by dietary methodology
B5 Summary illustrations of effects (e.g. Forest plots)
B6 Gene-nutrient interactions

C Assessment of heterogeneity within and between study types

D Factors influencing heterogeneity and meta-regression

E Narrative review on mechanistic studies

6. Discussion

The discussion should include a synthesis of the main findings, including methodological issues affecting the results and issues related to study quality. The discussion should be structured according to the main categories of exposure in the order specified in **Section 21**. Judgements as to whether causal relationships are more or less likely and extrapolation of the evidence to recommendations should not be included. The discussion should not include data on incidence and trends or any issues that apply to cancer in general. The

length of this discussion should be approximately 500 to 1500 words.

7. Summaries

   Each SLR must contain a summary, which will be the basis for the printed sections in the new report. See **Section 20** for further details.

8. References

20 SLR summaries

The SLR centres are asked to display the evidence in a neutral, quantified and objective style. Again, they are to stop short of assessing or judging the evidence as reviewed, and not to make recommendations. Summaries should be submitted with the full SLR report. The summary should comprise two parts.

20.1 Part 1

Part 1 should consist of a table summarising the amount of evidence for all exposures as shown in **Table 13**:

20.2 Part 2

Part 2 of the summaries should cover only exposures that warrant discussion by the Panel.

Selection of exposures
To select exposures for part 2 of the summaries the following criteria apply:

1) All exposures listed convincing, probable or possible in 1997 report.

OR

2) Exposures where there are at least 2 cohorts or at least 5 case-control studies. Aggregated exposures (eg total vegetables) and disaggregated exposures (eg cruciferous vegetables) should be counted separately.

OR

3) Robust and reproducible human or animal experimental studies

OR

4) Other exposures that SLR centres feel warrant discussion by the Panel but do not fulfil the above criteria eg when there are RCTs available. These exposures may be included as summaries with a statement justifying their inclusion.

Summary content

For each exposure within the summary the following should be included

1. Forest plots as shown in the example in **Section 16.1.2**.
2. Table of study characteristics (see **Table 14**).
3. Where available, supporting text should be included with information on:
    i) Sources of heterogeneity
    ii) Biological gradient
    iii) Issues related to the timing of exposure
    iv) Gene-nutrient interactions
    v) Animal experimental evidence (both related to exposure/outcome and mechanisms)
    vi) A comment on issues relating to quality of the studies included or excluded.

Table 13: The type of table to be included as part 1 of the SLR summary

Exposure	Number of RCTs		Summary estimate	Number of cohort studies		Summary RR and 95% CI	Number of case-control studies		Summary OR and 95% CI	Additional issues
	Total	Included in meta-analysis		Total	Included in meta-analysis		Total	Included in meta-analysis		

A template listing all exposures will be provided. The process of compiling this table will help determine which exposures should be entered into part 2 of the summary.

Table 14: Example tables of study characteristics to be included in part 2 of the summaries

Exposure:

Randomised controlled trials

Author, year	Number in intervention group	Number in control group	Inclusion criteria	Exclusion criteria	Ascertainment of follow-up	Details of intervention	Assessment of compliance	Blinding

Cohort studies

Author, year	Number of Cases	Size of cohort	Inclusion criteria	Exclusion criteria	Ascertainment of follow-up	Dietary assessment method

Case-control studies

Author, year	Number of Cases	Number of Controls	Source of cases	Source of controls	Inclusion criteria	Exclusion criteria	Dietary assessment method

21 Exposures

Please present exposures in the following order. This order corresponds to the proposed structure of Part 2 of the new report, and it is essential that the SLRs also follow this structure. These exposures are also programmed in to the Access database to be used for data extraction. The headings and sub-headings that are essential have been indicated below, as well as an indication of where it may be appropriate to be more flexible. For example with vitamins, minerals and bioactive compounds, there may be evidence on more items than currently listed. Any additions to and modifications to the exposure list should be included within the current exposure list in the most sensible place possible.

The exposures listed here represent the minimum list of exposures to be examined. It is of course appreciated that many of these headings are relevant only to cancers of some sites. Where a heading is not relevant to a particular cancer, please state clearly under the specified heading that no results were found for this exposure.

Wherever possible, use the sub-headings within the exposure list. For example, if a study reports results on wholegrain cereals this should be reported under '2.1.1.1 wholegrain cereals and cereal products', rather than under the broader headings that also apply such as '2.1 starchy foods', or '2.1.1 cereals (grains)'. Conversely, all exposures that are not reported in a form that clearly fits one of the subcategories should be placed under 'other'; the heading category (e.g. '3. Beverages) should be used as a category of its own only to represent the total or unspecified exposure (e.g. total beverages, or unspecified beverages). Any sub-category of the exposure should go under the available sub-headings if relevant, or 'other' if the exposure is not specified in the list, or is a combination of existing sub-headings.

1 Patterns of diet

1.1 Regionally defined diets

Include all regionally defined diets, evident in the literature. These are likely to include Mediterranean, Mesoamerican, oriental, including Japanese and Chinese, and "western type".

1.2 Socio-economically defined diets

To include diets of low-income, middle-income and high-income countries (presented, when available in this order). Rich and poor populations within low-income, middle-income and high-income countries should also be considered. This section should also include the concept of poverty diets (monotonous diets consumed by impoverished populations in the economically-developing world mostly made up of one starchy staple, and may be lacking in micronutrients).

1.3 Culturally defined diets

To include dietary patterns such as vegetarianism, vegan diets, macrobiotic diets and diets of Seventh-day Adventists.

1.4 Individual level dietary patterns

To include work on factor and cluster analysis, and various scores and indexes (e.g. Mediterranean type diet index) that do not fit into the headings above.

1.5 Other dietary patterns

Include under this heading any other dietary patterns present in the literature, that are not regionally, socio-economically, culturally or individually defined.

1.6 Breastfeeding

1.6.1 Mother
1.6.2 Child

Results concerning the effects of breastfeeding on the development of cancer should be disaggregated into effects on the mother and effects on the child. Wherever possible detailed information on duration of total and exclusive breastfeeding, and of complementary feeding should be included.

1.7 Other issues

For example results related to meal frequency, frequency of snacking, dessert-eating and breakfast-eating should be reported here.

2 Foods

2.1 Starchy foods

2.1.1 Cereals (grains)

2.1.1.1 Wholegrain cereals and cereal products
2.1.1.2 Refined cereals and cereal products

2.1.2 Starchy roots, tubers and plantains
2.1.3 Other starchy foods

2.2 Fruit and (non-starchy) vegetables

Results for "fruit and vegetables" should be reported here. If the definition of vegetables used here is different from that used in the first report, this should be highlighted.

2.2.1 Non-starchy vegetables

This heading should be used to report total non-starchy vegetables. If results about specific vegetables are reported they should be recorded under one of the sub-headings below or if not covered, they should be recorded under '2.2.1.5 other'.

2.2.1.1 Non-starchy root vegetables and tubers
2.2.1.2 Cruciferous vegetables
2.2.1.3 Allium vegetables
2.2.1.4 Green leafy vegetables (not including cruciferous vegetables)
2.2.1.5 Other non-starchy vegetables

Other non-starchy vegetables' should include foods that are botanically fruits but are eaten as vegetables, e.g. tomatoes, courgettes. In addition vegetables such as French beans that do not fit into the other categories, above.

If there is another sub-category of vegetables that does not easily fit into a category above eg salted root vegetables (ie you do not know if it is starchy or not) then report under 2.2.1.5. and note the precise definition used by the study. Note that the eg salted root vegetables should also be reported under 4.2.5.3 salted foods. If in doubt, enter the exposure more than once in this way.

2.2.1.6 Raw vegetables

This section should include any vegetables specified as eaten raw. Results concerning specific groups and type of raw vegetable should be reported twice i.e. also under the relevant headings 2.2.1.1 –2.2.1.5.

2.2.2 Fruits

2.2.2.1 Citrus fruit
2.2.2.2 Other

If results are available that consider other groups of fruit or a particular fruit please report under 'other', specifying the grouping/fruit used in the literature.

2.3 Pulses (legumes)

To include soya and soya products, peanuts (groundnuts), chickpeas, lentils. Where results are available for a specific pulse/legume, e.g. soya, please report under a separate heading.

2.4 Nuts and Seeds

To include all tree nuts and seeds, but not peanuts (groundnuts). Where results are available for a specific nut/seed, e.g. brazil nuts, please report under a separate heading.

2.5 Meat, poultry, fish and eggs

Wherever possible please differentiate between farmed and wild meat, poultry and fish.

2.5.1 Meat

This heading refers only to red meat: essentially beef, lamb, pork from farmed domesticated animals either fresh or frozen, or dried without any other form of preservation. It does not refer to poultry or fish.

Where there are data for offal (organs and other non-flesh parts of meat) and also when there are data for wild and non-domesticated animals, please show these separately under this general heading as a subcategory.

2.5.1.1 Fresh Meat
2.5.1.2 Processed meat

Repeat results concerning processed meat here and under the relevant section under 4. Food Production and Processing. Please record the definition of 'processed meat' used by each study.

2.5.1.3 Red meat

Where results are available for a particular type of meat, e.g. beef, pork or lamb, please report under a separate heading.

Show any data on wild meat (game) under this heading as a separate sub-category.

2.5.1.4 Poultry

Show any data on wild birds under this heading as a separate sub-category.

2.5.2 Fish

Wherever results are available for particular types of fish e.g. oily fish, white fish, please report under separate headings.

2.5.3 Shellfish and other seafood

2.5.4 Eggs

2.6 Fats, oils and sugars

2.6.1 Animal fats
2.6.2 Plant oils
2.6.3 Hydrogenated fats and oils

Results concerning hydrogenated fats and oils should be reported twice, here and under 4.3.2 Hydrogenation

2.6.4 Sugars

This heading refers to added (extrinsic) sugars and syrups as a food, that is refined sugars, such as table sugar, or sugar used in bakery products.

2.7 Milk and dairy products

Results concerning milk should be reported twice, here and under 3.3 Milk

2.8 Herbs, spices, condiments

The 1997 report found evidence concerning turmeric, saffron, cumin, ginger, pepper, chilli pepper and harissa.

2.9 Composite foods

Eg, snacks, crisps, desserts, pizza. Also report any mixed food exposures here ie if an exposure is reported as a combination of 2 or more foods that cross categories (eg bacon and eggs). Label each mixed food exposure.

3 Beverages

3.1 Total fluid intake
3.2 Water
3.3 Milk

For results concerning milk please report twice, here and under 2.7 Milk and Dairy Products.

3.4 Soft drinks

Soft drinks that are both carbonated and sugary should be reported under this general heading. Drinks that contain artificial sweeteners should be reported separately and labelled as such.

3.4.1 Sugary (not carbonated)
3.4.2 Carbonated (not sugary)

The precise definition used by the studies should be highlighted, as definitions used for various soft drinks vary greatly.

3.5 Fruit juices

The precise definition used by the studies should be highlighted, as definitions used for various fruit juices vary greatly.

3.6 Hot drinks

3.6.1 Coffee
3.6.2 Tea

Report herbal tea as a sub-category under tea.

3.6.2.1 Black tea
3.6.2.2 Green tea

3.6.3 Maté
3.6.4 Other hot drinks

3.7 Alcoholic drinks

3.7.1 Total

3.7.1.1 Beers
3.7.1.2 Wines
3.7.1.3 Spirits
3.7.1.4 Other alcoholic drinks

4 Food production, preservation, processing and preparation

4.1 Production

4.1.1 Traditional methods (*to include 'organic')*
4.1.2 Chemical contaminants

Only results based on human evidence should be reported here (see instructions for dealing with mechanistic studies). Please be comprehensive and cover the exposures listed below:

4.1.2.1 Pesticides
4.1.2.2 DDT
4.1.2.3 Herbicides
4.1.2.4 Fertilisers
4.1.2.5 Veterinary drugs
4.1.2.6 Other chemicals

4.1.2.6.1 Polychlorinated dibenzofurans (PCDFs)
4.1.2.6.2 Polychlorinated dibenzodioxins (PCDDs)
4.1.2.6.3 Polychlorinated biphenyls (PCBs)

4.1.2.7 Heavy metals

4.1.2.7.1 Cadmium
4.1.2.7.2 Arsenic

4.1.2.8 Waterborne residues

4.1.2.8.1 Chlorinated hydrocarbons

4.1.2.9 Other contaminants

Please also report any results that cover the cumulative effect of low doses of contaminants in this section.

4.2 Preservation

4.2.1 Drying

4.2.2 Storage
4.2.2.1 Mycotoxins
4.2.2.1.1 Aflatoxins
4.2.2.1.2 Others

4.2.3 Bottling, canning, vacuum packing
4.2.4 Refrigeration
4.2.5 Salt, salting
4.2.5.1 Salt
4.2.5.2 Salting
4.2.5.3 Salted foods

4.2.5.3.1 Salted animal food
4.2.5.3.2 Salted plant food

4.2.6 Pickling
4.2.7 Curing and smoking
4.2.7.1 Cured foods

4.2.7.1.1 Cured meats
4.2.7.1.2 Smoked foods

For some cancers e.g. colon, rectum, stomach and pancreas, it may be important to report results about specific cured foods, cured meats and smoked meats. N-*nitrososamines should also be covered here.*

4.3 Processing

4.3.1 Refining

Results concerning refined cereals and cereal products should be reported twice, here and under 2.1.1.2 refined cereals and cereal products.

4.3.2 Hydrogenation

Results concerning hydrogenated fats and oils should be reported twice, here and under 2.6.3 Hydrogenated fats and oils

4.3.3 Fermenting
4.3.4 Compositional manipulation

4.3.4.1 Fortification
4.3.4.2 Genetic modification
4.3.4.3 Other methods

4.3.5 Food additives

4.3.5.1 Flavours

Report results for monosodium glutamate as a separate category under 4.3.5.1 Flavours.

4.3.5.2 Sweeteners (non-caloric)
4.3.5.3 Colours
4.3.5.4 Preservatives

4.3.5.4.1 Nitrites and nitrates

4.3.5.5 Solvents
4.3.5.6 Fat substitutes
4.3.5.7 Other food additives

Please also report any results that cover the cumulative effect of low doses of additives.
Please also report any results that cover synthetic antioxidants

4.3.6 Packaging

4.3.6.1 Vinyl chloride
4.3.6.2 Phthalates

4.4 Preparation

4.4.1 Fresh food

4.4.1.1 Raw

Report results regarding all raw food other than fruit and vegetables here. There is a separate heading for raw fruit and vegetables (2.2.1.6).

4.4.1.2 Juiced

4.4.2 Cooked food

4.4.2.1 Steaming, boiling, poaching
4.4.2.2 Stewing, casseroling
4.4.2.3 Baking, roasting
4.4.2.4 Microwaving
4.4.2.5 Frying
4.4.2.6 Grilling (broiling) and barbecuing
4.4.2.7 Heating, re-heating

Some studies may have reported methods of cooking in terms of temperature or cooking medium, and also some studies may have indicated whether the food was cooked in a direct or indirect flame. When this information is available, it should be included in the SLR report.

Results linked to mechanisms e.g. heterocyclic amines, acrylamides and polycyclic aromatic hydrocarbons should also be reported here. There may also be some literature on burned food that should be reported in this section.

5 Dietary constituents

Food constituents' relationship to outcome needs to be considered in relation to dose and form including use in fortified foods, food supplements, nutrient supplements and specially formulated foods. Where relevant and possible these should be disaggregated.

5.1 Carbohydrate

5.1.1 Total carbohydrate
5.1.2 Non-starch polysaccharides/dietary fibre

5.1.2.1 Cereal fibre
5.1.2.2 Vegetable fibre
5.1.2.3 Fruit fibre

5.1.3 Starch

5.1.3.1 Resistant starch

5.1.4 Sugars

This heading refers to intrinsic sugars that are naturally incorporated into the cellular structure of foods, and also extrinsic sugars not incorporated into the cellular structure of foods. Results for intrinsic and extrinsic sugars should be presented separately. Count honey and sugars in fruit juices as extrinsic. They can be natural and unprocessed, such as honey, or refined such as table sugar. Any results related to specific sugars e.g. fructose should be reported here.

5.2 Lipids

5.2.1 Total fat
5.2.2 Saturated fatty acids
5.2.3 Monounsaturated fatty acids
5.2.4 Polyunsaturated fatty acids
5.2.4.1 n-3 fatty acids

Where available, results concerning alpha linolenic acid and long chain n-3 PUFA should be reported here, and if possible separately.

5.2.4.2 n-6 fatty acids
5.2.4.3 Conjugated linoleic acid

5.2.5 Trans fatty acids
5.2.6 Other dietary lipids, cholesterol, plant sterols and stanols.

For certain cancers, e.g. endometrium, lung, and pancreas, results concerning dietary cholesterol may be available. These results should be reported under this section.

5.3 Protein

5.3.1 Total protein
5.3.2 Plant protein
5.3.3 Animal protein

5.4 Alcohol

This section refers to ethanol the chemical. Results related to specific alcoholic drinks should be reported under 3.7 Alcoholic drinks.

5.5 Vitamins

5.5.1 Vitamin A

5.5.1.1 Retinol
5.5.1.2 Provitamin A carotenoids

5.5.2 Non-provitamin A carotenoids

Record total carotenoids under 5.5.2 as a separate category marked Total Carotenoids.

5.5.3 Folates and associated compounds

Examples of the associated compounds are lipotropes, methionine and other methyl donors.

5.5.4 Riboflavin
5.5.5 Thiamin (vitamin B1)
5.5.6 Niacin
5.5.7 Pyridoxine (vitamin B6)
5.5.8 Cobalamin (vitamin B12)
5.5.9 Vitamin C
5.5.10 Vitamin D (and calcium)
5.5.11 Vitamin E
5.5.12 Vitamin K
5.5.13 Other

If results are available concerning any other vitamins not listed here, then these should be reported at the end of this section. In addition, where information is available concerning multiple vitamin deficiencies, these should be reported at the end of this section under 'other'.

5.6 Minerals

5.6.1 Sodium
5.6.2 Iron
5.6.3 Calcium (and Vitamin D)
5.6.4 Selenium
5.6.5 Iodine
5.6.6 Other

Results are likely to be available on other minerals e.g. magnesium, potassium, zinc, copper, phosphorus, manganese and chromium for certain cancers. These should be reported at the end of this section when appropriate under 'other'.

5.7 Phytochemicals

5.7.1 Allium compounds
5.7.2 Isothiocyanates
5.7.3 Glucosinolates and indoles
5.7.4 Polyphenols
5.7.5 Phytoestrogens eg genistein
5.7.6 Caffeine
5.7.7 Other

Where available report results relating to other phytochemicals such as saponins and coumarins. Results concerning any other bioactive compounds, which are not phytochemicals should be reported under the separate heading 'other bioactive compounds'. Eg flavonoids, isoflavonoids, glycoalkaloids, cyanogens, oligosaccharides and anthocyanins should be reported separately under this heading.

5.8 Other bioactive compounds

6 Physical activity

6.1 Total physical activity (overall summary measures)

6.1.1 Type of activity

6.1.1.1 Occupational
6.1.1.2 Recreational
6.1.1.3 Household
6.1.1.4 Transportation

6.1.2 Frequency of physical activity
6.1.3 Intensity of physical activity
6.1.4 Duration of physical activity

6.2 Physical inactivity
6.3 Surrogate markers for physical activity e.g. occupation

7 Energy balance

7.1 Energy intake

7.1.1 Energy density of diet

7.2 Energy expenditure

8 Anthropometry

8.1 Markers of body composition

8.1.1 BMI
8.1.2 Other weight adjusted for height measures
8.1.3 Weight
8.1.4 Skinfold measurements
8.1.5 Other (e.g. DEXA, bio- impedance, etc)
8.1.6 Change in body composition (including weight gain)

8.2 Markers of distribution of fat

8.2.1 Waist circumference
8.2.2 Hips circumference
8.2.3 Waist to hip ratio
8.2.4 Skinfolds ratio
8.2.5 Other e.g. CT, ultrasound

8.3 Skeletal size

8.3.1 Height (and proxy measures)
8.3.2 Other (e.g. leg length)

8.4 Growth in fetal life, infancy or childhood

8.4.1 Birthweight,
8.4.2 Weight at one year

22 Terms and definitions

22.1 Exposures

All key concepts and terms will be defined in the second report in a glossary. The definitions used for exposures (dietary patterns, foods and drinks, food processing and preparation, dietary constituents, physical activity and energy balance) used in the first report should be regarded as the standard. Variation from the WCRF International definition stated in the first report or as specified in this manual must be clearly stated. The process of cross-checking of definitions will often require careful checking of the studies reviewed. For example, the first WCRF/AICR report defines 'vegetables' to exclude starchy roots and tubers, and this definition will also be used in the second report (some studies include potatoes as vegetables).

It is recognised that the literature defines exposures in different ways, and of course data should be extracted using the definitions used by the individual studies. The Access database has the ability to include notes on the definition of exposures. However, wherever possible please use the definitions below for aggregating the results in the literature. When studies use significantly different definitions, please highlight these in the SLR report. For example, if a study includes potatoes and other starchy tubers as 'vegetables', this should be highlighted in the SLR report. For some exposures (e.g. breastfeeding, physical activity) the definitions used in the literature will vary greatly and all variations in such cases should be recorded in the Access database. Other examples of varying definitions, are 'processed' or 'preserved' meat and other animal foods. It is important to record the precise definitions of exposure, particularly in relation to whether the exposure is from food only or from food and supplement intakes. These should be explicitly recorded whenever this information is available. Definitions of measures of exposure should also be recorded e.g. for alcohol recorded in units, the definition of a "unit" should be reported.

SLR centres should contact the SLR coordinator as they identify particular exposures with problematic or ambiguous definitions, to ensure both flexibility and consistency across all SLRs.

22.1.1 Exposure definitions

Below is a list of definitions for a number of 'complex terms'. The definitions have been prepared using the first report as a basis where appropriate and also using advice from Panel members and other relevant specialists. The definitions below are designed to correspond to consensual definitions in the literature as closely as possible.

Definitions for the following terms are complex for one of three reasons:

- Proper cut-off points are necessary to create categories and quantify the variable
- The current definition of the word is not clear
- The definition from the first report should be modified and clarified

Patterns of food and diets

Poverty diets
Monotonous diets consumed by impoverished populations usually in the economically developing world that are mostly made up of one or two starchy staples, and which are bulky, low in protein and fat, and very likely to be lacking in some micronutrients

Vegetarian diets
Contain little or no meat or other foods of animal origin; distinguish between:

- Semi-vegetarian (which only exclude selected kinds of meat, poultry, or fish)
- Lacto and lacto-ovo vegetarian (which exclude flesh foods, but include dairy products and eggs)
- Vegan (which exclude all foods of animal origin)

Breastfeeding

- **Exclusive breastfeeding** The infant/young child receives only breastmilk from his/her mother, or a wet nurse, or expressed breastmilk, and no other liquids or solids with the exception of drops or syrups consisting of vitamins, minerals, supplements, or medicine

- **Predominant breastfeeding** The infant/young child's predominant source of nourishment has been breastmilk. However, the infant may also have received water and water-based drinks (sweetened and flavoured water, teas, infusions, etc.); fruit juice; oral rehydration salts solution; drops and syrup forms of vitamins, minerals, and medicines; and ritual fluids; with the exception of fruit juice and sugar-water, no food-based fluid is allowed under this definition

- **Partial or complementary breastfeeding** The infant/young child has received both breastmilk and solid (or semi-solid) foods in varying proportions

- **Total breastfeeding** Classify duration of breastfeeding per child, and for the mother, total months of breastfeeding cumulative for all children in months

- **Duration** Classify all types and the total breastfeeding exposure (for all children) into the following quantiles: None; < 1 month; 1-2.9 months; 3-5.9 months; 6-11.9 months; 12-24 months, > 24 months

Note to SLR centres. The possible relationship between breastfeeding and chronic disease, for both the mother and the child, is now the subject of sustained study. It is recognised that existing studies use varying definitions of types and durations of breastfeeding. An added difficulty is that perhaps most studies have been carried out among populations where duration of breastfeeding has been very short, at least compared with traditional norms. The definitions above should be used whenever possible. But in case of doubt or difficulty in aggregating the literature into this (or any) definition), and notably if a substantial body of literature consistently uses other definitions, please contact the review coordinator.

Where possible also note:

- **Age of weaning** Time when foods other than breastmilk are introduced to the child's diet. Should be indicated as age in months

- **Duration of lactational amenorrhea** Months of lactational amenorrhea per child and cumulative months of amenorrhea while lactation, serves as an indication of prolonged progesterone effect during lactation

Food and drinks

Wholegrain cereals and cereal products
Cereals (grains) and their products made from grains that retain most or all of the germ and with the husk being essentially intact around the endosperm. Includes brown rice, whole oat or rolled oats, bread made from the whole grain of any cereal, and kibbled grains

Refined cereals and cereal products
Cereals (grains) and their products having an extensively disrupted structure or from which the husk and germ of the whole grain has entirely or mostly removed. Includes products made from white wheat flour or from “wholemeal” flour that has been made from blending finely milled grain fractions. Also includes ready-to-eat breakfast style cereals made from grains in which the original grain structure has been disrupted to such

an extent that the endosperm is readily accessible to digestive processes. Some examples include bread made from white or finely-ground wholemeal flour, white rice, expanded rice, puffed wheat, dehulled oat flakes, corn flakes, popped corn, cornmeal and gruels made from finely-ground cereal flours, and unleavened breads such as chapatti, tortilla, and pita, and noodles, pastas, dumplings, gruels and porridges and all other cereal products made from finely-ground cereal flours

Meat
The flesh of any terrestrial animal; beef, lamb, and pork from farmed domesticated cattle, sheep and pigs and other domesticated animals in fresh or frozen states, or dried without any other form of preservation. Excludes offal (the organs and other non-flesh parts of meat). *Meat from wild and undomesticated animals should be analysed separately*

Note to SLR centres. Please report findings on other forms of meat and on meat from wild animals separately. See ***Processed Meat.***

Poultry
Chicken, duck, turkey, and other domesticated birds. Meat from wild and undomesticated animals should be analysed separately

Note to SLR centres. Please report findings on wild birds separately. See ***Processed Meat****.*

Fish
All forms of fresh, frozen or dried fish, from rivers, seas, oceans, whether fished or farmed.

Note to SLR centres. If there are any findings that suggest different results from farmed as distinct from 'wild'(fished) fish, please display these. See ***Processed Meat.***

Sugars
Distinguish between extrinsic sugars used in manufactured food, in cooking, or at table, which include glucose, fructose, sucrose, honey, and syrups refined from cane, beet, corn, and other sources; and intrinsic sugars as contained within the cell walls of plant foods, particularly fruits

Milk and dairy products
Milk, cheese, fat products such as butter and ghee, and fermented products such as yoghurt, from cows and other domesticated animals such as buffalo, sheep, and goats. Does not include infant formulas

Food production, preservation, processing, preparation

Processed meat, poultry, fish Avoid the term 'processed meat,' instead group under meat, poultry, fish, shellfish, each divided as:

- Salted
- Fermented
- Pickled
- Cured
- Smoked
- Preserved in other ways (e.g. with chemical preservatives)
- Other processesd, not preserved
- But if the exposure is listed at "processed meat" leave it as such

Note to SLR centres. Practically all meat and other animal products are processed in some sense for consumption – cooking is a process. However, include here meat and other animal products that are not fresh (or frozen or dried) but which have been preserved in some way before the point of sale by the addition of some substance or process such as salting, fermenting, pickling, curing and smoking. Please classify types of processed meat etc under the process and not the product – eg smoked salmon goes under fish (smoked) and bacon under meat (cured). Note that hot dogs (frankfurters or wieners or wienies) are cured and therefore so classified here. Sausages are also usually preserved, with salt and chemical additives. Hamburgers made by industrial processes also include preservatives (and it may be advisable to analyse data on hamburgers separately). As already stated please refer any difficulties to the review coordinator.

Cooking classifications

- All methods that expose food to heat not exceeding 100˚C. Includes steaming, boiling, and stewing
- All methods that expose food to temperatures 100°- 200˚C, but not to direct flame. Includes baking, microwaving, roasting
- All methods that expose food to temperatures 200°- 400°, but not to direct flame. Includes frying
- All methods that expose food to temperatures 200°- 400˚C or higher and sometimes to direct flame. Includes grilling (broiling) and barbecuing

Physical activity and energy balance

Specific level of activity

Defined by the metabolic equivalents (METs), a measure of the energy cost of individual activities, as a multiple of BMR:

• Not active = <1.5 METs	Standing, sitting, talking
• Gentle = 1.5 – 2.9 METs	Strolling
• Moderate 3 – 5.9 METs	Jogging, brisk walking (moderate recreational)
• Vigorous = 6+ METs	Energetic/competitive recreational games, swimming, cycling, running

Note to SLR centres. METs and PARs (Physical activity ratios) are comparable. METs estimate the metabolic cost of physical activity, with 1 MET equaling the resting metabolic rate. Similarly, PARs estimate the energy cost of an activity, expressed as a multiple of BMR.

Overall activity level
Defined by the hours per week of each activity level above:

- < 1 hour of activity
- 1 - 1.9 hours of activity
- 2 – 3.9 hours of activity
- 4 – 6.9 hours of activity
- >= 7 hours of activity

Note to SLR centres. Both specific and overall activity level need to be reported across the lifespan, if this is included in the article. Use the following definition to incorporate this.

Duration (across lifespan):
- Lifelong
- Current
- Past (ceased more than three years ago)

Note to SLR centres. It is recognised that terminology and definitions of this very important exposure in the literature are variable. Please use these definitions in the aggregated analyses when feasible, and note all major variations. As before, please contact the review coordinator when it is most difficult to aggregate the literature into this (or any) definition.

Energy restriction Defined as restriction of <10%kcals, 10-19.9%kcals, 20-29.9%kcals, and ≥30%kcals of energy required. [The SLR centres will report length of studies and follow-ups and the description of the diet from the individual studies]

Body Mass Index (BMI) Weight (kg) /height $(m)^2$,
- < 18.5 = underweight
- 18.5 - 24.99 = normal (if available please also subdivide at 22.9)
- 25.0 - 29.99 = overweight (if available please also subdivide at 27.5)
- 30.0 - 39.99 = obese
- 40.0+ = morbidly obese

22.2 Study designs

Standard definitions of study design terms are available in **Appendix K**, and have been defined using the study design algorithm.

23 Style

Please follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, issued by the International Committee for Medical Journal Editors, and posted on the Lancet website (at *www.thelancet.com/info/info.isa?n1=authorinfo&n2= Uniform+requirements)*. Please follow these guidelines on style when writing the SLR, with exception of the following:

23.1 Word processing packages

Microsoft Word is recommended. If Microsoft Word is not used, please use a word processing package that is compatible. If in doubt please contact the Review Coordinator.

23.2 Typography

Times New Roman 18pt, 16pt and 14pt bold, to be used for main titles, main sub-headings, and sub-sub headings respectively, as in this manual.

Times New Roman 12pt, for the body text of documents.

Arial 10pt, for display of data in tables, figures and other graphic displays.

23.3 Format of tables

A recommended format for the results tables is presented in **Appendix M**. This format can be modified if necessary e.g. addition of other quality markers. The table represents the minimum information that should be presented in the results tables.

23.4 Spelling

As usual in international reports, please use UK English not USA English.

23.5 References

It is compulsory to use the Endnotes reference-managing package, or a system compatible with Endnotes for referencing the SLR reports. If in any doubt please contact the Review Coordinator.

Part 5
Peer review process

24 Introduction

A peer review process is necessary to ensure the SLRs (systematic literature reviews) are carried out to the highest standard. The Secretariat is responsible for ensuring that the specifications in the SLR specification manual are followed, but it is also important that external peer reviewers are used to identify any potential weaknesses in the SLRs. The Secretariat is responsible for managing the peer review process in a systematic way.

There will be two stages to the peer review process, each of which must be completed within a two week period.

> ***Stage I***- The peer reviewers will review a protocol for the search, data collection and analysis strategies. This must be approved before the SLR itself is started.
>
> ***Stage II***- The peer reviewers will review the SLR report in relation to the original protocol. The peer reviewers may suggest changes to the report before it is presented to the Panel for their assessment.

For any individual SLR, the same peer reviewers will be used for each stage of the process.

To help ensure that each SLR is peer reviewed in a similar, systematic way and to ensure that the required format is followed, peer reviewers will receive SLR protocol and SLR report checklists from the Secretariat (**Appendices G and H**). The same checklists are available to the SLR centres so that they can check that all necessary sections of the protocol or finished SLR report have been completed.

The peer review process is summarised in the flow chart in **Section 29**. Each stage of the process is described in more detail below.

25 Identification of peer reviewers

The team of peer reviewers for each SLR require a variety of skills in the following areas:

- Nutrition
- Cancer, specific to site in question
- Systematic literature review methodology
- Statistics related to systematic literature review

There must be an expert in each of these fields (cancer, nutrition, systematic review and statistics). However, some peer reviewers may have expertise in more than one area (e.g. nutrition and SLR, cancer and nutrition).

There is a very short turnaround time for each protocol or SLR report (two weeks) and some peer reviewers may not be able to complete the appraisal at the required time. To ensure that we obtain appraisals from each area of expertise we will aim to allocate at least two experts to each area. This will give a total of four to eight peer reviewers allocated to each cancer site.

The Secretariat will be responsible for identifying the peer reviewers for each cancer site. The potential peer reviewers will be identified from:

- Relevant panel members from 1997 report
- Relevant scientists cited in 1997 report under each cancer site.
- Relevant scientists from other reports e.g. COMA, WHO
- Relevant scientists from centres for systematic review e.g. Cochrane
- Peer reviewers from 1997 report
- Suggestions from the Secretariat and Advisory Group

The list of potential peer reviewers will be presented to the Advisory Group for approval. Further peer reviewers will be sought if a significant number are deemed unsuitable.

26 Communication with peer reviewers

The potential peer reviewers will initially be contacted by telephone or email by the Secretariat. A consistent approach will be used. The process of the peer review and what is expected of each peer reviewer will be made clear. It will be important to explain that a quick response to each protocol or SLR report is required. Once the peer reviewers have agreed in principle, they will be written to formally and sent a peer review pack to ensure they are familiar with the process. Each peer reviewer will be required to formally accept the invitation to participate in the external peer process. It will be suggested that each peer reviewer with statistics and systematic review expertise appraises four SLRs (both protocol and SLR report for each site) over the 15 months. However, the peer reviewers may select fewer SLRs.

For reasons of transparency and openness, all peer reviewers will be asked to sign a declaration of interests.

Once agreement has been obtained from the peer reviewers the Secretariat will select a set of peer reviewers for each cancer site. All peer reviews will be completed individually.

27 Appraisal of protocols

Around four to eight weeks before peer reviewers receive a protocol, they will be sent a note (by email, unless another method is more suitable) confirming the date they can expect to receive the protocol. If at this point the peer reviewer decides they are unable to appraise the protocol within two weeks they should inform the Secretariat. If several peer reviewers are unable to appraise the protocol replacements may need to be found.

The peer reviewers will be asked to assess the protocol within two weeks using the systematic literature review (SLR) protocol checklist that has been specially developed for the process (see **Appendix G**). The checklist will require the peer reviewer to indicate if each section is completed appropriately. The peer reviewers will be required to provide more details if a section is deemed not satisfactory. The peer reviewers will assess the protocol independently and will not converse with the other peer reviewers assessing the same protocol.

The peer reviewers will return their completed SLR protocol checklist to the Secretariat. The peer reviewers may select to see the revised changes. However if they do they will be made aware that comments will need to be made within 2-3 days. The Review Coordinator and the Secretariat will assess the checklists completed by the peer reviewers. The Review Coordinator will be responsible for resolving any minor discrepancies between the peer reviewers. If there are any major problems with the protocols (for example they are clearly not suitable) the Review Coordinator and Secretariat will converse with the Advisory.

The Review Coordinator will then liaise with the SLR centres to ensure that all necessary revisions are carried out. The identity of the peer reviewers will not be divulged to the SLR centres. The Review Coordinator and Secretariat can approve minor revisions to the protocol. Major changes may need to be approved by the peer reviewers and/or the Advisory Group.

Once final approval by the Secretariat or Advisory Group has been granted, the protocol will be placed on a website. This will ensure the transparency of the process and alert other potential reviewers to which questions we are addressing. It will also allow comment from those outside the review process, although the SLRs will be underway once the approval has been granted.

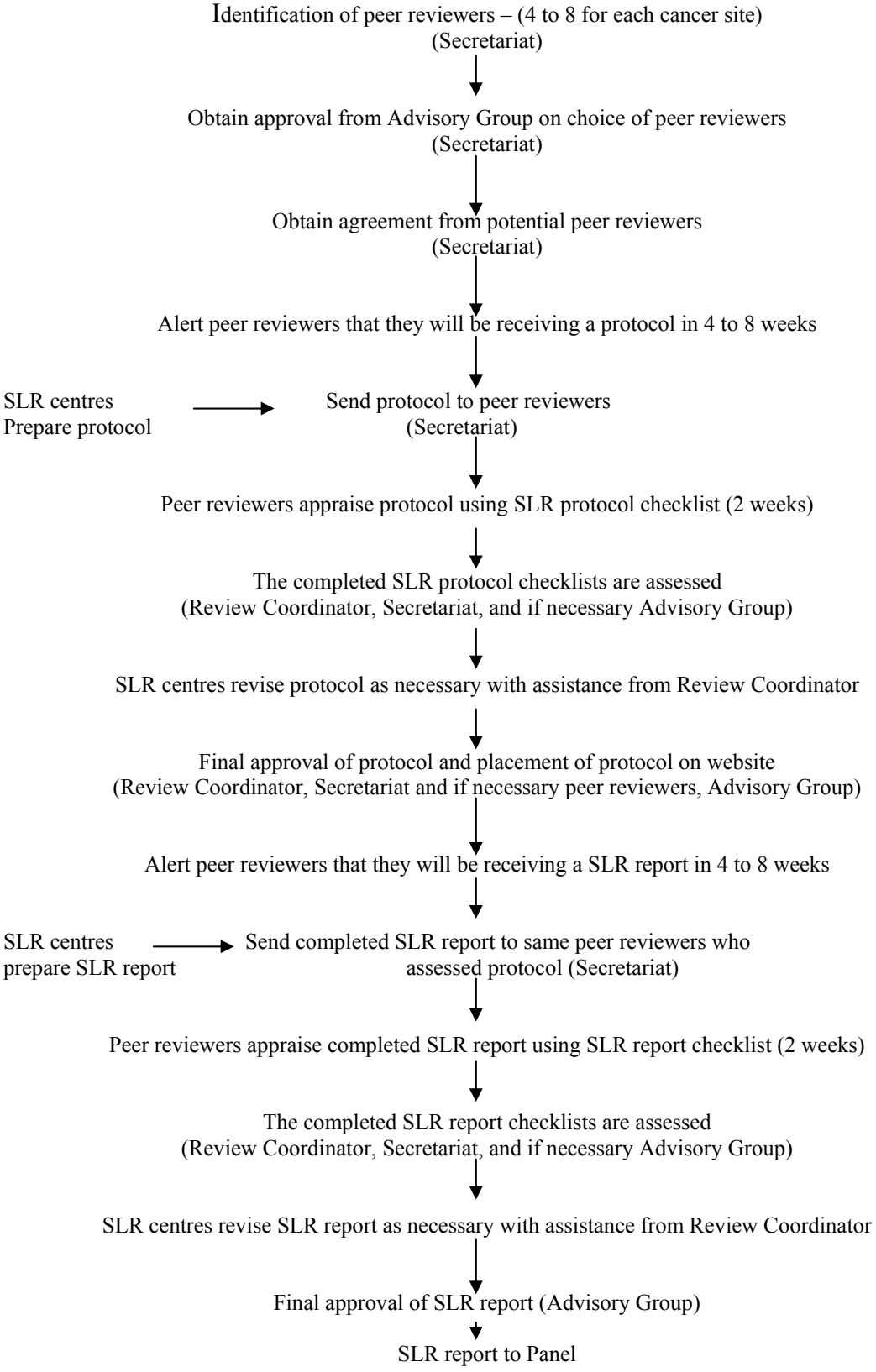
28 Appraisal of the SLR reports

The same process of alerting the peer reviewers when to expect a completed SLR report will be employed as detailed for appraising protocols. The peer reviewers will use a specially designed SLR report checklist (**Appendix H**).

The Review Coordinator and the Secretariat will assess the checklists completed by the peer reviewers. The Review Coordinator will be responsible for resolving any minor

discrepancies between the peer reviewers. If there are any major problems with the completed SLR reports (for example they are clearly not suitable) the Review Coordinator and Secretariat will liaise with the Advisory Group (one or more member/s). The Review Coordinator will then liaise with the SLR centres to ensure that all necessary revisions are carried out. Once any revisions have been made, the Advisory Group (one or more member/s) will be required to approve the final SLR report. They will receive a copy of the SLR report, peer reviewers' comments and a statement from the SLR centres on how they addressed the comments of the peer reviewers.

29 Flowchart of the peer review process



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Appendices

Appendix A

Methodology Task Force

Martin Wiseman (Chair)	WCRF International, London	UK
Sheila Bingham	Dunn Human Nutrition Unit, Cambridge	UK
Heiner Boeing	German Institute of Human Nutrition, Berlin	Germany
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Bas Bueno de Mesquita	National Institute of Public Health, Bilthoven	the Netherlands
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Andreas Gescher	University of Leicester	UK
Timothy Key	University of Oxford	UK
Jos Kleijnen	University of York	UK
Barrie Margetts	University of Southampton	UK
Robert Owen	German Cancer Research Centre, Heidelberg	Germany
Gillian Reeves	University of Oxford	UK
Elio Riboli	WHO International Agency for Research on Cancer, Lyon	France
Arthur Schatzkin	National Cancer Institute, Rockville, MD	USA
David Shuker	The Open University, Milton Keynes	UK
Michael Sjostrom	Karolinska Institute, Stockholm	Sweden
Pieter van't Veer	Wageningen University	the Netherlands
Chris Williams	Cochrane Cancer Network, Institute of Health Sciences, Oxford	UK

Co-opted members

Rudolf Kaaks	WHO International Agency for Research on Cancer, Lyon	France
Teresa Norat	WHO International Agency for Research on Cancer, Lyon	France

Observers

World Health Organization (WHO)	Pirjo Pietinen	Switzerland
Department of Health (England)	Sheela Reddy	UK

Appendix B

Panel

Michael Marmot (Chair)	University College London	UK
Tola Atinmo	University of Ibadan,	Nigeria
Tim Byers	University of Colorado Health Sciences Centre, Denver, CO	USA
Junshi Chen	Chinese Academy of Preventive Medicine, Beijing	China
Tomio Hirohata	Nakamura University, Fukuoka City	Japan
Alan Jackson	University of Southampton	UK
Philip James	International Obesity Task Force, London	UK
Laurence Kolonel	University of Hawaii, Honolulu, HA	USA
Shiriki Kumanyika	University of Pennsylvania School of Medicine, Philadelphia, PA	USA
Claus Leitzmann	Institute of Nutrition, Justus-Liebig University, Giessen	Germany
Jim Mann	University of Otago, Dunedin	New Zealand
Srinath Reddy	Institute of Medical Sciences, New Delhi	India
Elio Riboli	WHO International Agency for Research on Cancer, Lyon	France
Juan Rivera	Centro de Investigacion en Nutricion y Salud, Cuernavaca	Mexico
Hilary Powers	University of Sheffield	UK
Arthur Schatzkin	National Cancer Institute, Rockville, MD	USA
Jaap Seidell	Free University of Amsterdam	Netherlands
David Shuker	The Open University, Milton Keynes	UK
Ricardo Uauy	Instituto de Nuticion y Tecnologia de los Alimentos, Santiago	Chile
Walter Willett	Harvard School of Public Health, Boston, MA	USA
Steven Zeisel	University of North Carolina at Chapel Hill	USA

Observers

Food and Agriculture Organization of the United Nations (FAO)	Prakash Shetty	Italy
International Food Policy Research Institute (IFPRI)	Marie Ruel	USA
International Union of Nutritional Sciences (IUNS)	Mark Wahlqvist	Australia
Union Internationale Contre le Cancer (UICC)	Harald zur Hausen	Germany
United Nations Children Fund (UNICEF)	Rainer Gross	USA
World Health Organization (WHO)	TBC	Switzerland

Appendix C

Advisory Group

Geoffrey Cannon (Chair)	WCRF International
Michael Marmot	University College London
Ritva Butrum	AICR
Marilyn Gentry	WCRF International
Alan Jackson	University of Southampton
Jos Kleijnen	University of York
Jim Mann	University of Otago
Deirdre McGinley-Gieser	WCRF International
Gillian Reeves	University of Oxford
Elio Riboli	WHO International Agency for Research on Cancer
Arthur Schatzkin	National Cancer Institute
Ricardo Uauy	Instituto de Nurticion y Tecnologia de los Alimentos
Martin Wiseman	WCRF International

Appendix D

Executive Team

Martin Wiseman (Project Director)
Marilyn Gentry (WCRF International President)
Kelly Browning
Ritva Butrum
Geoffrey Cannon
Deirdre McGinley-Gieser
Kathy Ward

Appendix E

Secretariat

Steven Heggie (Project Manager)
Ritva Butrum
Geoffrey Cannon
Cara James
Anja Kroke
Lisa Miles
Elaine Stone
Rachel Thompson
Martin Wiseman

Appendix F

PubMed search strategy

Information Service staff at the Centre for Reviews and Dissemination (CRD), University of York have compiled a standard search strategy to be used by review centres when searching the epidemiological literature for studies on food, nutrition, physical activity and the prevention of cancer.

The search strategy aims to identify generic references on food, nutrition and physical activity. Specific cancer site search terms will be added at a later date by the individual review centres.

The search strategy (Section F1 below) has been designed to be run on the PubMed interface of the MEDLINE database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi). It was tested on 6 January 2004.

How the strategy was formulated

The search terms included in the strategy are based on the list of exposures provided by the WCRF to CRD. All the terms provided by WCRF have been included in the strategy, and additional terms have been added by CRD where it appeared necessary. Where a duplication of terms was identified, any redundant terms were deleted.

e.g. 'fat*' is a search term, therefore it is not necessary to search 'hydrogenated fat*', 'polyunsaturated fat*' etc. separately.

All textwords were mapped to MEDLINE indexing terms (Medical Subject Headings/MeSH terms). If a relevant MeSH term was identified, this was included in the search strategy.

A maximum number of 100 search strings can be entered into a PubMed database query. In order to maximise the number of search strings which are free to be used for specific cancer site terms, several food/nutrition/physical exercise terms have been included in each line of the standard search strategy provided.

OPERATIONAL ISSUES

1. SEARCH STRATEGY

Section F1 contains the suggested standard search strategy with details of how to access the PubMed interface.

Search terms are listed in lines, and the search string number is included for each line (**#1**…). The strategy is 21 lines long.

Textwords

All textwords should be searched for in the title and abstract fields only. This is denoted by [tiab] after each textword term.

The '*' symbol is used as the truncation symbol in PubMed, searching for all terms beginning with the given sequence of letters
e.g. 'activit*' - retrieves 'activity', 'activities'.

MeSH Headings

MeSH subject headings have [MeSH Terms] after each word/phrase. In the PubMed interface of MEDLINE, explosion of MeSH headings is automatic, therefore all indexing terms located below a specific MeSH term in the MEDLINE thesaurus hierarchy are automatically searched.

Human/Animal Studies

It is possible for the search strategy to be limited to human studies, and for some animal studies to be excluded. This can be done in PubMed, as outlined in Section F1. However, please note that:

1. This limit will only apply to MEDLINE citations only. This will not exclude animal studies from "in process" and "supplied by publisher" citations on PubMed as they have not yet completed the indexing process and do not carry the appropriate Human/Animal indexing terms on which the limit is based.
2. Not all studies appear to be tagged either 'Human' or 'Animal' in PubMed. Any animal studies not using the 'Animal' tag will not be excluded by using the limit suggested.
3. Caution is required with any use of the NOT operator, as this limit may risk excluding potentially relevant records if indexing has not been correctly applied.

It is therefore recommended that the search should only attempt to exclude animal studies if the number of references retrieved is too large for reasonable assessment.

2. SEARCHING NOTES

Section F2 contains a table listing all the textwords and MeSH terms used in the standard search strategy. For clarity, it is divided into the sections suggested for the systematic literature review reports.

The 'notes' field contains any information that CRD considers of relevance/interest to WCRF:

- Details of any 'redundant' terms included in WCRF's list of exposures which will be retrieved from MEDLINE by a broader search term, and therefore need not be searched individually
  e.g. Diet - *Includes*: regionally defined diets, socio-economically defined diets etc.

- Suggested ways in which 'noisy' terms (such as 'organic') could be combined with other terms (such as 'food*' or 'diet*') in order to reduce the number of irrelevant records retrieved. These combinations are optional, and decisions on whether to narrow the search should be made on the basis of whether the search strategy is required to be as *sensitive* as possible (retrieving large numbers of records, many of which may be irrelevant, but with less chance of missing useful records), or to be more *specific* (retrieving a smaller number of records of greater relevance, however with the potential for missing some relevant records). If used, terms should be combined using the 'AND' boolean operator, as adjacency operators are not available in PubMed.
  e.g. Intake - Combine with 'diet*' or 'food*'

SECTION F1

WCRF - PUBMED SEARCH STRATEGY

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed

Search tested: 6 January 2004

#1 diet therapy[MeSH Terms] OR nutrition[MeSH Terms]

#2 diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR intake[tiab] OR nutrient*[tiab] OR nutrition[tiab] OR vegetarian*[tiab] OR vegan*[tiab] OR "seventh day adventist"[tiab] OR macrobiotic[tiab] OR breastfeed*[tiab] OR breast feed*[tiab] OR breastfed[tiab] OR breast fed[tiab] OR breastmilk[tiab] OR breast milk[tiab]

#3 food and beverages[MeSH Terms]

#4 food*[tiab] OR cereal*[tiab] OR grain*[tiab] OR granary[tiab] OR wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable*[tiab] OR fruit*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab] OR peanut*[tiab] OR groundnut*[tiab] OR seeds[tiab] OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR fat[tiab] OR fats[tiab] OR fatty[tiab] OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR oils[tiab] OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper*[tiab] OR condiments[tiab]

#5 fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage*[tiab] OR ethanol[tiab] OR yerba mate[tiab] OR ilex paraguariensis[tiab]

#6 pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]

#7 pesticide*[tiab] OR herbicide*[tiab] OR DDT[tiab] OR fertiliser*[tiab] OR fertilizer*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate*[tiab] OR veterinary drug*[tiab] OR polychlorinated dibenzofuran*[tiab] OR PCDF*[tiab] OR polychlorinated dibenzodioxin*[tiab] OR PCDD*[tiab] OR polychlorinated biphenyl*[tiab] OR PCB*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated hydrocarbon*[tiab] OR microbial contamination*[tiab]

#8 food preservation[MeSH Terms]

#9 mycotoxin*[tiab] OR aflatoxin*[tiab] OR pickled[tiab] OR bottled[tiab] OR bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack*[tiab] OR refrigerate*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive*[tiab] OR colouring*[tiab] OR coloring*[tiab] OR flavouring*[tiab] OR flavoring*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment*[tiab] OR processed[tiab] OR antioxidant*[tiab] OR genetic modif*[tiab] OR genetically modif*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab]

#10 cookery[MeSH Terms]

#11 cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol*[tiab] OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR microwave[tiab] OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue*[tiab] OR chargrill*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab]

#12 dietary carbohydrates[MeSH Terms] OR dietary proteins[MeSH Terms] OR sweetening agents[MeSH Terms]

#13 salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR lipid*[tiab] OR linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab] OR sugar*[tiab] OR sweetener*[tiab] OR saccharin*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR protein[tiab] OR proteins[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

#14 vitamins[MeSH Terms]

#15 supplements[tiab] OR supplement[tiab] OR vitamin*[tiab] OR retinol[tiab] OR carotenoid*[tiab] OR tocopherol[tiab] OR folate*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral*[tiab] OR sodium[tiab] OR iron[tiab] OR calcium[tiab] OR selenium[tiab] OR iodine[tiab] OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate*[tiab] OR glucosinolate*[tiab] OR indoles[tiab] OR polyphenol*[tiab] OR phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab]

#16 physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] or walking[MeSH Terms]

#17 recreational activit*[tiab] OR household activit*[tiab] OR occupational activit*[tiab] OR physical activit*[tiab] OR physical inactivit*[tiab] OR exercise[tiab] OR exercising[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy balance[tiab] OR energy density[tiab]

#18 growth[MeSH Terms] OR anthropometry[MeSH Terms] OR body composition[MeSH Terms] OR body constitution[MeSH Terms]

#19 weight loss[tiab] or weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass[tiab] OR BMI[tiab] OR obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over weight[tiab] OR skinfold measurement*[tiab] OR skinfold thickness[tiab] OR DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR hip circumference[tiab] OR waist hip ratio*[tiab]

#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

Optional:
#21 animal[MeSH Terms] NOT human[MeSH Terms]

#22 #20 NOT #21

KEY:

[tiab]	searches the title and abstract fields only
[MeSH Terms]	searches the Medical Subject Headings field only NB - explosion of MeSH terms is automatic
*	truncation symbol - searches all words with this combination of letters at the beginning

SECTION F2
WCRF - SEARCH TERMS

SECTION	MeSH HEADINGS	TEXTWORDS	NOTES
1	exp Diet-Therapy/ exp Nutrition/ (includes child/infant nutrition, breastfeeding, diets, energy intake)	diet or diets or dietetic dietary eating intake nutrient* nutrition* vegetarian* vegan* seventh day adventist* macrobiotic breastfeed*, breast feed*, breastfed, breast fed, breast milk, breastmilk	Diet - *Includes*: regionally defined diets, socio-economically defined diets Dietary - *Includes*: dietary pattern, dietary protein Intake - Combine with 'diet*' or 'food*'
2	Exp Food-and-Beverages/ *Food* - includes all foodstuffs, supplements, genetically modified food, fat, fibre etc. *Beverages* - includes alcoholic and soft drinks	food* cereal* grain*, granary wholegrain, wholewheat roots plantain* tuber, tubers vegetable*	Food - *Includes*: food additives, refined food, smoked food, cured food, genetically modified food, salted food, dried food, fresh food, cooked food Cereal - *Includes*: refined cereal, cereal products Grain - *Includes*: refined grain Roots - Combine with 'diet*' or 'food' Vegetable - *Includes*: cruciferous vegetables, allium vegetables, green vegetables, leafy vegetables, raw

		fruit* pulses, beans, lentils chickpeas legume* soy, soya nut, nuts, peanut*, groundnut* seeds meat, beef, pork, lamb poultry, chicken, turkey, duck fish fat or fats or fatty egg or eggs bread oils shellfish, seafood sugar, syrup dairy milk herbs spices, chilli, chillis, pepper* condiments	vegetables Fruit - *Includes*: citrus Meat - *Includes*: red meat, white meat, wild meat, farmed meat Fish - *Includes*: oily fish, white fish Fatty - *Includes*: (omega-3/monounsaturated/ polyunsaturated/n-3/n-6) fatty acids Fat - *Includes*: saturated, monounsaturated, polyunsaturated, low fat Eggs - Combine with 'diet*' or 'food' or consumption
3	*See above*	fluid intake water drinks, drinking	 Water - Combine with 'consumption' or 'diet*' or 'drink*' Drinks - *Includes*: sugary drinks, soft drinks, carbonated

		tea coffee caffeine juice beer spirits liquor wine alcohol, alcoholic beverage* ethanol yerba mate, ilex paraguariensis	drinks, hot drinks Tea - *Includes*: black tea, green tea
4.1	Exp Pesticides/ (includes herbicides) Fertilizers/ Veterinary-Drugs/	pesticide* herbicide* DDT fertiliser*, fertilizer* organic contaminants, contaminate* veterinary drug* polychlorinated dibenzofuran*, PCDF* polychlorinated dibenzodioxin*, PCDD* polychlorinated biphenyl*, PCB* cadmium arsenic chlorinated hydrocarbon*	Organic - Combine with 'food', 'fruit', 'vegetables', 'produce', 'diet*', etc. Contaminants/contaminate - Combine with 'food'

		microbial contamination*	
4.2-4.3	Exp Food-Preservation/	mycotoxin*	
		aflatoxin*	
		pickled	
		bottled, bottling	
		vacuum pack*	
		refrigerate*, refrigeration	
		cured	Cured - Combine with 'food*'
		smoked	Smoked - Combine with 'food*'
		preserved, preservatives	Preserved/preservatives - Combine with 'food*'
		nitrosamine	
		hydrogenation	
		fortified	Fortified - Combine with 'food*'
		additive*	Additive - Combine with 'food*'
		colouring*, coloring*	
		flavouring*, flavoring*	
		nitrates, nitrites	
		solvent, solvents	
		ferment*	
		processed	Processed - Combine with 'food*'
		antioxidant*	
		genetically modif*, genetic modif*	
		vinyl chloride	
		packaging, labelling	Packaging/labelling - Combine with 'food'
		phthalates	
		canning	
		stanols	
4.4	Cookery/	cooking, cooked	
		grill, grilled	
		fried, fry	

		roast, bake, baked stewing, stewed, casserol* broil, broiled boil, boiled microwave, microwaved re-heating, heating, re-heated, reheated, reheating poach, poached steamed barbecue*, chargrill* heterocyclic amines polycyclic aromatic hydrocarbons	Reheating/heating etc. - Combine with 'food*'
5.1-5.4	Dietary-Carbohydrates/ exp Dietary-Proteins/ exp Sweetening-Agents/ (other food terms included in 'exp Food/' MeSH term - *see section 2*)	Salt salting, salted fiber, fibre polysaccharide* starch, starchy carbohydrate* lipid* hydrogenated dietary oils hydrogenated lard hydrogenated oils linoleic acid* sterols stanols sugar* sweetener*, saccharin* aspartame acesulfame k	Salt - Combine with 'food*' or 'diet*' or 'consumption' Fibre - *Includes*: cereal fibre, vegetable fibre, fruit fibre Sugar - *Includes*: intrinsic sugars, extrinsic sugars Combine with 'diet*' or 'food' or 'consumption'

		cyclamates maltose mannitol sorbitol sucrose xylitol cholesterol protein*	Protein - *Includes*: plant protein, animal protein
5.5-5.7	exp Vitamins/	supplements, supplement vitamin* retinol carotenoid* tocopherol folate* folic acid methionine riboflavin thiamine niacin pyridoxine cobalamin mineral* sodium iron calcium selenium iodine magnesium potassium zinc copper	Supplements - Combine with 'diet*' or 'food'

		phosphorus manganese chromium phytochemical allium isothiocyanate* glucosinolate* indoles polyphenol* phytoestrogen* genistein saponin* coumarin*	
6-7	Physical-Fitness/ exp Exertion/ (includes exercise exp physical endurance/ Walking/	recreational activit* household activit* occupational activit* physical activit* physical inactivit* exercise, exercising energy intake energy expenditure energy balance energy density	
8	exp Growth/ (includes height, weight, weight gain/loss, obesity, birth weight) exp Anthropometry/ (includes body height/weight, BMI)	weight loss, weight gain anthropometry birthweight, birth-weight, birth weight child development height body composition body mass, BMI	Body mass - *Includes*: body mass index

		obesity, obese, overweight, over-weight skinfold measurement* skinfold thickness DEXA bio-impedence waist circumference hip circumference waist hip ratio*	NB - 'childhood growth' not included as this is not a PubMed recognised phrase

Appendix G

SLR protocol checklist (for Peer Reviewers)

SLR Protocol Checklist (for Peer Reviewers)

Peer reviewer

Area of expertise

Cancer site

Date for return of protocol checklist

Please email completed form to

Summary of protocol appraisal

Acceptable in current form ☐

Acceptable with minor modifications ☐

May be acceptable after major revising ☐

Wish to see revised protocol after revision Yes ☐ No ☐

Unacceptable ☐

Comments to Secretariat and Advisory Group only
(The box below will expand as you type)

The Systematic Literature Review (SLR) centres are required to follow instructions in the SLR Specification Manual in order to conduct their SLRs. It is the responsibility of the Secretariat to ensure that the instructions in the SLR Specification Manual (which have been peer-reviewed) have been followed. There are some sections that allow the SLRs more flexibility in their approach. These sections are listed below and we would like you to make comments on the items that are within your area of expertise. As a guide we have indicated the type of expertise required for each item.

Please check the relevant box and give further details if checked 'No' or 'Unsure'.

Yes No Unsure

1. Background {*cancer and nutrition specialists*}

A brief background should include evidence from previous systematic literature reviews including the 1997 report. ☐ ☐ ☐

2. Study selection criteria for cancer site {*cancer specialist*}

Are the outcomes for the cancer site described? Are they appropriate and comprehensive? ☐ ☐ ☐

3. Search strategy {*cancer, nutrition and SLR specialists*}

i) Are the cancer site-specific, additional exposure and lifecourse search terms to be used to search PubMed appropriate and comprehensive? ☐ ☐ ☐

ii) Have other necessary cancer site-specific literature databases been included? ☐ ☐ ☐

4. Data analysis {*Statistician*}

i) Is the issue of confounding and effect modification addressed appropriately? ☐ ☐ ☐

ii) Are the methods of assessing heterogeneity appropriate? ☐ ☐ ☐

iv) Have the characteristics to explore heterogeneity by meta-regression been stated? Are they appropriate? ☐ ☐ ☐

v) Have appropriate sensitivity analyses been described? ☐ ☐ ☐

Comments to the SLR centres

Please provide further details on questions checked 'No' or 'Unsure'. Other comments on the protocol may also be included here. The box below will expand as you type.

Appendix H

SLR report checklist (for Peer Reviewers)

Peer reviewer

Area of expertise
(Please tick all boxes that apply)

- Cancer ☐
- Nutrition ☐
- SLR methodology ☐
- Statistics ☐

Cancer site

Date for return of SLR report checklist

Please email completed form to j.kirkwood@wcrf.org

Summary of SLR report appraisal

Acceptable in current form ☐

Acceptable with minor modifications ☐

May be acceptable after major revising ☐

Wish to see revised SLR Report after revision
- Yes ☐
- No ☐

Unacceptable ☐

Comments to Secretariat and Advisory Group only
(The box below will expand as you type)

The Systematic Literature Review (SLR) centres are required to follow instructions in the SLR Specification Manual in order to conduct their SLRs. It is the responsibility of the Secretariat to ensure that the instructions in the SLR Specification Manual (which have been peer reviewed) have been followed. There are some sections which allow the SLRs more flexibility in their approach. These sections are listed below and we would like you to make comments on the items that are within your area of expertise. As a guide we have indicated the type of expertise required for each item.

Please tick the relevant box and give further details if checked 'No' or 'Unsure'.

		Yes	No	Unsure
1. Analysis of results ***{Statisician + SLR specialists}***				
i)	Has publication bias been assessed appropriately?	☐	☐	☐
ii)	Has the presence of heterogeneity been highlighted and possible sources considered?	☐	☐	☐
iii)	Has meta-analysis been used appropriately?	☐	☐	☐
iv)	Has the dose-response effect been adequately described?	☐	☐	☐
v)	Has metaregression been used appropriately?	☐	☐	☐
xii)	Have sensitivity analyses been done appropriately?	☐	☐	☐
2.	**Presentation of results {cancer + nutrition specialists}**			
i)	Are the tables of results clear and informative?	☐	☐	☐
ii)	Is the supporting text for the epidemiological studies accurate and adequate?	☐	☐	☐
iii)	Has the lifecourse approach been addressed adequately?	☐	☐	☐
iv)	Have gene-nutrient interactions been reported where appropriate?	☐	☐	☐
v)	Is the narrative review of experimental and mechanistic data adequate?	☐	☐	☐

vi) Have the key mechanisms relating to this cancer site been covered? ☐ ☐ ☐

3. Discussion and summaries {*all*}

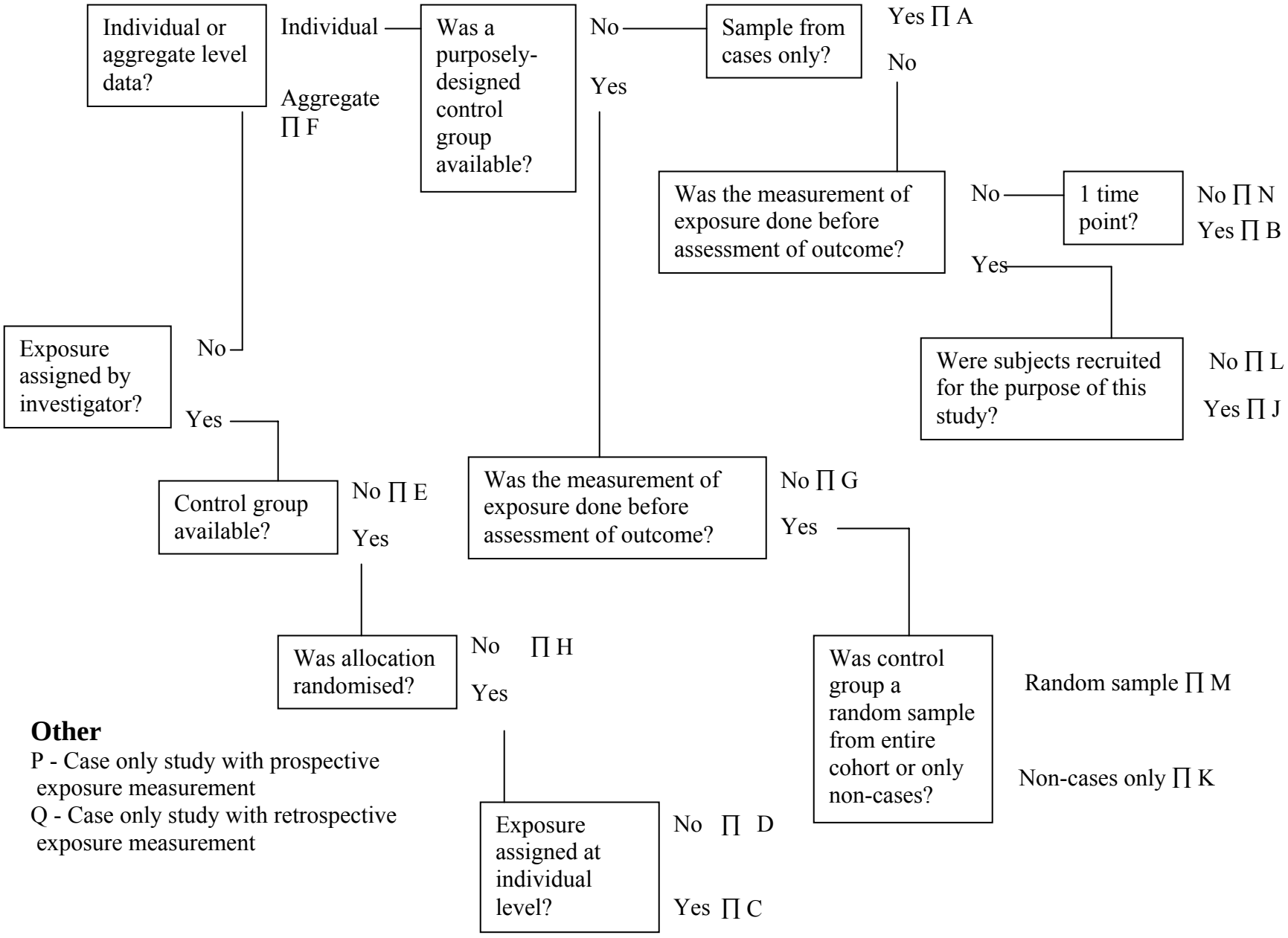
i) Are the limitations of the studies and the SLR process stated (e.g. measurement error)? ☐ ☐ ☐

ii) Has a commentary on study quality been included? Are there any other quality issues that should be addressed? ☐ ☐ ☐

Comments to the SLR centres

Please provide further details on questions checked 'No' or 'Unsure'. Other comments on the review may also be included here.
(The box below will expand as you type)

Appendix J: Study design algorithm


Individual or aggregate level data?
Individual
Aggregate ∏ F
Was a purposely-designed control group available?
No
Yes
Sample from cases only?
Yes ∏ A
No
Was the measurement of exposure done before assessment of outcome?
No
1 time point?
No ∏ N
Yes ∏ B
Yes
Were subjects recruited for the purpose of this study?
No ∏ L
Yes ∏ J
Exposure assigned by investigator?
No
Yes
Control group available?
No ∏ E
Yes
Was the measurement of exposure done before assessment of outcome?
No ∏ G
Yes
Was allocation randomised?
No ∏ H
Yes
Was control group a random sample from entire cohort or only non-cases?
Random sample ∏ M
Non-cases only ∏ K
Exposure assigned at individual level?
No ∏ D
Yes ∏ C
Other
P - Case only study with prospective exposure measurement
Q - Case only study with retrospective exposure measurement

Key to study design algorithm

Study design A	Case-study / case series
Study design B	Cross-sectional study
Study design C	Randomised controlled trial
Study design D	Group randomised control trial
Study design E	Uncontrolled trial
Study design F	Ecologic study
Study design G	Case-control study
Study design H	Non-randomised control trial
Study design J	Prospective cohort study
Study design K	Nested case-control study
Study design L	Historical cohort study
Study design M	Case-cohort study
Study design N	Time series with multiple measurement

Other (see definitions in Appendix K)

Study design P	Case only study with prospective exposure measurement
Study design Q	Case only study with retrospective exposure measurement

Appendix K

Study design definitions

A: Case series, case reports

Case report = Description of a person with a particular disease. Mainly used by clinicians to report about special cases/treatment effects etc.
Case series = Series of case reports, sometime representing all cases with a certain disease in a defined time period and/or geographical area. Case series can result from case sampling in different (clinical) centres (→ multi-centre study)

B: Cross-sectional studies

This is used to estimate the distribution (or joint distribution) of certain quantities (e.g. dietary exposure and disease rate) in a target population at a certain moment in time. Special characteristic is the simultaneous assessment of exposure and outcome.
Cross-sectional studies measure both exposure and outcome in the present and at the same point in time. Generally cross-sectional studies sample from the population in such a way as to reflect the population characteristics for both exposure and outcome.

C: Randomised controlled trial

This is an (epidemiological) experimental study in which conditions are controlled and manipulated by the investigator. Study subjects are randomly allocated to intervention or control groups. Results are assessed by comparison of disease rates or other outcome among intervention and control groups.

Randomised means allocation to study group entirely based on chance. Randomisation should follow a strict plan, usually some form of centralised randomisation scheme, an on-site computer system or sealed opaque envelopes.

Based on these principles, different design features can be differentiated:

Factorial design
In a factorial experimental design, the effects of a number of different factors can be investigated at the same time. The interventions are formed by all possible combinations that can be formed from the different factors. For example there are two interventions A and B and a control group C. The possible combinations are AB AC BC A B C so allowing the independent effects of each intervention to be assessed, as well as any interaction between them.

Testing of more than one intervention in one study (but not in one subject). Each participant is randomly allocated to intervention A or control B, and separately to intervention C or control D.

Cross-over design
The comparison of two or more interventions in which subjects upon completion of one treatment are switched to the other, with or without a washout period between them.

D: Group Randomised controlled trial (=Community trial)

This is principally the same as randomised controlled trial with the difference that the unit of allocation to the intervention is not a single subject but a group of subjects. The group may be a household, a worksite, GP practice, a community etc.

E: Uncontrolled Trial

An uncontrolled trial is an experimental study without control group. Upon an intervention, multiple measurements of changes in a physiological or pathological parameter are performed. Single centre and multi-centre studies are possible.

F: Ecologic study

A type of correlation study with a focus on characteristics of populations or groups rather than individuals. Population or group indices of dietary intake (e.g. population per capita consumption) are related to population or group indices of disease.

G: Case-Control Study

(Synonyms: case comparison study, case history study, case referent study, retrospective study)

In case-control studies outcome is measured in the present and the past exposure is ascertained. Case-control studies sample from the population of people with the outcome of interest (with unknown levels of exposure)
This study starts with the identification of cases, then selection of appropriate controls.
Exposure is assessed retrospectively.
Case-control studies can be multi-centre studies, in which cases are recruited and corresponding controls are selected in an identical manner at different study centres.

Migrant populations can be selected for the study.

H: Non-Randomised Controlled Trial

This is the same as a randomised controlled trial, but without randomisation into the treatment or control group.

J: Prospective cohort study

(Synonyms: concurrent study, follow-up study, incidence study longitudinal study, prospective study)
In cohort studies exposure is measured in the present and outcome ascertained in the future. Cohort studies sample from groups of people with different levels of exposure (but unknown or unmeasured outcome). The sample for a cohort study is not always selected to represent the distribution within the whole population; it may be weighted to maximize heterogeneity of exposure.
A defined population (the cohort) is identified that consists of exposed and unexposed (to the exposure of interest) subjects. Exposure is assessed and then disease incidence (or other outcomes) is ascertained during the (prospective) follow-up period.

Single centre and multi-centre studies are possible.

K: Nested case-control study

This is a case-control study where cases and controls are drawn from the population of a prospective cohort study. The cases arising in the cohort become the cases and a sample of unaffected subjects from the cohort become the controls. Exposure is characterised prior to outcome being known.

Single centre and multi-centre studies are possible.
Migrant population may be included.

L: Retrospective cohort study

(Synonym: historical cohort study, non-concurrent prospective study, prospective study in retrospect)
A cohort study conducted by reconstructing data about persons at a time or times in the past. Uses existing records about the exposure in the past and relates this to current or past (but after exposure occurred) outcome status.

Single centre and multi-centre studies are possible.

M: Case-cohort study

This is a method of sampling from an assembled epidemiological cohort study or a (clinical) trial. A random sample of the cohort (sub-cohort) is used as a comparison for all cases that occur in the cohort. This design is used when the assessment of covariates is too expensive to collect on all study subjects.

Single centre and multi-centre studies are possible.

N: Time series with multiple measurements

This is an observational study that repeatedly measures a certain factor in a population as a means of epidemiological surveillance. Time series can also be used to monitor the effects of an intervention.

P: Case only study with retrospective exposure measurement

Case-only studies can examine the association between an exposure and a genotype among case subjects only. Controls are not used in the analysis. However, the case-only study is built upon a classic case-control study then the design so it is a case only study with retrospective exposure measurement.

Q: Case only study with prospective exposure measurement

Case-only studies can examine the association between an exposure and a genotype among case subjects only. Controls are not used in the analysis. However, the case-only study is built upon a nested case-control study then the design will be a case only study with prospective exposure measurement.

Appendix L

Fields for data extraction

Case series

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers

Cross-sectional study

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Subjects	Region/country
	Ethnicity
	Gender
	Age
Sampling	Recruitment procedure
	Inclusion criteria
	Exclusion criteria
	Final sample size
Dietary exposure	Type of exposure (pattern, group, supplement)
	Assessment method
	Details
Laboratory measurements (biomarkers)	
	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Anthropometry	Details
Physical activity	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
Statistical analysis	Type of analysis
	Power estimation
Results	Exposure
	Quantiles / categories / continuous
	No. of quantiles/categories
	Range of intake
	Unadjusted B
	95% CI
	Unadjusted r
	95% CI
	Unadjusted r^2
	p value
	Adjusted for
	Adjusted B
	95% CI
	Adjusted r
	95% CI
	r^2

p value

Randomised controlled trial

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Design	Design type (factorial/crossover)
	Randomisation
	Blinding
Subjects	Region/country
	Ethnicity
	Gender
	Age
Sampling	Recruitment procedure
	Inclusion criteria
	Exclusion criteria
	Final sample size
Intervention	Type (supplement/food)
	Method (Advice/food given)
	Length of time
	No of groups
	Details
Dietary exposure	Type of exposure (pattern, group, supplement)
	Assessment method
	Details
Laboratory measurements (biomarkers)	
	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Anthropometry	Details
Physical activity	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
Adverse effects	
Statistical analysis	Type of analysis
	Power estimation
Results	Control exposure
	Intervention exposure
	Difference in outcome
	RR
	95% CI
	p value

Group RCT

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Design	Design type (factorial/crossover)
	Randomisation
	Blinding
Subjects	Region/country
	Ethnicity
	Gender
	Age
Sampling	Recruitment procedure
	Inclusion criteria
	Exclusion criteria
	Final sample size
Intervention	Type (supplement/food)
	Method (Advice/food given)
	Length of time
	No of groups
	Details
Dietary exposure	Type of exposure (pattern/ group/supplement)
	Assessment method
	Details
Laboratory measurements (biomarkers)	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Anthropometry	Details
Physical activity	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
Adverse effects	
Statistical analysis	Type of analysis
	Power estimation
Results	Control exposure
	Intervention exposure
	Difference in outcome
	RR
	95% CI
	p value

Uncontrolled trial

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Design	Design type
	Blinding
	Details
Subjects	Region/country
	Ethnicity
	Gender
	Age
Sampling	Recruitment procedure
	Inclusion criteria
	Exclusion criteria
	Final sample size
Intervention	Type (supplement/food)
	Method (Advice/food given)
	Length of time
	Details
Dietary exposure	Type of exposure (pattern, group, supplement)
	Assessment method
	Details
Laboratory measurements (biomarkers)	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Anthropometry	Details
Physical activity	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
Adverse effects	
Statistical analysis	Type of analysis
	Power estimation
Results	Exposure
	Outcome before
	Outcome after
	Delta
	95% CI
	p value

Ecologic study

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Design	Number of populations
	Migration study?
Exposure data	Type (pattern/group etc)
	Source
	No of populations
	Reference time period
Anthropometry	Details
Physical activity	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
Statistical analysis	Type of analysis
Results	Exposure
	Quantiles / categories / continuous
	No. of quantiles/categories
	Range of intake
	Unadjusted
	B
	95% CI
	r
	95% CI
	r^2
	p value
	Adjusted for
	Adjusted B
	95% CI
	Adjusted r
	95% CI
	r^2
	p value

Case control study

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Subjects	Region/country
	Ethnicity
	Gender
	Age
Sampling	Recruitment procedure
	Matching
	Source population - cases
	Source population - controls
	Inclusion criteria - cases
	Inclusion criteria - controls
	Exclusion criteria - cases
	Exclusion criteria - controls
	Response rate - cases
	Response rate - controls
	Case-control ratio
	Total number of cases
	Total number of controls
Dietary exposure	Type of exposure (pattern, group, supplement)
	Assessment method
	Details
Laboratory measurements (biomarkers)	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Anthropometry	Details
Physical activity	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Outcome	Type (e.g. cancer incidence/cancer death)
	Confirmation of cases
Statistical analysis	Type of analysis
	Power estimation
Results	Exposure
	Range of intake
	Quantiles or categories
	No. of quantiles/categories
	Levels of exposure
	Interval of measured levels
	Midpoint (level or percentile)
	Number of cases per exposure category
	Number of non-cases per exposure category

Sum of cases and non-cases
Stratified (yes/no)
Stratified groups
Unadjusted OR
95% CI
p value
Adjustment made for measurement error in exposure variable?
Number of variables controlled for in minimally adjusted analysis
Adjusted for
Adjusted OR
95% CI
Adjusted p value
Number of variables controlled for in maximally adjusted analysis
Adjusted for
Adjusted OR
95% CI
Adjusted p value

Non-randomised controlled trial

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Design	Blinding
	Design type (factorial/crossover)
	Intervention allocation procedure
	Details
Subjects	Region/country
	Ethnicity
	Gender
	Age
Sampling	Recruitment procedure
	Inclusion criteria
	Exclusion criteria
	Final sample size
Intervention	Type
	Method
	Length of time
	No of groups
	Details
Dietary exposure	Type of exposure (pattern, group, supplement)
	Assessment method
	Details
Laboratory measurements (biomarkers)	
	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Anthropometry	Assessment method
	Details
Physical activity	Assessment method
	Details
	Variable (summary score, energy expenditure)
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
Adverse effects	
Statistical analysis	Type of analysis
	Power estimation
Results	Control exposure
	Intervention exposure
	Difference in outcome
	RR
	95% CI

p value

Prospective cohort

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Subjects	Region/country
	Ethnicity
	Gender
	Age
Sampling	Recruitment procedure
	Inclusion criteria
	Exclusion criteria
	Response rate
	Size of cohort
	Length of follow-up
	Loss to follow-up
	Total number of cases
Dietary exposure	Type of exposure (pattern, group, supplement)
	Assessment method
	Details
Laboratory measurements (biomarkers)	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Anthropometry	Details
Physical activity	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
	Early outcome events treated separately?
Statistical analysis	Type of analysis
	Power estimation
Results	Exposure
	Quantiles or categories
	No. of quantiles/categories
	Stratified (yes/no)
	Stratified groups
	Is there a measure of continuous effect?
	Increment
	Range of intake
	Levels of exposure
	Interval of measured levels
	Midpoint (level or percentile)
	Number of cases per exposure category

Number of non-cases per exposure category
Sum of cases and non-cases
Unadjusted
Reference group
Median/range for lowest and highest quantile/category
Unadjusted RR
95% CI
p value for trend
Adjustment made for measurement error in exposure variable?
Number of variables controlled for in minimally adjusted analysis
Adjusted for
Adjusted RR
95% CI
Adjusted p value for trend
Number of variables controlled for in maximally adjusted analysis
Adjusted for
Adjusted RR
95% CI
Adjusted p value for trend

Nested case control study

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Subjects	Region/country
	Ethnicity
	Gender
	Age
	Source of controls (internal/external)
Sampling	Recruitment procedure
	Matching
	Inclusion criteria - cases
	Inclusion criteria - controls
	Exclusion criteria - cases
	Exclusion criteria - controls
	Size of cohort
	Length of follow-up
	Loss to follow-up
	Case-control ratio
	Total number of cases
	Total number of controls
Dietary exposure	Type of exposure (pattern, group, supplement)
	Assessment method
Anthropometry	Details
Physical activity	Details
	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
	Early outcome events treated separately?
Laboratory measurements (biomarkers)	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Statistical analysis	Type of analysis
	Power estimation
Results	Exposure
	Range of intake
	Quantiles or categories
	No. of quantiles/categories
	Levels of exposure
	Interval of measured levels
	Midpoint (level or percentile)

Number of cases per exposure category
Number of non-cases per exposure category
Sum of cases and non-cases
Stratified (yes/no)
Stratified groups
Unadjusted OR
95% CI
p value
Adjustment made for measurement error in exposure variable?
Number of variables controlled for in minimally adjusted analysis
Adjusted for
Adjusted OR
95% CI
Adjusted p value
Number of variables controlled for in maximally adjusted analysis
Adjusted for
Adjusted OR
95% CI
Adjusted p value

Historical cohort

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Subjects	Region/country
	Ethnicity
	Gender
	Age
Sampling	Recruitment procedure
	Inclusion criteria
	Exclusion criteria
	Response rate
	Size of cohort
	Length of follow-up
	Loss to follow-up
	Total number of cases
Dietary exposure	Type of exposure (pattern, group, supplement)
	Assessment method
	Details
Laboratory measurements (biomarkers)	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Anthropometry	Assessment details
Physical activity	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
	Early outcome events treated separately?
Statistical analysis	Type of analysis
	Power estimation
Results	Exposure
	Quantiles or categories
	No. of quantiles/categories
	Stratified (yes/no)
	Stratified groups
	Is there a measure of continuous effect?
	Increment
	Range of intake
	Levels of exposure
	Interval of measured levels
	Midpoint (level or percentile)
	Number of cases per exposure category

Number of non-cases per exposure category
Sum of cases and non-cases
Unadjusted
Reference group
Median/range for lowest and highest quantile/category
Unadjusted RR
95% CI
p value for trend
Adjustment made for measurement error in exposure variable?
Number of variables controlled for in minimally adjusted analysis
Adjusted for
Adjusted RR
95% CI
Adjusted p value for trend
Number of variables controlled for in maximally adjusted analysis
Adjusted for
Adjusted RR
95% CI
Adjusted p value for trend

Case cohort

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Subjects	Region/country
	Ethnicity
	Gender
	Age
Sampling	Recruitment procedure
	Matching
	Inclusion criteria - cases
	Inclusion criteria - controls
	Exclusion criteria - cases
	Exclusion criteria - controls
	Size of cohort
	Length of follow-up
	Loss to follow-up
	Case-control ratio
	Total number of cases
	Total number of controls
	Type of exposure (pattern, group, supplement)
	Assessment method
Dietary exposure	Details
Anthropometry	Details
Physical activity	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Laboratory measurements (biomarkers)	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
	Early outcome events treated separately?
Statistical analysis	Type of analysis
	Power estimation
Results	Exposure
	Range of intake
	Quantiles or categories
	No. of quantiles/categories
	Levels of exposure

Interval of measured levels
Midpoint (level or percentile)
Number of cases per exposure category
Number of non-cases per exposure category
Sum of cases and non-cases
Stratified (yes/no)
Stratified groups
Unadjusted OR
95% CI
p value
Adjustment made for measurement error in exposure variable?
Number of variables controlled for in minimally adjusted analysis
Adjusted for
Adjusted OR
95% CI
Adjusted p value
Number of variables controlled for in maximally adjusted analysis
Adjusted for
Adjusted OR
95% CI
Adjusted p value

Time series with multiple measurements

Study code	
Reference details	Author
	Year
	Title
	Journal
	Volume
	Page numbers
Study centre	Number
	Comparability across study centres
Subjects	Region/country
	Ethnicity
	Gender
	Age
Sampling	Recruitment procedure
	Inclusion criteria
	Exclusion criteria
	Final sample size
Dietary exposure	Type of exposure (pattern, group, supplement)
	Assessment method
	Details
Laboratory measurements (biomarkers)	Details
	Coefficient of variation of assay
	Average years from blood collection to diagnosis
Anthropometry	Details
Physical activity	Assessment details
	Unit/measure of exposure (summary score, energy expenditure)
Outcome	Type (cancer incidence/cancer death)
	Confirmation of cases
Statistical analysis	Type of analysis
	Power estimation
Results	Exposure
	Quantiles / categories / continuous
	No. of quantiles/categories
	Range of intake
	Unadjusted
	B
	95% CI
	r
	95% CI
	r^2
	p value
	Adjusted for
	Adjusted B
	95% CI
	Adjusted r
	95% CI
	r^2

p value

Appendix M

Recommended format for tables

The table should be split in two based on study characteristics (part 1) and results (part 2). Grouped categories for adjustments e.g. reproducibility factors can be used for the final columns to indicate adjustment factors. This format is followed for the outcomes generated by the Access software

A separate table, in two parts as below, should be produced for each study design.

Part 1:

Study identifier	*Author*	*Year*	*Exposure*	*Exposure range*	*Assessment Tool*	*Country*	*Ethnicity of subjects*	*No of subjects analysed*	*Age/Sex of subjects*

Part 2:

Study identifier	*No. cases*	*No. controls*	*No. categories*	*RR/OR*	*Ref group*	*CI*	*P value*	*p value for trend*	*Adjusted for*

Appendix N

Illustration with Stata code of analyses based on quantiles: Taking the mean difference approach

For this we use the example used by Chêne and Thompson extracted from their paper [13] shown in **Table 9** in the main body of this paper. This example shows results from the British Regional Heart Study on the relation between albumin concentration and mortality.
These data were entered into a Stata dataset with corresponding variable names **quantile**, **group**, **c**, **d**, and **n** respectively To estimate mean albumin among individuals who died, we first derive the cumulative proportions, normal deviates and weights. In the following output, commands are shown in bold font.

```
. gen pd=sum(d)/655
. label var pd "Cumulative proportion (d)"
. gen zd=invnorm(pd)
(1 missing value generated)
. label var zd "Normal deviate (d)"

. gen phid=normden(zd)
(1 missing value generated)
. gen wd=(phid^2)/(pd*(1-pd))
(1 missing value generated)
. label var wd "Weight (d)"
```

Following the approach of Chêne and Thompson [13], we now normalise the weights so that their mean is 1.

```
. summ wd
Variable |       Obs        Mean    Std. Dev.       Min        Max
-------------+--------------------------------------------------------
          wd |         5    0.4306309   0.1715616  0.2337325  0.6362461
. gen wdnorm=wd/r(mean)
(1 missing value generated)

. list quantile group c d zd pd phid wdnorm, clean noobs
quantile     group     c    d         zd        pd      phid    wdnorm
       1      < 40  39.5   45  -1.485526  .0687023  .1323465  .6357111
       2  >=40-<42  41.5   81  -.8692091  .1923664  .2734324   1.11751
       3  >=42-<44  43.5  191  -.0401934  .4839695  .3986202  1.477475
       4  >=44-<46  45.5  182   .7122082  .7618321  .3095738  1.226537
       5  >=46-<48  47.5  121   1.612422  .9465649  .1087297  .5427677
       6      >=48     .   35          .         1         .         .
```

To estimate the mean and standard deviation of albumin in individuals who died, we now conduct a weighted regression of **c** on **zd**:

```
. regress c zd [aw=wdnorm]
 (sum of wgt is   5.0000e+00)

------------------------------------------------------------------------------
           c |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          zd |   2.565403   .0916996    27.98   0.000     2.273574    2.857232
       _cons |   43.58541   .0848691   513.56   0.000     43.31532     43.8555
------------------------------------------------------------------------------
```

Mean albumin in individuals who died ($\bar{x}_D$) is therefore estimated by the intercept (43.585), while the standard deviation of albumin in these individuals is estimated by the regression coefficient for **zd** (2.565). Using exactly the same procedure for individuals who did not die. leads to an estimated mean albumin of 44.630 ($\bar{x}_H$), with standard deviation of 2.457

We can now estimate the mean difference and its standard error, by conducting a *t*-test:

```
. ttesti 655 43.585 2.565 7035 44.630 2.457

Two-sample t test with equal variances
         |  Obs       Mean   Std. Err.  Std. Dev.  [95% Conf Interval]
---------+--------------------------------------------------------------
       x |  655     43.585   .1002228      2.565    43.3882    43.7818
       y | 7035      44.63   .0292936      2.457   44.57258   44.68742
---------+--------------------------------------------------------------
combined | 7690   44.54099   .0283194   2.483405   44.48548   44.59651
---------+--------------------------------------------------------------
    diff |          -1.045   .1007555             -1.242508  -.8474917
------------------------------------------------------------------------------
Degrees of freedom: 7688

                    Ho: mean(x) - mean(y) = diff = 0

                        Ha: diff != 0
                           t = -10.3716
                 P > |t| =   0.0000
```

Mean albumin is estimated to be 1.045g/litre lower (standard error 0.101) in individuals who died ($\bar{x}_D - \bar{x}_H = -1.045$, $se_{DIFF} = 0.101$).

To run a "parallel regression", as suggested by Chêne and Thompson [13], we need to "reshape" the data:

```
drop phid phih wd wh
rename pd p1
rename zd z1
rename wdnorm w1
rename ph p0
rename zh z0
rename whnorm w0
```

```
reshape long p w z, i(quantile) j(outcome)
(note: j = 0 1)
Data                               wide   ->   long
-----------------------------------------------------------
Number of obs.                        6   ->      12
Number of variables                  12   ->      10
j variable (2 values)                     ->   outcome
xij variables:
                                  p0 p1   ->   p
                                  w0 w1   ->   w
                                  z0 z1   ->   z
-----------------------------------------------------------

. sort outcome quantile group c
. list outcome quantile group c p z w, noobs clean
outcome  quantile     group     c         p          z         w
      0         1      < 40  39.5  .0201848  -2.049947   .295538
      0         2  >=40-<42  41.5  .1016347  -1.272292   .847835
      0         3  >=42-<44  43.5  .3182658  -.4725537  1.440205
      0         4  >=44-<46  45.5  .6358209   .3473104  1.495457
      0         5  >=46-<48  47.5  .8821606   1.185857  .9209642
      0         6      >=48     .         1          .         .
      1         1      < 40  39.5  .0687023  -1.485526  .6357111
      1         2  >=40-<42  41.5  .1923664  -.8692091   1.11751
      1         3  >=42-<44  43.5  .4839695  -.0401934  1.477474
      1         4  >=44-<46  45.5  .7618321   .7122082  1.226537
      1         5  >=46-<48  47.5  .9465649   1.612422  .5427677
      1         6      >=48     .         1          .         .
```

We can now run a "parallel regression" of *c* on *z*, in which we assume that the slope is the same in individuals with and without disease.

```
. regress c z outcome [aw=w]
(sum of wgt is   1.0000e+01)
------------------------------------------------------------------------------
           c |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           z |   2.511091   .0481448    52.16   0.000     2.397246    2.624935
     outcome |  -1.054906   .0892864   -11.81   0.000    -1.266035   -.8437775
       _cons |   44.63785   .0634492   703.52   0.000     44.48782    44.78789
------------------------------------------------------------------------------
```

The estimated mean difference between individuals with and without disease (and the vertical distance between the parallel lines) is given by the regression coefficient for **outcome** and is equal to $\bar{x}_D - \bar{x}_H = -1.055$. The estimated standard deviation, assumed to be the same in individuals with and without disease, is given by the regression coefficient for **z** and is equal to $\sigma_X = 2.511$. The standard error of $\bar{x}_D - \bar{x}_H$, se_{DIFF}, is estimated by $\sigma_X \sqrt{1/d + 1/h} = 2.511\sqrt{1/655 + 1/7035} = 0.1026$.

Finally, we can estimate the log odds ratio and its standard error using these results. We will choose the results from the parallel regression to do this. Based on **Section 16.2.5.3**, we find that:

$$\log(OR_X) = \frac{\bar{x}_D - \bar{x}_H}{\sigma_X^2} = \frac{-1.055}{2.511^2} = -0.1673, \text{ while}$$

$$se_{\log(OR_X)} = \frac{se_{DIFF}}{\sigma_X^2} = \frac{0.1026}{2.511^2} = 0.0163.$$

Appendix P

Illustration with Stata code of analyses based on quantiles: Taking a logistic regression approach

Chêne and Thompson [13] (Table 4 page 613) estimated the overall mean albumin to be 44.54, with standard deviation 2.486. The following Stata code derives the estimated mean in each group. Note that we have to deal separately with the first and last quantiles.

```
. gen phi=normden(z)
(1 missing value generated)
. gen cumz=norm(z)
(1 missing value generated)
. replace cumz=1 in 6
(1 real change made)
. replace phi=0 in 6
(1 real change made)
. gen m=44.54+2.486*(phi[_n-1]-phi)/(cumz-cumz[_n-1])
(1 missing value generated)
. replace m=44.54+2.486*(-phi)/(cumz) in 1
(1 real change made)

. list quantile group c n z phi cumz m, clean noobs
quantile    group    c    n         z        phi       cumz          m
       1     < 40 39.5  187 -1.971781    .057103   .0243173   38.70226
       2 >=40-<42 41.5  654 -1.229924    .187253   .1093628   40.73553
       3 >=42-<44 43.5 1715 -.4333515   .3631878   .3323797   42.57883
       4 >=44-<46 45.5 2416  .3760335   .3717108    .646554   44.47256
       5 >=46-<48 47.5 1854  1.214106   .1909078   .8876463   46.40433
       6     >=48    .  864         .          0          1   48.76413
```

Having estimated the mean in each group, we can use the total number individuals with and without disease in each quantile to fit a logistic regression model that directly estimates the log odds ratio per unit increase in *X*. The following Stata code does this. Note that this uses the reshaped data, that variable **`freq`** contains the number of individuals in each quantile with and without disease, and that the analysis uses "frequency weights" **`[fw=freq]`** to tell Stata to assume that each line in the dataset represents the number of individuals given by variable **`freq`**.

```
. list outcome quantile group m freq, noobs clean
```

```
    outcome   quantile      group          m   freq
          0          1       < 40   38.70226    142
          0          2   >=40-<42   40.73553    573
          0          3   >=42-<44   42.57883   1524
          0          4   >=44-<46   44.47256   2234
          0          5   >=46-<48   46.40433   1733
          0          6       >=48   48.76413    829
          1          1       < 40   38.70226     45
          1          2   >=40-<42   40.73553     81
          1          3   >=42-<44   42.57883    191
          1          4   >=44-<46   44.47256    182
          1          5   >=46-<48   46.40433    121
          1          6       >=48   48.76413     35
```

```
. logit outcome m [fw=freq]
Logit estimates                           Number of obs   =       7690

------------------------------------------------------------------------------
outcome |      Coef.  Std. Err.      z    P>|z|     [95% Conf Interval]
--------+---------------------------------------------------------------------
      m | -.1699656   .0172556    -9.85   0.000    -.2037859   -.1361453
  _cons |   5.127644   .7558948     6.78   0.000     3.646117    6.60917
------------------------------------------------------------------------------
```

The estimated value of $\log(OR_X)$ is –0.170, with standard error $se_{\log(OR_X)}$. =0.0173. These values are fairly consistent with the values derived by converting the estimated mean difference. We can use the output on the odds ratio scale to see the estimated odds ratio (OR_X) with its 95% confidence interval.

```
. logit, or
------------------------------------------------------------------------------
outcome | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf.
Interval]
--------+---------------------------------------------------------------------
      m |   .8436939   .0145584    -9.85   0.000      .815637
.8727158
------------------------------------------------------------------------------
```

Appendix Q

Illustration with Stata code of analyses based on quantiles: Estimating dose-response slope from reported odds ratios

We use the example of Greenland and Longnecker [14], shown in **Table 10** in the main body of this paper. This example examines the association between alcohol use and breast cancer. The data were entered into a Stata dataset with corresponding variable names **x** (assumed group mean), **N** (total cases and controls in group), **A** (cases in each group), **R** (reported adjusted odds ratio compared to the baseline group) and **v** (variance of the adjusted log odds ratio. The standard error of the adjusted log odds ratio can be derived from the OR and 95% CI (*LCI*, *UCI*) as the mean of log(*OR*/*LCI*)/1.96 and log(*UCI*/*OR*)/1.96).

```
. use greenland_js.dta, clear
. list, clean noobs
    group    x     N     A      R   LCI    UCI       v
        0    0   337   165      1     .      .       .
        1    2   167    74     .8   .51   1.27   .0542
        2    6   186    90   1.16   .73   1.85   .0563
        3   11   212   122   1.57   .99   2.51   .0563
```

Part 1: We define the other variables needed in the calculations, as on Greenland and Longnecker [14] page 1302:

```
. scalar N0=337
. scalar M1=451
. gen L=log(R)
```

Part 2: We fit cell counts to the interior of the total data table using the fitting algorithm in Greenland and Longnecker [14] Appendix 2 page 1309. The procedure iterates until there is little change in the estimated number of cases (variable **Anew**) in successive iterations:

```
. gen Anew=A
. format Anew %8.2f
. gen Aold=0
. gen c=.
(4 missing values generated)
. gen e=.
(4 missing values generated)
. local matdim=_N-1
. local inc=100
. local i 1
. while `i'<=50&`inc'>0.001 {
  2.   quietly {
  3.   summ Anew in 2/l
  4.   local Atot=r(N)*r(mean)
  5.   local A0=M1-`Atot'
  6.   replace c=(1/Anew)+(1/(N-Anew))
  7.   replace e=L+log(`A0')+log(N-Anew)-log(Anew)-log(N0-`A0') in 2/l
  8.   matrix I=I(`matdim')
```

```
 9.   forvalues j=1/`matdim' {
10.     matrix I[`j',`j']=c[`j'+1]
11.   }
12.   matrix J=J(`matdim',`matdim',c[1])
13.   matrix H=I+J
14.   mkmat e, matrix(temp)
15.   matrix E=temp[2..(`matdim'+1),1]
16.   matrix Anew=syminv(H)*E
17.   svmat Anew, name(anew)
18.   gen anewnew=anew1[_n-1]
19.   replace anewnew=0 in 1
20.   replace Aold=Anew
21.   replace Anew=Anew+anewnew
22.   }
23.   display _n "Iteration `i'"
24.   list Anew, clean
25.   qui summ anewnew
26.   local inc=r(mean)*r(N)
27.   drop anew1 anewnew
28.   local i=`i'+1
29. }

Iteration 1
        Anew
  1.   165.00
  2.    70.31
  3.    95.49
  4.   124.69

Iteration 2
        Anew
  1.   165.00
  2.    70.33
  3.    95.49
  4.   124.68

Iteration 3
        Anew
  1.   165.00
  2.    70.33
  3.    95.49
  4.   124.68

. local i=`i'-1

. quietly summ Anew in 2/l
. local newtot=r(N)*r(mean)
. replace Anew=M1-`newtot' in 1
(1 real change made)
. gen Bnew=N-Anew
. format Bnew %8.2f
```

Variables Anew and Bnew contain the fitted numbers of cases and controls in each group:

```
. list group x Anew Bnew N, clean noobs
```

```
 group    x     Anew     Bnew     N
     0    0   160.51   176.49   337
     1    2    70.33    96.67   167
     2    6    95.49    90.51   186
     3   11   124.68    87.32   212
```

Part 3: Estimate the asymptotic correlations between the log ORs in the different groups (Greenland and Longnecker [14] pages 1302-1303). In the output below, variable **s** gives the crude estimate of the variance of the log OR in each group, and matrix **r1** gives the estimated correlations between the log ORs.

```
. local A0=Anew[1]
. local B0=Bnew[1]
. drop in 1
(1 observation deleted)
. gen s=sqrt((1/Anew)+(1/Bnew)+(1/`A0')+(1/`B0'))
. list group x s, clean
      group    x          s
  1.      1    2   .1909433
  2.      2    6   .1828031
  3.      3   11   .1771121

. replace s=1/s
(3 real changes made)
. mkmat s
. gen f=(1/`A0')+(1/`B0')
. mkmat f
. matrix f=diag(f)
. matrix r1=f*s*s'
. matrix list r1

symmetric r1[3,3]
           r1         r2         r3
r1  .32628713
r2  .34081666  .35599319
r3  .35176767  .36743185  .37923806
```

Part 4: Estimate the asymptotic covariance of the log ORs in the different groups (Greenland and Longnecker [14] pages 1302-1303). In the output below, matrix c is the asymptotic variance-covariance matrix for the log ORs.

```
. matrix rxzm = r1-diag(vecdiag(r1))+I(`matdim')
. gen vr1 = sqrt(v)
. mkmat vr1
. matrix vr=diag(vr1)
. matrix c = vr*rxzm*vr
. matrix list c
symmetric c[3,3]
           r1         r2         r3
r1      .0542
r2  .01882672      .0563
r3  .01943165  .02068641      .0563
```

Part 5: Finally, we estimate the log OR per group by weighted least squares for correlated outcomes

```
. matrix ci = syminv(c)
. mkmat x
. matrix vb = syminv(x'*ci*x)
. mkmat L
. matrix b = vb*x'*ci*L

. scalar slope=b[1,1]
. scalar var_slope=vb[1,1]
. scalar se_slope=sqrt(var_slope)
. scalar list slope var_slope se_slope
     slope =  .04543022
 var_slope =  .00042682
  se_slope =  .02065966
```

Appendix R

List of files required by WCRF International

Each of these files should be sent to the Review Coordinator and the Secretariat (s.heggie@wcrf.org). The deadlines for each individual SLR are available in the contracts.

1. Protocol
2. EndNote file 1. See **Section 13.11.2** for details.
3 Data extraction sheets/database (before any data is entered)
4 EndNote file 2. See **Section 13.11.2** for details.
5 EndNote file 3. See **Section 13.11.2** for details.
6 Table to identify papers from the same study.
7 Completed data extraction sheets/database.
8 Original sources of all references
9 Completed SLR report and SLR summary.
10 Final update of the SLR report in 2006.

Appendix S

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END