Continuous update of the WCRF-AICR report on diet and cancer

Protocol: Pancreatic Cancer

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WCRF/AICR has been the global leader in elucidating the relationship between food, nutrition, physical activity and cancer. The first and second expert reports represent the most extensive analysis of the existing science on the subject to date. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update project, in collaboration with Imperial College London (ICL).

The Continuous Update will provide the scientific community with a comprehensive and up to date depiction of scientific developments on the relationship between diet, physical activity, obesity and cancer. It will also provide an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising WCRF/AICR's cancer prevention recommendations based on the 2007 Second Expert Report.

WCRF/AICR has convened a panel of experts (the Continuous Update Panel) consisting of leading scientists in the field of diet, physical activity, obesity and cancer who will consider the evidence produced by the systematic literature review and meta-analysis, and will consider the results and draw conclusions before making recommendations.

In the same way that the Second Expert Report was informed by a process of systematic literature reviews (SLRs), the continuous update will systematically review all of the science as it is published. The ongoing systematic literature review will be conducted by a team of scientists at ICL in liaison with the SLR centres where possible.

The current protocol for the continuous update of pancreatic cancer should ensure consistency of approach to the evidence, common approach to the analysis and format for displaying the evidence used in the literature reviews[1] for the Second Expert Report.

The starting point for this protocol are:

- The convention for conducting systematic reviews[1] developed by WCRF International for the Second Expert Report.
- The protocol developed by the SLR group on pancreatic cancer for the Second Expert Report (Leeds) [2].

The peer-reviewed protocol will represent the agreed plan for the Continuous Update. Should departure from the agreed plan be considered necessary at a later stage, this must be agreed by the Continuous Update Panel (CUP) and the reasons documented.

Background.

In the judgment of the Panel of the **WCRF-AICR Second Expert Report** [3], the factors listed below modify the risk of pancreatic cancer. Judgments are graded according to the strength of the evidence.

PANCREATIC CANCER		
	DECREASES RISK	INCREASES RISK
Convincing	No factor identified	Body fatness
Probable	Foods containing folate	Abdominal fatness Adult attained height
Limited –suggestive	Fruits Physical activity	Red meat
Limited –no conclusion	Cereals (grains) and their products; dietary fibre; vegetables; pulses (legumes); soya and soya products; processed meat; poultry, fish ; eggs; milk and dairy products; total fat; butter; plant oils; margarine,; cholesterol; sugar (sucrose); black tea; green tea; alcohol; nitrate and nitrite; total carbohydrate; folic acid supplements; vitamin C; vegetarianism; age at menarche; lactation; energy intake	
Substantial effect on risk unlikely	Coffee	

1. Research question

The research topic is:

The associations between food, nutrition and physical activity and the risk of pancreatic cancer.

2. Review team

Name	Current position at IC	Role within team
Teresa Norat	Principal Research Fellow	Principal investigator
Rui Vieira	Data manager	Responsible of the data management, the design and architecture of the database

Doris Chan	Research Assistant	Nutritional epidemiologist, supervisor of data entry, analyst
Rosa Lau	Research Assistant	Nutritional epidemiologist, reviewer
To be named	Research Assistant	Nutritional epidemiologist, reviewer

Review coordinator, WCRF: Rachel Thompson

Statistical advisor: Darren Greenwood, senior Research Lecturer, University of Leeds

3. Timeline.

The SLR on pancreatic cancer for the Second Expert Report[2] ended in December 30th 2005. A pre-publication update extended the search to June 30th 2006 for exposures and cancer sites with suggestive, probable, convincing associations with the exposure of interest.

In order to ensure the completeness of the database, the ICL team will repeat the search conducted for the pre-publication update. Therefore, the Continuous Update will include the articles added to Medline from January 1st 2006. The reviewer will verify that there are not duplicities in the database. With that purpose, a module for article search has been implemented in the interface for data entry.

List of tasks and deadlines for the Continuous Update on pancreatic cancer:

Task	Deadline
Start Medline search of relevant articles published between January 2006 and December 2009	1st March, 2010*
Review abstracts and citations identified in initial electronic search. Select papers for complete review	Monthly **
Review relevant papers. Select papers for data extraction	Monthly **
Data extraction	Monthly **
End data extraction	30th August 2010
Start quantitative analysis	1st September 2010
End of quantitative analysis	30th November 2010
Send report to WCRF-AICR	20th December 2010
Transfer Endnote files to WCRF	20th December 2010

*Assuming the research assistant to be named as reviewer starts working at Imperial College in March 2010.
** Until the end of data extraction programmed to be 30th August 2010

4. Search strategy

The search will be conducted in Medline using PubMed as interface. The ICL team will use the search strategy established in the SLR Guidelines with the modifications

implemented by the SLR centre (Leeds)[2] for the 2nd Expert Report[1] . The search will not be limited to "human studies" as it can not be guaranteed that all studies on PubMed have been coded as human. The full search strategy is in Annex 1.

5. Selection of articles

Only articles that match the inclusion criteria (see 5.1) will be updated in the database. Pooled analysis and meta-analysis will be identified in the search, but they will not be included in the database. The results of these studies will be used as support document in the preparation of the report.

5.1 Inclusion criteria

The articles to be included in the review:

- Have to be included in Medline from January 1st 2006 (closure date of the database for the Second Expert Report[1]).
- Have to present results from an epidemiologic study of one of the following types†:
    - Randomized controlled trial
    - Group randomized controlled trial (Community trial)
    - Prospective cohort study
    - Nested case-control study
    - Case-cohort study
    - Historical cohort study
- Must have as outcome of interest pancreatic cancer incidence or mortality.
- Have to present results on the relevant exposures
- Published in English language†††*

† *The selection of these study designs is based on the short life expectancy of pancreatic cancer cases after diagnosis and the potential bias of case-control studies. Filters for study design will not be implemented in the search strategy.*

* *The extent of the update has to be adequate to time and resources. For this reason the proposal is to give priority to articles published in English language. Most, if not all, high quality studies will be published in peer-reviewed journals in English language and referenced in the Medline database.*

5.2 Exclusion criteria

The articles to be excluded from the review:

- Are out of the research topic

- Do not report measure of association between the exposure and the risk of pancreatic cancer
- The measure of the relationship between exposure and outcome is only the mean difference of exposure
- Are supplement to the main manuscript (e.g. Authors' Reply).
- Are published on-line only as "Epub ahead of print" or "In Press". The data of these articles will be extracted after the definitive version is released.
- Are not in English language

6. Exposures

The Continuous Update will use the labels and exposure codes listed in the SLR Guidelines[1] for the Second Expert Report.

During the SLR for the Second Expert Report, the SLR centres assigned subcodes for exposures that were more detailed than the WCRF list of exposures. The codification used was not the same in all centres. These differences did not affect the quality of the review in each centre for the Second Expert Report. However, the codes and labels of the sub-exposures were recoded to ensure the identity of sub-exposure codes and labels in the MySQL database generated at Imperial College from the ACCESS databases for each cancer site generated for the SLRs.

The updated list of sub-exposures and codes is in Annex 2. The codes defined in the SLR Guidelines remained the same. The exposures listed represent the minimum list of exposures to be examined. These exposures are programmed in the interface for data entry to facilitate this process.

6.1 Biomarkers of exposure

In the SLR for the Second Expert Report[1], biomarkers of exposure were included under the heading and with the code of the corresponding exposure. Some review centres decided to include only biomarkers for which there was some evidence on reliability or validity, while other centres included in the database results on all the biomarkers retrieved in the search, independently of their validity. During the process of evaluation of the evidence, the Panel of Experts took in consideration the validity of the reported biomarkers.

The SLR centre on prostate cancer (Bristol) prepared a list of biomarkers to be included and excluded, based on data of studies on validity and repeatability of the biomarkers. The list of included and excluded biomarkers and the reasons for exclusion prepared by the SLR Bristol are in Annex 3.

Study results on all biomarkers of diet will be extracted in the database of the Continuous Update, including "new" biomarkers whose validity has not yet been fully proved. For the preparation of reports and meta-analysis, the Continuous Update on pancreatic cancer will use the same guidelines for exclusion of biomarkers proposed by the SLR Bristol (Annex 3).

The excluded biomarkers are:

Vit D: 1.25 $(OH)_2D$, Alkaline phosphatase activity (serum)

Iron (serum, hair, nails)

Copper (plasma, serum, hair)

Glutathione peroxidase (plasma, serum, erythrocytes, blood)

Zinc, metallotein levels (any)

Lipids: total fats (any)

Cholesterol, LDL (any)

Lipoprotein levels (serum)

Monounsaturated fatty acids (oleic acid) (plasma, adipose tissue)

Saturated fatty acids (palmitic acid, stearic acids) (plasma)

Protein (any)

Biomarkers of effect of exposure and biomarkers of cancer are not included in this review.

7. Outcome

The outcome of interest is pancreatic cancer encompassing incidence and mortality. Pancreatic cancer has one major histological morphology, adenocarcinoma that represents more than 95% of all diagnoses[4]. This nearly always represents a tumour located in the ductal exocrine cells of the pancreas and thus almost all epidemiological studies have either only considered this single entity or, under the general heading of "pancreatic cancer" have considered this along with a very small proportion of variant types. Islet cell (endocrine) tumours are much rarer, representing less than 5% of total cases. Hardly any studies have been conducted specifically on endocrine pancreatic tumours [2].

Most pancreas cancer is located at the 'head' of the pancreas with varying proportions, usually less than 10%, located in the body or tail regions[4]. Although this topology is important for clinical management, epidemiology studies hardly ever discriminate risks in relation to tumour location. However, whenever studies report on pancreatic cancer at specific locations, the information will be extracted in the database.

Pancreatic cancer is also nearly always diagnosed at a very advanced stage and survival rates beyond a few months are extremely low. As a result, there are virtually no differences between cancer incidence and cancer mortality rates. For cohort studies, this means that there is no particular advantage in distinguishing between incidence and mortality as outcomes (assuming the information concerning both registrations and deaths is equally valid and reliable). For that reason, study results on incidence and mortality will be presented and analyzed altogether. When provided by the papers, the proportion of incident and fatal cases in the study will be noted in the database.

8. Search databases

Only the Medline database will be initially searched. Data provided from the Second Expert Report[1] indicates that 95% of the articles included in the review have been retrieved from the Medline database. However, in the SLR of pancreatic cancer, 168 (77%) out of 219 articles identified electronically and included in the review were identified through PubMed and another 30 articles were identified through hand searching.

9. Hand searching for cited references

For feasibility reasons, it was decided that journals will not be hand searched in the Continuous Update. In addition, most articles included in the SLR of breast, colorectal and prostate cancer were identified through PubMed.
However, due to the relatively high number of articles (30) identified by hand searching in review articles during the SLR of pancreatic cancer, the ICL team will check the reference list of all review articles identified in the search. This will allow identifying potentially missing articles published after 2005. If there are articles missed by PubMed, the Imperial College team will consider other strategies, such as modifying the search strategy and looking into other databases.

10. Selecting articles

The results of the PubMed searches will be downloaded into a Reference Manager Database monthly.

Initially a further electronic search will be undertaken within Reference Manager to identify and remove irrelevant records. This will be achieved by generating a list of stop words. The list of stop words was developed and tested by the SLR Leeds during the preparation of the WCRF-AICR 2nd expert report on pancreatic cancer. The list of stop words (Annex 4) was compiled from terms that describe surgical, diagnostic or oncology procedures relevant to pancreatic cancer. Also included in the stop word are terms referring to animal studies and in vitro studies. These terms will be used to identify non human studies. All references that include any of these stop words in the title of the citation will be excluded and stored in a separate Reference Manager database.

In a second step the remaining articles downloaded from PubMed will be inspected by a reviewer, who will indicate which articles are potentially relevant, articles to be excluded and articles that cannot be classified upon reading the title and abstracts.

The complete article of potentially relevant references and of references that cannot be excluded upon reading the title and abstracts will be retrieved. A second assessment will be done after review of the complete papers.

The assessment of papers will be checked by a second reviewer. It is envisaged that 10% of the non relevant articles will be randomly selected and double-checked.

11. Labelling of references

For consistency, the ICL team will use the same labelling of articles employed during the SLR process for the Second Expert Report[1]: the unique identifier for an article

will be constructed using a 3-letter code to represent the cancer site (e.g. PAN for pancreatic cancer), followed by a 5-digit number that will be allocated in sequence.

12. Reference Manager Files

Reference Manager files containing the references retrieved on the initial search are generated in the Continuous Update. The variables contained in the Reference manager files are those generated using the filter Medline for importing data. Additionally, customized fields will be implemented.

Three Reference Manager files will be created:

1) A file containing the results of the initial search. The study identifier should be entered under a customized field titled 'label'. Another customised field named 'inclusion' 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.
2) A file containing the excluded papers. The study identifier should be entered under a customized field titled 'label'. Another customised field named 'reasons' should include the reason for exclusion for each paper. This file will be named Pancreas excluded.
3) A file containing the included papers. The study identifier should be entered under a customized field titled 'label'. Another customised field named "study design" should include a letter (A-Q) representing the study design of each paper, allocated using the study design algorithm in Annex 5. This file will be named Pancreas included.

The Reference Management databases will be converted to EndNote and sent once per year to the WCRF Secretariat.

13. Data extraction

The ICL team will update the database using the interface created at Imperial College for this purpose. The interface allows the update of all the information included in the Access databases generated during the SLRs for the Second Expert Report. This includes information on study design, name of cohort study, characteristics of study population, methods of exposure assessment, study results, analytical methods, adjustment variables, matching variables, and whether methods for correction of measurement error were used.

The study design algorithm devised for use of the SLR centres for the Second Expert Report will be used to allocate study designs to papers (Annex 5). In some cases it will be appropriate to assign more than one design to a particular paper (e.g. analyses in the entire cohort and nested case-control).

13.1 Quality control

Data extraction will not be performed in duplicate. This would have required important resources. Instead, 10% of the data extracted throughout the continuous update will be checked by a second reviewer at Imperial College.

The extracted data will be also checked automatically by the data manager, who will prepare monthly reports of the errors identified for its correction by the reviewer. Examples of automatic checks are checking if the confidence interval contains the effect estimate and if it is symmetrical, checking that the sum of cases and non case individuals by categories of exposure add up to the total number of cases and non case individuals.

13.2 Choice of Result

There could be several results for a particular exposure within a study according to the number of models presented in the article (unadjusted, minimally, maximally) and the number of subgroup or stratified analyses conducted (by gender, race, outcome type, etc.)

The results obtained using all the models reported in the paper and all the subgroup or stratified analysis should be extracted by the reviewer.

The reviewer should label the results as not adjusted, minimally adjusted, intermediately adjusted and maximally adjusted. In addition, the IC reviewer should indicate results obtained with a "best model" for inclusion in reports. This serves the dual purpose of marking that result to be exported to the reports and also flagging it as the best model for potential inclusion in a meta-analysis.

The identification of "best model" will be undertaken firstly on the appropriateness of adjustment. The most adjusted one will be considered to be the best model. Exception to this criterion will be "mechanistic" models, adjusting for variables likely to be in the causal pathway. When such results (over adjusted results) are reported, the most adjusted results that are not over adjusted will be extracted. Smoking is the main lifestyle risk factor identified so far and the evidence on the association of body fatness with pancreatic cancer is considered convincing [2] . The "best model" has to be controlled for confounding by smoking and body fatness. Models adjusted only for age, gender and energy intake are considered "intermediately adjusted models". In the case that there is no "best model", the maximally adjusted model reported in the paper will be used in the meta-analysis and sensitivity tests will be conducted excluding these models from the analysis.

Potential risk factors of pancreatic cancer are:

Sex
Age
Race
Energy intake
Height
Socioeconomic status
Physical activity
Body mass index

Tobacco smoking and environmental tobacco exposure
Personal history of diabetes
Chronic pancreatitis
Family history of pancreatic cancer in a parent, sibling or child.

Sometimes, potential risk factors are not kept in the model because their inclusion does not modify the risk estimates. If this is specified in the article text, this model should also be considered the "best model".

Other subsidiary criteria to consider for identifying the 'best model' for meta-analysis are the number of cases (highest), and in certain circumstances the completeness of the data (e.g. where quantile ranges are provided over where missing).

13.3 Effect modification and interaction

The ICL team should report whether interaction or heterogeneity tests were conducted and extract the results of these tests.

In the SLR for the 2nd Expert Report, the results of interaction analyses were extracted using the same module of data entry by creating new "double entry" sub-exposures (e.g. alcohol and folate intake as a single sub-exposure). The results of stratified analyses following a significant interaction test were included in the database as subgroup analyses.

To avoid the creation of new "double entry" exposures in the Continuous Update, the ICL team has developed a new module for data entry of results of interaction analysis. The module 'interaction' allows the use of existing headings of single exposures during data entry that will be automatically linked in the database. The reviewer will not need to create new sub-exposures codes. The results of stratified analyses will be extracted using the module "Subgroup analysis", similarly to what has been done in the SLR for the Second Report.

13.4 Gene-nutrient interaction

No attempt was made to critically appraise or analyse the studies that reported gene-nutrient interactions in the Second Expert Report. The results of these studies were described in the narrative review under the relevant exposures.

In the Continuous Update, the information on gene-nutrient interactions in the articles retrieved will be extracted in the database using the module "Interaction".

13.5 Multiple articles

The data of all relevant papers should be extracted, even if there is more than one paper from the same study reporting the same results. The most appropriate data set for analyses will be selected to ensure there is no duplication of data from the same study. Multiple reports from the same study will be identified using first the study name but also geographic location, recruitment dates and participant characteristics. The criteria for selecting the best data set for meta-analyses are listed under Section 14.2 .

If needed, the ICL team should contact the authors for clarification. If the matter remains unresolved the review coordinator of the Continuous Update will discuss the issue with the WCRF Secretariat and the CUP, if necessary.

14. Data analysis

Meta-analytic and narrative aspects of the data analysis will complement each other. The meta-analyses will examine the evidence for dose-response effects.

Non-linear dose-response meta-analysis will be conducted if the data suggest a non-linear shape.

STATA version 11.0 (College Station, TX, USA) will be used to analyse the data.

14.1 When to do a meta-analysis

A meta-analysis for a particular exposure and outcome will be conducted when 3 or more trials or cohort studies have been published in the period reviewed, and if the total number of studies in the database totalise to more than 3 trials or 5 cohort studies with enough information to conduct a dose-response meta-analysis or providing data to calculate the required information.

The study results extracted during the SLR and the studies identified in the Continuous Update will be included in the meta-analysis. Special care will be taken to avoid including the results of the same study more than once (see 14.2).

14.2 Selection of results for meta-analyses and reporting.

The following guidelines for inclusion of studies in the meta-analysis will be applied:

1. Where more than one paper was published from the same study, the paper using the larger number of cases for analysis will be selected. This is often the most recent paper.

2. Where the same exposure was analysed in more than one way with different levels of adjustment, the best model will be the one with the most appropriate adjustment for confounding. This is often the maximally adjusted analysis (except mechanistic models) (see 13.2).

3. Where an exposure was presented for all study participants, and by subgroup, the analysis of all study participants will be used.

4. Where an exposure was presented only by subgroup, the subgroups will be pooled first and then included in the meta-analysis. This is essentially equivalent to including the overall estimate and will provide a better estimate of heterogeneity across studies.

5. Where a paper presented results from two separate studies and included a pooled analysis of different studies (e.g. the Nurses Health Study and the Health Professionals Follow-up Study), then the studies will be included separately and the pooled result will not be included. This maintains the independence of observations included and permits to look at heterogeneity across study results. The results of the pooled analysis will be mentioned in the narrative review.

14.3 Statistical Methods

To enable comparison of different studies, the relative risk for a linear dose-response across the exposure will be estimated. This will be done using the methods of Greenland & Longnecker[5] (the pool last approach) and Chêne and Thompson[6]. The same methods were used to do the linear dose-response meta-analyses in the SLRs for the Second Expert Report. The advantage of the method proposed by Greenland & Longnecker[5] is that it provides dose-response estimates that take account of the correlation induced by using the same reference group. The relative risk estimates for each unit of increase of the exposure will be derived with the method of DerSimonian and Laird[7] using the assumption of a random effects model that incorporates between-study variability. The unit of increment will be kept as the same unit used in the SLR. We will use the "best" (most adjusted risk estimate) from each study.

14.4 Derivation of data required for meta-analyses.

The information required for data to be usable for meta-analysis, for each type of result is:

Dose-response data (regression coefficients)

-Estimated odds, risk, or hazard ratio per unit increase in exposure with confidence interval (or standard error of log ratio or p value)
-Unit of measurement

Quantile-based or category data

-No. of cases and non cases (or person-time denominator for cohort studies) in each group; or total number of cases and non cases (or study size) plus explicitly defined equal-sized groups (for quantile-based data)
-Estimated odds, risk, or hazard ratios with confidence intervals (or standard error of log ratio or p value) compared with the baseline group, for each non baseline group.
-Range, mean, or median of exposure in each group
-Unit of measurement

The data needed to estimate the dose-response associations are often incompletely reported, which may result in exclusion of results from meta-analyses. Failure to include all available evidence will reduce precision of summary estimates and may also lead to bias if propensity to report results in sufficient detail is associated with the magnitude and/or direction of associations.

A number of approaches have to be taken in order to derive the information required. These will be applied in the following order of priority:

1. Where the exposure was measured as a continuous variable, and the dose-response slope given, then this will be used directly.

2. Where the slope (and its standard error or confidence interval) was not given in the text, these will be estimated applying the methods of Greenland & Longnecker[5] and using the mean exposure in each category given in the paper. No additional assumptions are required.

3. Greenland & Longnecker's method[5] requires the total numbers of cases and controls to be known, and starting estimates for the number of cases in each category. Where these were not presented, values will be estimated based on the categorisation into quantiles or on the information contained in each category estimated from the width of the confidence intervals.

4. Mean exposure for each category is rarely given, so the methods of Chene & Thompson[6] will be used to estimate the means. This approach made the assumption of a normally distributed exposure, or a distribution that could be transformed to normality.

5. Where it is not possible to derive mean exposures in each category, the midpoints will be used instead as a basis for the Greenland & Longnecker[5] method.

6. Where no confidence intervals were given in the paper, but approximate standard errors can be obtained from the cell counts, these will be used to derive approximate confidence intervals for the adjusted relative risks. Greenland & Longnecker's method[5] will then be applied using means given in the paper or estimated assuming normality, based on these derived confidence intervals.

7. Where there is a category representing a zero exposure, such as "non-drinker" or "not consumed", this will be treated separately for the purposes of estimating means in each category. Such "never" categories often lead to a peak in the distribution at zero, and the data will not follow neither a normal nor a lognormal distribution. By using a mean of zero for the "never" category and estimating means for the other categories separately, distributional assumptions could be made and more studies could be included in the meta-analysis.

8. The decision whether to log-transform will be made on an exposure by exposure basis. This will based on the SLR on pancreatic cancer (Leeds)[2] for the Second Expert Report and on the estimated means derived for use in the Greenland & Longnecker's method[5] for deriving dose-response estimates.

14.4 Missing values.

A recent review showed that only 64% of the results of cohort studies provide enough data to be included in dose-response meta-analysis[8]. Moreover, results that showed evidence of an association were more likely to be usable in dose-response meta-analysis than results that found no such evidence. Insufficient detail in reporting of results of observational studies can lead to exclusion of these results from meta-analyses and is an important threat to the validity of systematic reviews of such research.

The most frequently occurring problems in reporting and the suggested solutions to make results usable in a dose-response meta-analysis are [8] :

Type of data	Problem	Assumptions
Dose-response data	Serving size is not quantified or ranges are missing, but group descriptions are given	Use serving size recommended in SLR Prostate (Annex 6)
	Standard error missing	The p value (either exact or the upper bound) is used to estimate the standard error
Quantile-based data	Numbers of controls (or the denominator in cohort studies) are missing	Group sizes are assumed to be approximately equal
	Odds ratio is missing	Unadjusted odds ratios are calculated by using numbers of cases and controls in each group
	Confidence interval is missing	Standard error and hence confidence interval were calculated from raw numbers (although doing so may result in a somewhat smaller standard error than would be obtained in an adjusted analysis)
	Group means are missing	This information may be estimated by using the method of Chene and Thompson [6] with a normal or lognormal distribution, as appropriate, or by taking midpoints (scaled in unbounded groups according to group numbers) if the number of groups is too small to calculate a distribution (see 14.3)
Category data	Numbers of cases and controls (or the denominator in cohort studies) is missing	These numbers may be inferred based on numbers of cases and the reported odds ratio (proportions will be correct unless adjustment for confounding factors considerably alter the crude odds ratios)

14. 5 Analysis of heterogeneity and potential bias

Heterogeneity between studies will be assessed with the I^2 statistic as a measure of the proportion of total variation in estimates that is due to heterogeneity, where I^2 values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity [9].

Meta-regression will be performed to investigate sources of heterogeneity if there are enough studies to do it. The variables that will be examined as sources of heterogeneity are geographic area (North-America –Non black population, North-America –Black population, Europe, Asia, Other), gender, outcome (proportion of fatal cases), and if possible number of categories used in the adjustment for smoking

Length of follow-up is a concern in prospective studies of cancer due to the long latency of the disease. As most diagnoses of pancreatic cancer are made at advanced stages[4], it is likely that there is a fairly long pre-diagnostic period when malignant disease is present. Pancreatic cancer has few early symptoms and most individuals should not have experienced changes in patterns of physical activity or diet due to cancer-related symptoms. Biomarker level might be modified during asymptomatic pre-clinical disease. If the number of cohort studies in the database allows it, we will investigate the effect of length of follow-up on heterogeneity of study results.

Other variables that may be considered as source of heterogeneity are characterisation of the exposure (FFQ, recall, diary, anthropometry etc.), exposure range (including correction for measurement error, length of intervention) and age at recruitment.

The interpretation of the exploration of heterogeneity should be cautious. 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 between the study characteristics and the size of associations.

Small study bias (e.g. publication bias) was explored through visual examination of funnel plots and through Egger's test.

We will do influence-analyses where each individual study will be omitted in turn to investigate the sensitivity of the pooled estimates to inclusion or exclusion of particular studies [10] .

14.6 Non linear trends in meta-analysis.

Non-linear meta-analysis will be applied when the data suggest that the dose-response curve is non-linear and when detecting a threshold of exposure might be of interest.

Considering a non-linear dose-response curve using the Greenland and Longnecker's pool-last approach is not possible[6] but it is possible if means and covariances of the individual studies are pooled before estimating the slope (pool first approach).

Non-linear dose-response meta-analysis will be conducted using the pool first approach method implemented within Stata by Darren Greenwood (personal communication) . The best fitting nonlinear dose-response curve from a family of fractional polynomials will be selected. The best model will be the one that gave the most improvement (decrease) in deviance compared to the linear model.

15. Reports

Annual reports will be produced by the IC team. The report will include the following elements:

15.1 Results of the search

Information on number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of papers included. The reasons for excluding papers should also be described.
This information will be summarised in a flowchart.

15. 2 Description of studies identified in the Continuous Update

Number of studies by study design and publication year.
Number of studies by population characteristics (gender, geographic area, others)
Number of studies by exposure (main heading and selected subheadings) and publication year
Number of studies by exposure and outcome subtype

15.3 Summary of number of studies by exposure and study type in the database, separated on studies identified in the continuous update and in the SLR..

Example of table of summary study numbers:

Exposure Code	Exposure Name	Outcome	Number of controlled trials			Number of cohort studies		
			Total	SLR	Continuous update	Total	SLR	Continuous update

15.4 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) of the new studies will be summarised in tables using the same format as for the SLR for the Second Expert Report[1].
Within this table the studies should be ordered according to design (trials, cohort studies).

Example of table of study characteristics (in two parts below):

Author, Year, country, WCRF Code	Study design	Country, Ethnicity, other characteristics	Age (mean)	Cases (n)	Non cases (n/person-years)	Case ascertainment	Follow-up (years)

Assessment	Category	Subgroup	No	OR	(95%	p	Adjustment factors

details	of exposure	Subgroup	cat	OR	CI)	trend	Adjustment factors						
							A	B	C	D	E	F	G

Where
A : Age, sex
B : Socioeconomic status
C : Smoking
D : Anthropometry: height, BMI, others
E : Energy intake, other dietary factors
F: Personal antecedents of disease: diabetes, chronic pancreatitis
G : Others, e.g. family history, physical activity, marital status, race

15. 5 Graphic presentation

Tabular presentation may be complemented with graphic displays when the number of studies justifies it. Study results will be displayed in forest plots showing relative risk estimates and 95% confidence interval of ‘‘high versus low’’ comparisons for each study. No summary effect estimate of high versus low comparison will be calculated. Studies will be ordered chronologically.
Dose-response graphs are given for individual studies in which the information is available.

15.6 Results of meta-analysis

Main characteristics of included and excluded studies in dose-response meta-analysis will be tabulated, and reasons for exclusions will be detailed.
The results of meta-analysis will be presented in tables and dose-response forest plots, as well as the results of the exploration of heterogeneity and sensitivity analyses. Studies already included in a meta-analysis during the SLR for the Second Expert Report will be identified with asterisks (*). Studies will be labelled “I” or “M” if only incident cases (I) or fatal cases (M) were included.

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8. Bekkering GE et al. How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? Am J Epidemiol (2008);167(9):1017-26.

9. JP Higgins and SG Thompson, Quantifying heterogeneity in a meta-analysis, Stat Med 21 (2002), pp. 1539–1558.

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Annex 1.
WCRF - PUBMED SEARCH STRATEGY (with modifications implemented by the SLR centre Leeds)

a) Searching for all studies relating to prostate cancer:

#1 pancreatic neoplasms [MeSH terms]
#2 pancreatic neoplas* [tiab] OR pancreas neoplas*
#3 pancreatic cancer* [tiab[OR pancreas cancer*
#4 pancreatic carcin* [tiab] OR pancreas carcin*
#5 pancreatic tumo* [tiab] OR pancreas tumo*
#6 pancreatic metasta* [tiab] OR pancreas metasta*
#7 pancreatic malign* [tiab] OR pancreas malign*
#8 pancreatic adenocarinoma* [tiab] OR pancreas adenocarcinoma*
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

b) Searching for all studies relating to food, nutrition and physical activity:

#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]
#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] and (diet*[tiab] OR food*[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]) AND (diet*[tiab] or food*[tiab] or adipose[tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR (oils[tiab] AND and (diet*[tiab] or food*[tiab] or adipose[tiab] or blood[tiab]or serum[tiab] or plasma[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] OR tomato*[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] and (drink*[tiab] or intake[tiab] or consumption[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] and (diet*[tiab] or food*[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 ((carbohydrates[MeSH Terms] OR proteins[MeSH Terms]) and (diet*[tiab] or food*[tiab])) 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]) AND (diet*[tiab] or food*[tiab] or adipose [tiab] or blood[tiab] or serum[tiab] or plasma[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] AND (diet*[tiab] or food*[tiab])) OR iron[tiab] OR ((calcium[tiab] AND (diet*[tiab] or food*[tiab] or supplement*[tiab])) OR selenium[tiab] OR (iodine[tiab] AND and (diet*[tiab] or food*[tiab] or supplement*[tiab] or deficiency)) 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] OR lycopene[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 body weight [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
#21 animal[MeSH Terms] NOT human[MeSH Terms]
#22 #20 NOT #21

Annex 2. List of exposure codes (new sub-exposure codes indicated with *)

1 Patterns of diet

1.1 Regionally defined diets

*1.1.1 Mediterranean diet

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. diet diversity indexes) 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

Include here also age at first lactation, duration of breastfeeding, number of children breast-fed

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 diet diversity, meal frequency, frequency of snacking, dessert-eating and breakfast-eating should be reported here. Eating out of home should be reported here.

2 Foods

*2.0.1 Plant foods

2.1 Starchy foods

2.1.1 Cereals (grains)

* 2.1.1.0.1 Rice, pasta, noodles
* 2.1.1.0.2 Bread
* 2.1.1.0.3 Cereal

** Report under this subheading the cereals when it is not specified if they are wholegrain or refined cereals (e.g. fortified cereals)*

2.1.1.1 Wholegrain cereals and cereal products

* 2.1.1.1.1 Wholegrain rice, pasta, noodles
* 2.1.1.1.2 Wholegrain bread
* 2.1.1.1.3 Wholegrain cereal

2.1.1.2 Refined cereals and cereal products

* 2.1.1.2.1 Refined rice, pasta, noodles
* 2.1.1.2.2 Refined bread
* 2.1.1.2.3 Refined cereal

2.1.2 Starchy roots, tubers and plantains

* 2.1.2.1 Potatoes

2.1.3 Other starchy foods

**Report polenta under this heading*

2.2 Fruit and (non-starchy) vegetables

Results for "fruit and vegetables" and "fruits, vegetables and fruit juices" 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

*2.2.1.1.1 Carrots

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

*2.2.1.5.13 Tomatoes
*2.2.1.5.1 Fresh beans (e.g. string beans, French beans) and peas

Other non-starchy vegetables' should include foods that are botanically fruits but are eaten as vegetables, e.g. 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. 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

*2.2.2.0.1 Fruit, dried
*2.2.2.0.2 Fruit, canned
*2.2.2.0.3 Fruit, cooked

2.2.2.1 Citrus fruit

2.2.2.1.1 Oranges
2.2.2.1.2 Other citrus fruits (e.g. grapefruits)

2.2.2.2 Other fruits

*2.2.2.2.1 Bananas
*2.2.2.2.4 Melon
*2.2.2.2.5 Papaya
*2.2.2.2.7 Blueberries, strawberries and other berries
*2.2.2.2.8 Apples, pears
*2.2.2.2.10 Peaches, apricots, plums
*2.2.2.2.11 Grapes

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.

2.3Pulses (legumes)

*2.3.1 Soya, soya products

*2.3.1.1 Miso, soya paste soup
*2.3.1.2 Soya juice
*2.3.1.4 Soya milk

*2.3.1.5 Tofu

*2.3.2 Dried beans, chickpeas, lentiles
*2.3.4 Peanuts, peanut products

Where results are available for a specific pulse/legume, please report under a separate heading.

2.4Nuts 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

*2.5.1.2.1 Ham
*2.5.1.2.1.7 Burgers
*2.5.1.2.8 Bacon
*2.5.1.2.9 Hot dogs
*2.5.1.2.10 Sausages

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

*2.5.1.3.1 Beef
*2.5.1.3.2 Lamb
*2.5.1.3.3 Pork
*2.5.1.3.6 Horse, rabbit, wild meat (game)

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.

*2.5.1.5 Offals, offal products (organ meats)

2.5.2 Fish

*2.5.2.3 Fish, processed (dried, salted, smoked)
*2.5.2.5 Fatty Fish
*2.5.2.7 Dried Fish
*2.5.2.9 White fish, lean fish

2.5.3 Shellfish and other seafood

2.5.4 Eggs

2.6 Fats, oils and sugars

2.6.1 Animal fats

*2.6.1.1 Butter
*2.6.1.2 Lard
*2.6.1.3 Gravy
*2.6.1.4 Fish oil

2.6.2 Plant oils
2.6.3 Hydrogenated fats and oils

*2.6.3.1 Margarine

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

*2.7.1 Milk, fresh milk, dried milk

*2.7.1.1 Whole milk, full-fat milks
*2.7.1.2 Semi skimmed milk, skimmed milk, low fat milk, 2% Milk

*2.7.2 Cheese

*2.7.2.1 Cottage cheese
*2.7.2.2 Cheese, low fat

*2.7.3 Yoghurt, buttermilk, sour milk, fermented milk drinks

*2.7.3.1 Fermented whole milk

*2.7.3.2 Fermented skimmed milk

*2.7.7 Ice cream

2.8 Herbs, spices, condiments

*2.8.1 Ginseng
*2.8.2 Chili pepper, green chili pepper, red chili pepper

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.

*2.9.1 Cakes, biscuits and pastry
*2.9.2 Cookies
*2.9.3 Confectionery
*2.9.4 Soups
*2.9.5 Pizza
*2.9.6 Chocolate, candy bars
*2.9.7 Snacks

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 and vegetable juices

*3.5.1 Citrus fruit juice
*3.5.2 Fruit juice
*3.5.3 Vegetable juice
*3.5.4 Tomato juice

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.

1 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
*5.1.5 Glycemic index, glycemic load

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. Past alcohol refers, for example, to intake at age 18, during adolescence, etc.

*5.4.1 Total Alcohol (as ethanol)

*5.4.1.1 Alcohol (as ethanol) from beer
*5.4.1.2 Alcohol (as ethanol) from wine
*5.4.1.3 Alcohol (as ethanol) from spirits
*5.4.1.4 Alcohol (as ethanol) from other alcoholic drinks
* 5.4.1.5 Total alcohol (as ethanol), lifetime exposure

* 5.4.1.6 Total alcohol (as ethanol), past

5.5 Vitamins

*5.5.0 Vitamin supplements
*5.5.0.1 Vitamin and mineral supplements
*5.5.0.2 Vitamin B supplement

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

*5.5.3.1 Total folate
*5.5.3.2 Dietary folate
*5.5.3.3 Folate from supplements

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

*6.1.2.1 Frequency of occupational physical activity
*6.1.2.2 Frequency of recreational physical activity

6.1.3 Intensity of physical activity

*6.1.3.1 Intensity of occupational physical activity
*6.1.3.2 Intensity of recreational physical activity

6.1.4 Duration of physical activity

*6.1.4.1 Duration of occupational physical activity
*6.1.4.2 Duration of recreational physical activity

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

7 Energy balance

7.1 Energy intake

*7.1.0.1 Energy from fats
*7.1.0.2 Energy from protein
*7.1.0.3 Energy from carbohydrates
*7.1.0.4 Energy from alcohol
*7.1.0.5 Energy from all other sources

7.1.1 Energy density of diet

7.2 Energy expenditure

1.1.1 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

Annex 3. Tables of excluded and included biomarkers proposed by the SLR centre Bristol.

Extracted from: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective
Systematic Literature Review – Support Resource
SLR Prostate Cancer (pp 1185-1186)

The reviewers of the SLR centre Bristol used two chapters (Willet: Nutritional epidemiology (Chapter 9), 1998; Margetts and Nelson: Design concepts in nutritional epidemiology (Chapter 7), 1997) to guide their decisions. If there was no info, the biomarker was excluded. If one of the chapters stated the biomarker was useful, the data on validity were checked. Biomarkers with a correlation >0.20 were included. If the chapters stated that there were no good biomarkers for a nutrient or that the biomarker was valid for certain range of intake only, the biomarker was excluded. It was assumed that if biomarkers measured in plasma were valid, this would also be true for serum and vice versa.
The reviewers of the SLR centre Bristol have been more inclusive with respect to the validation required for biomarkers of important nutrients and have therefore added serum/plasma retinol, retinol binding protein, vit B6, ferritin, magnesium, erythrocyte superoxide dismutase (more details below). They have also included biomarkers where validity is not possible: this happens in the case of toxins and phytochemicals where dietary data are sparse. Various contaminants, such as cadmium, lead, PCBs in the serum are also included now although validity data are not available. The level of these chemicals in human tissues is often the only available measure of ingestion.

Measured in	Include	Exclude
Serum	Provit A carotenoids: Carotene, B-carotene, Alpha-carotene Nonprovit A carotenoids: Carotenoids, Lycopene, Cryptoxanthin (B-), Lutein+zeaxanthin Vit E: alpha-tocopherol, gamma tocopherol Selenium n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic) Magnesium Vit A: Retinol &Retinol Binding Protein Pyridoxic acid (vit B6) Phytoestrogen: Genistein, Daidzein* [glycitein, O-desmethylangolensin, equol, enterodiol, and enterolactone] Chemical food contaminants Polychlorinated biphenyls (PCBs) Phytochemicals	Prealbumin Minerals: Zinc, Copper, Copper/zinc ratio, Zinc/retinol ratio Other dietary lipids: Cholesterol, Triglycerides Saturated fatty acids, Monounsaturated fatty acids, Polyunsaturated fatty acids Lipids (as nutrients), Total fat (as nutrients), Total protein
Urine	4-pyridoxic acid (vit B6) in 24-h urine	Nitrosamines Xanthurenic acid in 24-h urine Arsenic Ferritin
Saliva		Other dietary lipids: Cholesterol, Triglycerides
Erythrocyte	Linoleic acid Selenium Superoxide dismutase Cadmium	Minerals: Zinc, Copper Monounsaturated fatty acids n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic) n-6 fatty acids (other than linoleic acid) Polyunsaturated fatty acids, Saturated fatty acids Glutathione peroxidase

Measured in	**Include**	**Exclude**
Plasma	Vit D Vit E: alpha-tocopherol, gamma tocopherol Vit C Provit A carotenoids: Carotene, Alpha-carotene, B-carotene Nonprovit A carotenoids: Lycopene, Cryptoxanthin (B-), zeaxanthin, Lutein Selenium, Selenoprotein Folate, Iron: ferritin Vit A Retinol: Retinol Binding Protein Cadmium, Cadmium/zinc ratio EPA DHA fatty acids	Alkaline phosphatase Minerals: Zinc, Copper, caeruloplasmin Other dietary lipids: Cholesterol, Triglycerides, LDL, HDL
Adipose tissue	n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic) n-6 fatty acids Trans fatty acids , Polyunsaturated fatty acids, Saturated fatty acids	Unsaturated fat, Monounsaturated fatty acids n-9 fatty acids other measures of polyunsat fa: M:S ratio, M:P ratio, n3-n6 ratio
leucocyte	Vit C	Zinc
Erythrocyte membrane	n-6 fatty acids: linoleic	n-6 fatty acids (other than linoleic) n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic)
Hair		Minerals: Zinc, Copper, Manganese, Iron Cadmium
Toenails or fingernails	Selenium	Cadmium, zinc

Reasons for exclusion and inclusion of biomarkers proposed by the SLR centre Bristol.

Extracted from: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective
Systematic Literature Review – Support Resource
SLR Prostate Cancer (pp 1187-1189)
(Source: Willet: Nutritional epidemiology (Chapter 9), 1998; Margetts and Nelson: Design concepts in nutritional epidemiology (Chapter 7), 1997)

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Retinol	Plasma/serum	Yes	Can be measured adequately, but limited interpretability in well-nourished population (p 190).	Main biochemical marker of vit A intake is serum retinol (p 194) although in western countries dietary intake of this vitamin is only a very minor determinant of its plasma levels.
Retinol-Binding protein	Serum	Yes	Retinol levels are highly correlated to RBP(p192).	May be measure of physiologically available form. Not if certain disease processes exist (p 192).
Beta-carotene	Plasma	Yes	Yes (p 194) although blood levels much more responsive to supplemental beta-carotene than beta-carotene from food sources (p 193)	Yes (p 197)
Alpha-carotene Beta-cryptoxanthin Lutein+zeaxanthin Lycopene	Plasma	Yes	Yes (p 194)	There is some evidence for interaction between carotenoids during intestinal absorption, which may complicate relationship between intake and blood levels (p 198)
Vit E	Plasma	Yes	Yes (p 196) NB. Strong confounding with serum cholesterol and total lipid concentrations (p 196).	Plasma, red and white blood cells. Yes, if used for vit E supplements. Yes, although if used for diet, associations are only moderate (p199)

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Vit D: D25 (OH)D	Plasma Serum	Yes	Yes (P 198/199) NB. Seasonal variation exists, especially in elderly populations, decreasing in winter and rising during summer (p 198) Sunshine exposure is most important determinant; level is better marker of dietary intake in subjects with low sun exposure	Both can be used to measure vit D status, but the higher plasma concentration and lesser metabolic control of d25 makes this, by far, the better option (p 198).
Vit D: 1.25 (OH)2D		No	No. Influenced by calcium and phosphate levels and parathyroid hormone (p 199).	
Vit D: Alkaline phosphatase activity	Serum	No	No. Is indirect measure of vit D status and is susceptible to other disease processes (p 199)	No info
Vit C	Plasma Leukocyte Serum	Yes	Yes (p 200). Leukocyte may be preferred for long-term intake and plasma and serum reflects more recent intake (p 201)	Yes (p 209), vit C exhibits the strongest and most significant correlation between intake and biochemical indices. Known confounders are: gender, smoking
Vitamin B6	Plasma	Yes	Yes response to supplementation shows response in PLP. PLP better measure of short term rather than long term	Recent studies show that there is unlikely to be a strong correlation between dietary intake and plasma pyridoxal phosphate levels (PPL)
PLP and 4 Pyridoxic acid	Urinary	Yes	Urinary B6 may be more responsive to recent dietary intake than plasma PLP. Random samples of urine 4 –pyridoxic acid correlate well with 24 hour collections	
Folacin (folate)	Serum Erythrocyte	Yes	Yes good correlation with dietary folate in both serum and erythrocytes	Used for assessing folate status Table 7.11p
Magnesium	Serum	Yes	Yes stronger correlation with supplement users than with dietary Mg	
Iron	Serum Hair/nails	No No	No, short-term variability is very high (p 208). No, remains to be determined	
Iron: Ferritin	Serum	Yes	Meat intake predicts serum ferritin level (p 208)	No marker of iron intake is satisfactory (p. 192)

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Copper : Superoxide dismutase	Erythrocyte	Yes	Among four men fed a copper deficient diet for 4 months, erythrocyte S.O.D declined for all 4. Copper repletion restored S.O.D levels	
Copper	Plasma/serum	No	No (p 211): large number of lifestyle factors/pathologic conditions probably alter blood copper concentrations (smoking, infections)	
Copper	Hair	No	No evidence (212) and data suggests influenced by external contamination	No. Copper-dependent enzyme superoxide dismutase in erythrocytes and copper-protein complex caeroplasmin in serum have been shown to be associated with copper intake, but these markers may be influenced by nondietary factors (p 193)
Selenium	Blood components Toenails	Yes	Yes. Erythrocyte is probably superior to serum as measure of long-term intake (p 206). Lower influence of environment in countries where wearing shoes is norm (toenails). Selenium status is reduced by smoking, also in older persons (p 207); Relationship of selenium with disease may be modified by other antioxidants (vit E and C)	Yes (p 193). Relationship between selenium intake and biomarkers is reasonably good. Urine: reasonable marker, plasma reflects intake provided that the range of variation is large. Red cell and glutathione perioxidase are markers of longer-term intakes. Hair and toenails are alternative possibilities, although contamination of hair samples with shampoo must be controlled for
Glutathione perioxidase	Plasma Serum Erythrocytes Blood	No	Is poor measure of selenium intake among persons with moderate and high exposure (p 206)	

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Zinc Metallothionein levels	Any	No No	No (p 212) May be marker of short-term intake (p 213)	No biochemical marker is a good indicator of zinc intake (p 192/193). This is, in general terms, also true for other trace metal nutrients such as copper, manganese, chromium, etc
Lipids: total fats	Any	No	No (p 213)	No, there are no markers of total fat intake (p 215)
Cholesterol, LDL Lipoprotein levels	Serum	No	No, but may be useful to predict dietary changes but not for dietary intake (p 215)	No, relationship dietary cholesterol and lipoprotein levels of cholesterol are complex and appears to vary across range of intake (p218)
Linoleic acid	Plasma Adipose tissue	No Yes	Plasma linoleic acid can discriminate between groups with relatively large differences in intake but performs less well on an individual basis (p 220) Yes (p 220)	No consistent relation between dietary linoleic acid intake and plasma linoleic acid (p 220). Across the range of fatty acids in the diet, fatty acids levels in blood and other tissue (adipose tissue) reflect the dietary levels. NB levels are not comparable across tissues
Marine omega-3 fatty acids (EPA, DHA)	Serum Plasma Adipose tissue	Yes	Yes (p 222/223), although dose-response relation remains to be determined	
Monounsat fatty acids (oleic acid)	Plasma Adipose tissue	No No	No, plasma levels are poor predictors of oleic acid intake, but adipose tissue may weakly reflect oleic acid intake (p. 224). Validity is too low	
Polyunsat fatty acids	Adipose tissue	Yes	Yes (p 220)	No info

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Saturated fatty acids (Palmitic acid, stearic acids)	Adipose tissue Plasma	Yes No	Yes, long term sat fatty acid intake may be reflected in adipose tissue levels (p 224) No, levels of palmitic and stearic acids in plasma do not provide a simple index of intake (p 224).	No info
Trans-fatty acids	Adipose tissue	Yes	Yes (p 225)	No info
Protein	Any	No	No (p 226)	No info
Nitrogen	Urine	Yes	Yes, but several 24-h samples are needed to provide a stable estimate of nitrogen intake (p 227) Nitrogen excretion increases with body size and exercise and decreased caloric intake	Yes (p 219) One assumes that subjects are in nitrogen Balance

Data on validity and reliability of included biomarkers
Extracted from: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective
Systematic Literature Review – Support Resource
SLR Prostate Cancer (pp 1187-1189)

Nutrient	Biologic tissue	Val./reproduc	Coef	Details
Retinol	Plasma	Validity	0.17	Borderline Correlation between pre-formed vit A intake and plasma retinol. However plasma retinol is a recognized marker of vit A nutritional status for undernourished populations
Beta-carotene			0.51	Correlation between plasma beta-carotene level (averaged from 2 samples taken 1 week apart) and a 7-day diet record estimate of beta-carotene in 98 non-smoking women (Willett, p 194).
			0.38	Cross-sectional correlation between dietary intake of carotene and plasma betacarotene in 902 adult females. In males (n=880): r=0.20 (Margetts, table 7.9a).
	Plasma	Reproducibility	0.45	Correlation for carotene (80% beta-carotene, 20% alpha-carotene) between two measurements taken 6 years apart (Willett, p 194).
Beta-cryptoxanthin	Plasma	Validity	0.49	Correlation between plasma beta-carotene level (averaged from 2 samples taken 1 week apart) and a 7-day diet record estimate of beta carotene in 98 non-smoking women (Willett, p 194)
Lutein+zeaxanthin	Plasma	Validity	0.31	
Lycopene	Plasma	Validity	0.50	
Alpha-carotene	Plasma	Validity	0.58	
Alpha-carotene	Plasma	Validity	0.43	Cross-sectional correlation between dietary intake of carotene and plasma alphacarotene in 902 adult females. In males (n=880): r=0.41 (Margetts, table 7.9a).
Carotenoids	Plasma	Reproducibility	≥080	Within-person variability of plasma levels over 1 week (Willett, p 194).
Vitamin E	Plasma	Validity	0.53	Lipid-adjusted alpha-tocopherol measurements and estimated intake (incl. supplements). After excluding supplement users: r=0.35 (Willett, p 196)
	Plasma	Reproducibility	0.65	Unadjusted repeated measures over a 6-year period (p 188). Adjusting for serum cholesterol reduced correlation to r=0.46 (p 188). Also r=0.65 was found over a 4-year period in 105 adults in Finland (Willett, p 196).
	Plasma	Validity	0.20	Cross-sectional correlation between dietary intake of vit E and plasma vit E in 880 adult males. In females (n=906): r=0.14 (Margetts, table 7.9a)

Nutrient	Biologic tissue	Val./reproduc	Coef	Details
Vitamin D: D25 (OH)D	Plasma	Validity	0.35	Correlation between FFQ estimate of vit D intake (including supplements) with plasma D25 (OH)D (n=139). Correlation excluding supplement users: r=0.25 (Willett, p 199)
			0.18	Cross-sectional correlation between dietary intake of nutrients and biochemical markers in UK pre-school child study in females (n=350). In males (n=365) r=0.06 (Margetts, table 7.9b).
	Serum	Validity	0.24	Correlation between estimated vit D intake from food and supplements (based on 24 h recall) and serum D25 (OH)D (n=373 healthy women). Food only: r=0.11 (Willett, p 199).
Vitamin C	Plasma	Validity	0.43	Unadjusted correlation between questionnaire-derived dietary ascorbic acid intake and plasma ascorbic acid concentration in a heterogeneous population. Diet only: r=38 (Table 9.1). Correlation is 0.31 for leukocyte ascorbic acid concentration.(Willett, p 200)
		Reproducibility	0.28	Repeated measures in men obtained 6 years apart (Willett, p 201)
		Validity	0.43	Cross-sectional correlation between dietary intake of nutrients and biochemical markers in UK pre-school child study in males (n=369). In females (n=354) r=0.39 (Margetts, table 7.9b).
	Serum	Validity	0.55	Correlation between food-frequency questionnaire estimate of vit C intake and serum vit C values (in smokers) in 196 men in Scotland (adjusted for total energy intake, BMI and serum cholesterol level). Non-smokers: 0.58 (Willett, p 200/201)
	Leukocyte	Validity	0.49	Correlation between one week of intake data and a single leukocyte ascorbate measurement for men. For women: r=0.36. Nutrition survey of elderly in UK (Margetts, p 211)
Vitamin B6	Plasma Urinary	Validity Validity	0.37 -	Correlation between B6 and plasma pyridoxal phosphate levels in 280 healthy men =0.37 (Willett p203)
Folacin	Serum Erythrocyte	Validity	0.56 0.51	Correlation of 0.56 in Framington Heart study 385 subjects (serum) Correlation in 19 elderly subjects (erythrocyte) (Willet p204)
Magnesium	Serum	Validity	0.27	Correlation between intake with supplements 0.27 in 139 men and 0.15 without supplements (Willett p211)

Nutrient	Biologic tissue	Val./reproduc	Coef	Details
Iron (ferritin)	Serum	Validity	0.16	Borderline 0.16 correlation with heme intake but only r-0.15 with total iron intake (Willett p 208). Included as marker of iron storage
Copper (Superoxide dismutase)	Erythrocyte	-	-	S.O.D levels reflect both depletion and repletion of Cu (Willett p 212)
Selenium	Serum	Validity	0.63	Correlation between selenium intake and serum selenium in South Dakotans (n=44)(Willett, p 186)
		Reproducibility	0.76	Average correlation between repeated measurements at four 3-month intervals in 78 adults (Willett, p 188)
	Toenails	Validity	0.59	Correlation between selenium intake and toenail selenium level in South Dakotans (n=44) (Willett, p 186)`
		Reproducibility	0.48	Correlation for selenium levels in toenails collected 6 years apart from 127 US women (Willett, p 206)
	Whole blood	Validity	0.62	Correlation between selenium intake and whole blood selenium in South Dakotans (n=44) (Willett, p 186)
		Reproducibility	0.95	Average correlation between repeated measurements at four 3-month intervals in 78 adults (Willett, p 188)
Linoleic acid	Adipose tissue	Validity	0.57	Correlation between dietary linoleic acid intakes determined from 7-day weighted diet records and the relative proportion of linoleic acid in adipose tissue in Scottish men (n=164). Also correlation between linoleic acid measured in adipose tissue and calculated from FFQ in 118 Boston-area men (Willett, p 220)
Eicosapentaenoic (n-3)	Adipose tissue	Validity	0.40	Correlation with intake estimated from three 7-day weighted food records (Willett, p 223).
		Reproducibility	0.68	Correlation over 8 months in 27 men and women aged 20-29 (Willett, p 223).
	Plasma	Validity	0.23	Correlation of cholesterol ester fraction and intake in 3,570 adults (Willett, p 223)
		Reproducibility	0.38	Correlation of two measurements taken 6 years apart in study of 759 Finnish youths (Willett, p 219)
Nutrient	**Biologic**	**Val./reproduc**	**Coef**	**Details**

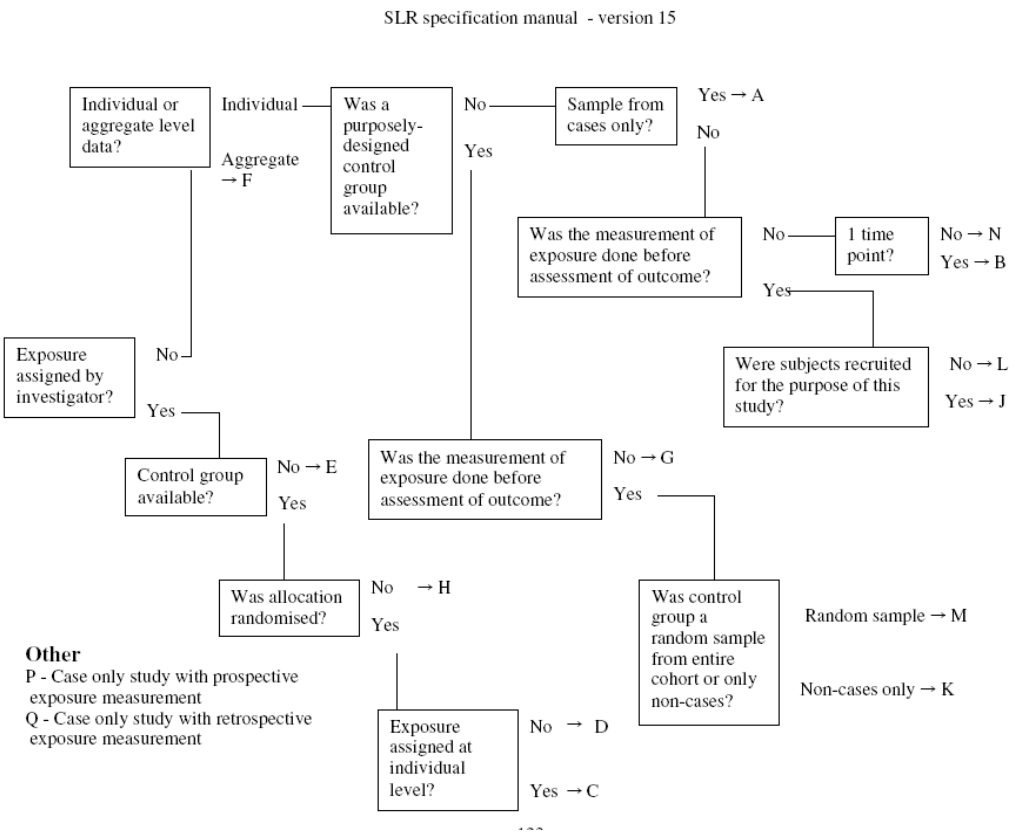
	tissue			
Docosahexaenoic (n-3)	Adipose Tissue	Validity	0.66	Correlation with intake estimated from three 7-day weighted food records (Willett, p 223)
		Reproducibility	0.93	Correlation over 8 months in 27 men and women aged 20-29 (Willett, p 223).
	Plasma	Validity	0.42	Correlation of cholesterol ester fraction and intake in 3,570 adults (Willett, p 223)
		Reproducibility	0.38	Correlation of two measurements taken 6 years apart in study of 759 Finnish youths (Willett, p 219)
Polyunsaturated fatty acids	Adipose tissue	Validity	0.80	Correlation between % of polyunsaturated fatty acid relative to total fatty acid intake and relative % of adipose tissue polyunsaturated fatty acid (Willett, p 220)
Palmitic acid	Adipose tissue	Validity	0.27	Correlation adipose tissue measurement with a FFQ estimate among 118 men. A correlation of 0.14 was reported among women. Among 20 healthy subjects, correlations between normal intake of total saturated fatty acids and fatty acid composition of triglycerides in adipose tissue was 0.57 (Willett, p 224)
Stearic acid	Adipose tissue	Validity	0.56	Among 20 healthy subjects, correlations between normal intake of total saturated fatty acids and fatty acid composition of triglycerides in adipose tissue (Willett, p 224)
Trans fatty acids	Adipose tissue	Validity	0.40	Correlation between adipose trans and intake estimated from the average of two FFQ among 140 Boston-area women. Previous study: 115 Boston area women, correlation of 0.51 between trans intake estimated from a single FFQ and a fatty acid measurement. Among 118 Boston-area men: correlation of 0.29 between trans fatty acid measured in adipose and by FFQ (Willett, p 225)
Nitrogen	Urine	Validity	0.69	Correlation between nitrogen intakes estimated from weighted food records of 16 days and the average of six 24-h urine nitrogen levels (160 women) (Willett, p 227)
Phyto Oestrogens Genistein, daidzein	Plasma 24 hr urine	Validity	0.97 0.92	Urinary excretion (24 h) and plasma concentrations of PO were significantly related to measured dietary PO intake (r 0.97, P<0.001 and r 0.92, P<0.001 respectively). These findings validate the PO database and indicate that 24 h urinary excretion and timed plasma concentrations can be used as biomarkers of PO intake. Br J Nutr. 2004 Mar;91(3):447-57

Nutrient	Biologic tissue	Val./reproduc	Coef	Details
Enterodiol Enterolactone	Serum Urine	Validity	0.13 to 0.29	Urinary enterodiol and enterolactone and serum enterolactone were significantly correlated with dietary fiber intake (r = 0.13-0.29) Cancer Epidemiol Biomarkers Prev. 2004 May;13(5):698-708

Appendix 4 Stop Words for use within Reference Manager database

Pancreatectomy
Pancreaticoduodenectomy
Resection
Stent
MRI (magnetic resonance imaging)
PET (positron emission tomography
ERCP (endoscopic retrograde cholangiopancreatography)
EUS (endoscopic ultrasonography)
CT (computer tomography
Endosonography
Radiotherapy
Radiochemotherapy
Cisplatin
Fluorouracil
5 FU
Gemcitabine
Antineoplastic
Pancreatitis
Zollinger Ellison
Ampulla of vater
Insulinoma
Hypoglycemia
Glucagons
Ketosis
Peptides
Cell
Inhibitor
Novel
Model
Receptor
Antibody
P53
Transgenic
Mice
Hamster
Rat
Dog
Cat
In vitro

Annex 5. Study design algorithm



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

Annex 6. List of conversion units

In cases where the units of measurement differed between results the units would be converted, where possible, such that all results used the same measurement. Where assumptions had to be made on portion or serving sizes an agreement was reached after discussion between team members and consultation of various sources. The following general sizes were agreed upon:

Beer	400ml serving
Cereals	60g serving
Cheese	35g serving
Dried fish	10g serving
Eggs	55g serving (1 egg)
Fats	10g serving
Fruit & Vegetables	80g serving
Fruit Juice	125ml serving
General drinks inc soft & hot drinks	200ml serving
Meat & Fish	120g serving
Milk	50ml serving
Milk as beverage	200ml serving
Processed cheese slice	10g serving
Processed meat	50g serving
Shellfish	60g serving
Spirits	25ml serving
Staple foods (rice, pasta, potatoes, beans & lentils, foods boiled in soy sauce)	150g serving
Water & Fluid intake	8oz cup
Wine	125ml serving