Appendix I:

Protocol for Systematic Literature Review

A systematic review of the evidence of the benefits and risks of different dietary carbohydrates on cardio-metabolic health and disease

Nutritional Epidemiology Group
University of Leeds
Leeds

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1.0 Research question:

The research topic is:

The associations between dietary carbohydrate consumption and cardio-metabolic disease in humans.

The question to be answered by this review is 'In healthy humans, does exposure to variation in consumption of dietary carbohydrates (in terms of type, quantity and associated dietary pattern) influence cardio-metabolic health?

This research question will be passed to the information specialist (IG) to shape the search strategy.

2.0 Review team

Team members:

Dr Victoria Burley (lead)	MSc, PhD
Dr Darren Greenwood	MSc, PhD
Dr Lucinda Summers	MB BS, FRCP, DPhil
Dr Chris Gale	MB BS, MRCP, PhD
Ms Charlotte Evans	MSc
Ms Iris Gordon	MSc
Ms Cristina Cleghorn	MSc
Ms Diane Threapleton	MSc
Mr James Thomas	BSc
Ms Camilla Nykjaer	BSc

2.1 Expert independent steering panel

Professor Tom Sanders (King's College, University of London) has agreed to sit on a steering panel, with Dr Lucinda Summers and Dr Chris Gale as local experts

3.0 Timeline

Key provisional dates for the review are tabulated below:

Task	**Completion Date / Provisional Milestone**
Approval of protocol	21st September 2009
List of included references prepared	11th January 2010
Access database prepared to receive data	31st October 2009
Data extraction complete	June 2010
Statistical analysis complete for draft report Tables ready for inclusion in report	August 2010
Draft report delivered	30th September 2010
Amended report delivered	22nd December 2010
Report approved	28th February 2011

4.0 Background

Coronary heart disease (CHD) is the commonest cause of death in the UK[1]. Over the past decade there have been significant improvements in the burden of cardiovascular disease in the UK[1]. In part, this is the result of substantial investment in cardiac services[2]. However, there remain major geographical differences in the risk, treatment and outcome from CHD[3] and although the mortality from acute coronary syndromes (ACS) in England has declined, it still generates a massive burden of disease[1,4]. Approximately 20% of men and 14% of women die from the disease, and it causes 101,000 deaths in the UK each year[1,5]. Capewell and colleagues[6] for the British Heart Foundation have recently highlighted the need for continued efforts to tackle cardiovascular problems in the years to come due to the anticipated extra burden this disease will place on health care services in the future.

In 2005 there were an estimated 2.26 million people in England with diabetes. This is about 4.48% of the population. By 2025 it is estimated that diabetes prevalence will increase to 6.48%[7]. Approximately 43% of the increase in diabetes prevalence will be due to the ageing population and 57% will be due to increasing obesity. Obesity is associated with metabolic changes that tend to increase the risk of cardiovascular diseases and type 2 diabetes. These conditions have a number of risk factors in common, such as abnormal blood lipid profiles (including low-HDL cholesterol and high blood triglyceride levels), hypertension, and insulin resistance. This particular cluster of conditions in combination with centrally located (abdominal) obesity is a feature of the metabolic syndrome[8]. Although there are issues to do with characterisation of the metabolic syndrome, it is estimated that approximately 25% of the UK population demonstrate signs of the metabolic syndrome, and the health and social welfare costs associated with obesity, diabetes and the metabolic syndrome in the UK are expected to rise to unsustainable levels in the early part of the century. Clearly, these statistics, coupled with the well publicised predictions of increasing adiposity in the UK highlight the need for prevention strategies based upon the best systematically gathered evidence.

It is now generally recognised that a diet which is high in fat, particularly saturated fat, sodium and sugar and which is low in complex carbohydrates, fruit and vegetables increases the risk of chronic diseases – particularly cardiovascular disease (CVD) and cancer. These risks are outlined in the World Health Organization 2003 report 'Diet, Nutrition and the Prevention of Chronic Diseases'[9]. The dietary changes which would help to reduce rates of coronary heart disease (CHD) in the UK population were detailed in the 1994 report of the Government's Committee on the Medical Aspects of Food and Nutrition Policy (COMA)[10].

The Committee on Medical Aspects of Food Policy concluded that diets high in dietary carbohydrate were associated with higher fasting concentrations of plasma triglyceride and lower HDL cholesterol[10]. Nonetheless, due to the reciprocal relationship between dietary carbohydrate and dietary fat, such high carbohydrate diets tended to be low in fat and consequently were associated with lower LDL cholesterol levels and low risk of CHD. At that time there was limited evidence that the type of carbohydrate (sugars or starches) was important, although the panel did find evidence that diets rich in non starch polysaccharide were associated with lower post prandial plasma insulin and glucose levels, and LDL cholesterol levels. The panel recommended a reduction in fat intake, particularly saturated fat intake, a reduction in sodium intake and an increase in fruit and vegetable and complex carbohydrate intake. Somewhat more recently, the World Health Organisation summarised the strength of evidence on lifestyle factors and risk of developing cardiovascular diseases, type 2 diabetes and obesity[9]. They found the evidence *convincing* or *probable* for a decreased risk of these conditions with diets high in dietary fibre and *probable* that a high intake of sugars-sweetened beverages increase the risk of obesity. However, at that time the panel concluded that there was insufficient evidence concerning the relationship between total carbohydrate and risk of cardiovascular disease and that the evidence was indicative of a *possible* decreased risk of obesity with diets composed of low glycaemic index foods.

Since these reports were prepared further evidence has accrued on these issues. In particular a wealth of studies have been published on the relationship between cardio-metabolic health and dietary glycaemic index and load, wholegrain consumption and other dietary patterns associated with dietary carbohydrates[11-16]. There is a pressing need for these additional studies to be systematically evaluated and included in the

body of evidence that exists to permit the Scientific Advisory Committee on Nutrition to assess whether existing dietary recommendations concerning dietary carbohydrates need to be revised.

5.0 Search strategy

Searching on Medline will be carried out using the Ovid interface.

Two strategies have been developed (appendices 1 and 2). A main strategy with the cardio-metabolic health outcomes listed below in mind and a supplementary search which focuses on capturing the literature on energy intake and satiety (and related subjective states). The latter search differs by the inclusion of further study design-related terms (Cross-over studies/ and text word terms 'repeated measures' and 'within subject'). This approach has been adopted to minimise the number of false hits obtained when the 2 strategies were initially run separately. The outputs of the 2 searches will be merged and de-duplicated before proceeding to subsequent steps.

5.1 Databases

Multi-database searching will be used to ensure comprehensive article retrieval. The following online databases will be searched:

Medline
PREM (MEDLINE In-Process & Other Non-Indexed Citations)
Embase
CAB Abstracts
ISI Web of Science
BIOSIS
The Cochrane Library

5.2 Publication selection

• Only published peer-reviewed full papers presenting original data will be included in the review
• Published abstracts will not be included in the review
• In-press articles will be included in the review
• Grey literature such as dissertations, conference proceedings, reports and other non peer-reviewed research will not be included.

5.3 Hand searching for cited references

Hand searching of selected journals will be undertaken to supplement the electronic searches. These journals will include:

Journal of Nutrition
Journal of the American Dietetic Association
American Journal of Clinical Nutrition
Diabetes Care
European Journal of Clinical Nutrition
British Journal of Nutrition

Additionally, the reference lists of published relevant systematic literature reviews and meta-analyses will be cross checked against our electronic searches databases. Existing Reference Manager databases of 'diet and hypertension' and 'carbohydrate and insulin resistance' held by the team will also be searched.

5.4 Date range

Literature searches will be conducted to capture studies with a publication date from 1990 to December 2009. Pre-1990 studies included in earlier reports from the Committee on Medical Aspects of Food Policy (COMA) [10,17,18] relevant to this review will not be eligible for full inclusion in the review. However, in the report, where each outcome/exposure is discussed we will include a section on 'Previous COMA data' to alert the SACN panel to these older studies.

5.5 Language

Only papers published in English will be eligible for inclusion in this review.

5.6 Inclusion and exclusion criteria

On completion of the database searches, studies will be included or excluded from the review based on the following criteria:

Included

- Studies concerning the role of diet in cardio-metabolic disease aetiology or prevention in UK-relevant populations
- Studies comparing the effect of individual high carbohydrate foods, or high carbohydrate diets, with other diets or foods with lower levels
- Studies comparing the effect of type or source of carbohydrate, with a different type or source of carbohydrate or a food or diet with lower levels of that type of carbohydrate
- Study types
    - prospective or cohort studies (with 3+ years of follow-up)
    - randomised controlled trials (intervention phase of 6+ weeks) either cross-over or parallel groups
    - for energy intake and satiety outcomes, controlled trials will be included if the intervention phase is 3 or more consecutive days in duration

- All randomised controlled trials that have specifically focused on the prevention of weight gain will be included, provided the intervention duration is 6 weeks or more in duration
- Weight loss trials of duration of one year or longer using *ad libitum* diets will be included (*ad libitum* consumption being the provision or recommendation to consume freely from a range of foods possessing the characteristic in question e.g. high or low GI or high or low fibre). Many trials in this area have evaluated the effect of dietary interventions on weight loss. As the focus of this SLR is the *causation* of weight gain and obesity (rather than treatment) the inclusion of weight loss trials will be limited.

- Publication date – from 1990 onwards
- Study participants
    - children (aged 5+ yr), adolescents, adults aged 18 years up to 70 years
    - healthy or with an intermediate stage of ill health only such as glucose intolerance or overweight/obese with no other health conditions
    - studies on Caucasian populations. However, studies on immigrant populations such as African-Americans, Japanese Americans and British Asians will be included

Excluded

- Studies relating to diagnosis or management of disease e.g. studies to improve glycaemic control in people with type 2 diabetes
- Weight loss trials of less than one year in duration and those that have not prescribed an *ad libitum* dietary regimen
- Intervention studies that include a mixture of dietary and other lifestyle modifications (e.g. physical activity) which do not permit the effect of diet to be isolated
- Interventions that use a dietary portfolio (combination diet) or mixed component regimen, e.g. the prescribed diet included plant sterols, soy protein, viscous fibres, and nuts etc. or studies that do not permit the effect of carbohydrate/carbohydrate type to be evaluated
- Study participants
    - Participants with type 2 diabetes, heart disease (myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, or angina pectoris or coronary artery disease defined by angiography), hypertensive at the onset of the study
    - Pregnant women
    - Major proportion of the participants taking anti-hypertensive medication, lipid-lowering drugs (e.g. statins) or other medication for management of long-term chronic health conditions
    - People with eating disorders e.g. bulimia nervosa
    - Oriental, African and Asian studies, and other populations whose characteristics and/or dietary practices are not relevant to the UK population

5.7 Definition of exposures

Exposures that will be included in the review:

- Carbohydrate e.g. total carbohydrate, sugars reported as a nutrient (fructose, sucrose, lactose, glucose), starch, oligosaccharides and inulin, soluble fibres (including guar gum, psyllium, beta glucans), non starch polysaccharides/dietary fibre (but not crude fibre).

- Dietary sources e.g. cereal fibre, fruit fibre, vegetable fibre (including legumes, but excluding soy and soy isolates), wholegrain (wheat, oats, rice, rye), refined grains, table sugar and other extrinsic sugars (syrups)

- Characteristics of carbohydrate or carbohydrate containing foods e.g. glycaemic index, glycaemic load, food format (liquid vs. solid, which will include sugar-sweetened beverages).

During data extraction, particular attention will be paid to capture the precise definition of each exposure, including where reported, the analysis method for dietary fibre (NSP, AOAC, Southgate fibre etc.), definition of whole grain used (e.g. FDA or other) and the methodology used to derive dietary glycaemic index and load. The use of drop-down menus within the access database permits systematic capture of this type of exposure detail and then if sufficient studies exist this would then permit analysis of outcomes including and excluding studies using a certain exposure definition e.g. all cohort studies using the FDA definition of wholegrain or a more inclusive approach.

5.8 Relevant outcomes

Outcomes in both adulthood and childhood will be included, although reported separately

Cardiovascular disease

- Incidence of fatal cardiovascular disease (CVD)
    - Fatal myocardial infarction
    - Fatal stroke
- Incidence of non-fatal cardiovascular disease
    - Acute coronary syndrome (ACS) including: acute myocardial infarction (AMI), ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), troponin +ve ACS, troponin –ve ACS, unstable angina.
    - Ischaemic heart disease (IHD) including: angina, chronic stable angina, coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI).
    - Stroke disease including: haemorrhagic and thrombotic stroke, transient ischaemic accident (TIA).
- Markers of CVD
    - Incident hypertension, and blood pressure as a continuous variable
    - Markers of vascular function
        - Arterial stiffness
        - Endothelial dysfunction
        - Flow mediated dilation
        - Nitric oxide metabolites and enzymes
    - Blood lipids (fasting and random)
        - Total cholesterol
        - LDL cholesterol (including small dense LDL particles, VLDL)
        - HDL cholesterol
        - Triglycerides
        - Apo lipoprotein B
        - Apo lipoprotein A1

Markers of inflammation

- C-reactive protein (CRP, hsCRP)
- Fibrinogen
- Serum amyloid A
- Cytokines eg IL-6, IL-1, TNFα
- Adhesion molecules eg ICAMs, VCAMs

Diabetes Mellitus

- Incidence of diabetes mellitus (type II)
- Incidence of impaired glucose tolerance
- Incidence of impaired fasting glucose
- Markers relating to impaired glucose tolerance / insulin resistance
    - Glycaemic control, glycated haemoglobin (Hba1c)
    - Insulin resistance/sensitivity, HOMA
    - Hyperinsulinaemia

Obesity

- Incidence of overweight and obesity

- Markers of obesity
    - Markers of weight gain
    - Markers of body composition (BMI, other weight adjusted for height measures, weight, skinfold measurements, other measures such as DEXA, bio-impedance, change in body composition, ectopic fat)
    - Markers of distribution of fat (waist circumference, hip circumference, waist to hip ratio, skinfolds ratio, other measures such as CT, ultrasound)

- Energy intake and satiety

5.9 Retrieving papers

Papers identified as satisfying the inclusion criteria will be retrieved, either from the University of Leeds library, directly from the journal website, by e-mail request from the authors, or from the British Inter-Library loan system.

5.10 Labelling of references

All references identified in the review will be entered into Reference Manager (version 11) databases. A unique identifier will be assigned to each reference. The references (hard and electronic copies) will also be labelled with the reference number. At the end of the review process, all original sources of data (i.e. all references) will be scanned, converted to pdf format and sent to the FSA, together with the Reference Manager databases.

5.11 Bibliographic databases

Three Reference Manager files will be sent to the FSA as follows:
1. A file containing the results of the initial search.
2. A file containing the papers excluded after reading full text.
3. A file containing the papers included after reading full text.

6.0 Study selection procedure

The initial searches will generate a number of sets of references from each online database. Each of these lists will then be downloaded to separate Reference Manager files using the appropriate import filters or by hand if necessary. In this way, each of the search outputs will be saved individually. Following this, all of the Reference Manager databases will be merged and all duplicate references will be removed, and stored in a duplicates database. The combined and de-duplicated database will be sent to the FSA.

The study selection procedure will then follow a three-step process:-

a) The references will be scanned by title and abstract by one reviewer after first undergoing some preliminary assessments of pilot data to agree article relevancy. Those articles that are clearly not relevant to the scope of the review will be marked as ‘not relevant’. These false hits are articles that ‘slip through’ the search strategy terms and contain completely different subject matter e.g. cancer treatment studies, or surgical procedures. Only studies in humans will be included initially. Papers will not be excluded on the basis of quality. A second reviewer will check the accuracy of this approach by double checking a 10% sample of the excluded hits. If there is a discrepancy rate of >5% then the full list will be checked in duplicate.

b) The full manuscript of all papers identified as potentially relevant (in step (a)) for the SLR will be obtained.

c) The full manuscript will be used to determine whether each paper is included or excluded in the review. This process will be conducted separately by 2 members of the review team with reference to an inclusion/exclusion form which will be developed specifically for this project. Where disagreement exists, a third member of the team will arbitrate in this decision. The excluded papers and reason for exclusion will be recorded in a separate file and the included papers and study type will be recorded in a third file. The second and third Reference Manager files will also be sent to the FSA.

7.0 Study quality

This review will not be restricted on the basis of perceived quality of papers or the process of obtaining data cited in primary studies. By limiting the scope of the review to prospective studies and controlled intervention trials many studies of poor quality will automatically be excluded. However, within included studies, study characteristics that may influence risk of bias or are general indicators of study quality will be captured and will be available for display in tables on request.

7.1 Observational studies:

While formal quality grading of observational studies will not be performed on an individual study basis, markers of study quality such as aspects of study design (e.g. study size, duration of follow-up etc.) or methods of exposure assessment (e.g. FFQ vs. food diary, self reported body weight vs. investigator measured etc.) will be used to explore potential sources of bias. Using this approach to quality assessment permits an exploration of quality differences as an explanation for heterogeneity in study results and provides a guide for interpretation of findings and an aid to determining the strength of inferences.

For cohort studies the following aspects of study quality will be extracted:

i. Cohort size
ii. Losses to follow-up (where reported)
iii. Duration of follow-up (reported either as the maximum, the minimum or the average or as person years)
iv. If reported, the sampling method to generate the cohort and the response rate e.g. Health screening clinics – however, it should be noted that this information is not always reported in long standing cohorts and all cohorts suffer to some extent from healthy volunteer bias
v. Characteristics of participants: age (range), gender, other notable characteristics e.g. whether all smokers, US Nurses, Whitehall Civil Servants etc.
vi. Method of assessing diet and whether repeated

7.2 Intervention trials:

In evaluating intervention trial quality, the Cochrane Collaboration's 'Risk of bias' tool will be used in the review[19]. This tool, addresses six specific domains; sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'. Physician blinding (for the purpose of diagnosing or assessing outcomes) makes little difference where cardiovascular mortality is the outcome, but is important for most other outcomes. We will report for each trial whether this was 'adequate', 'inadequate' or 'unclear'. Participant blinding is problematic in most dietary trials, but possible in certain metabolic studies where all the food is provided. Again, this will be assessed as 'adequate', 'inadequate' or 'unclear'.

An assessment of the risk of bias for each of these domains will be undertaken by 2 reviewers for each trial and in the case of disagreement, a third reviewer will arbitrate. A summary risk of bias will be generated for

each trial following guidelines outlined in the Cochrane Collaboration handbook[19]. Categorisation by the 6 domains will be used to explore sources of heterogeneity in the meta-analysis.

Reviewers assessing risk of bias will not be blinded to the names of the authors, institutions, journal and results of a study when they assess its methods.

We will make every attempt to avoid using the 'unclear' criterion for rating trial quality on sources of bias. Where reporting of trial methodology is unclear or missing from a paper, we will make attempts to obtain further information by cross-referencing against other publications relating to that trial, by reference to the published trial protocol (if available) and as a last resort by making contact with the authors.

We will also address the quality of outcome assessment used in studies by capturing details of the methodology used to ascertain data e.g. for outcomes such as incidence of hypertension, how the diagnosis was achieved (e.g. cut points for diastolic/systolic blood pressure), whether assessment was repeated and the source of reporting (self-report, GP report, hospital records etc.). For continuous outcomes such as insulin resistance, the method used will be captured e.g. HOMA, indices using fasting insulin. Should sufficient studies be available for meta-analysis for a particular exposure-outcome combination, the methods of outcome measure will then potentially be available for inclusion in testing for sources of heterogeneity.

Since a comprehensive approach to extracting data is important, Access-based software purposefully designed in the Nutrition Epidemiology Group will be used. This software is flexible, and permits systematic capture of relevant study characteristics related to quality and export to tables in any format required to display these relevant characteristics.

8.0 Data extraction

Study data will be obtained from full versions of papers. All data will be entered using data extraction software initially designed in the Nutrition Epidemiology Group at the University of Leeds for use in the World Cancer Research Fund (WCRF) systematic literature reviews that contributed to the Second Expert Report[20]. Data will not be extracted directly into Word format tables since previous experience has indicated that a more flexible approach using intermediary software is more efficient. Ultimately, data can be exported from the data extraction software into tables complying with the SACN format, or with appropriate table headings as requested by the Working Group.

The software is designed to collect all relevant information depending on the study designs and populations. The information collected covers the following areas

- Bibliographic information
- Study subject information, e.g. Age, Gender, Ethnicity etc
- Dietary assessment tools utilised in study
- Statistical matters; power calculations, sampling
- Randomisation design and matching criteria
- Study quality
- Quality of outcome assessment e.g. method of assessment of insulin resistance
- The impact of potential bias of each trial

In addition the software also allows the grouping of publications by study name (such as 'The Nurses Health Study' or the CARDIA study). This reduces the chances that data from linked publications are duplicated in the review.

The software is designed with output of results in tabular format and meta-analysis in mind. Its functionality permits the entry of;

- A detailed exposure list and additional exposure detail, allowing easy reporting across exposures

- Numerous formats of result reporting
    - Quantiles
    - Categories
    - Continuous
    - Means
    - Correlations
- Statistical adjustments for results are collected - adjustment applied in the analysis can be captured under broad or more precise headings e.g. adjustment for smoking as ever/never or adjustment for smoking as pack years
- Different outcomes can be input e.g. incidence of type 2 diabetes, weight gain, cardiovascular events (mortality or incidence)

All data entered into the software is coded into to numerical variables to aid the analysis of data.

9.0 Consideration of how to deal with potential confounding factors within observational studies

Within observational studies, a confounder is related to both the exposure and outcome variable but does not lie in the causal pathway between them. A number of such potential confounding factors have previously been identified for cardiovascular disease. These may include age, sex, ethnicity, family history, genetic variability (e.g. apo E), physical activity and smoking. However, it is clear that it is important to distinguish between confounding and effect modification. An effect modifier modifies the effect of the exposure of interest on the outcome, and may therefore be represented by a statistical interaction term. Whilst confounding is a bias that investigators hope to prevent or remove from the effect estimate, 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. Potential effect modifiers for cardiovascular disease may include age, sex, smoking and ethnicity. If data are available, sub-group analyses of e.g. body mass index, smoking group and pre/post menopausal status will be reported. When results of a stratified analysis are presented for a study, data will be extracted when possible for each sub-group analysed (e.g. in smokers and non-smokers or obese/non obese). Ultimately, if there are enough publications that have presented data in this way, this will permit meta-analysis to be undertaken separately for each sub-group. Similarly, since the method of dietary reporting will be captured, this would permit an investigation of the effects of dietary exposures according to method of dietary data collection (if sufficient studies emerge).

10.0 Data analysis

The main objective of data synthesis is to collate and summarise the results of studies included in the systematic literature review. Meta-analytic and narrative approaches will be used in a complementary fashion, since neither approach used in isolation is capable of capturing and exploring all the caveats and short comings of the literature reviewed. Our aim is to undertake a meta-analytic approach where possible, but we will take into consideration the nature and magnitude of the evidence base and the extent of heterogeneity in the data.

It is anticipated that results from the articles identified will have been presented in a variety of different formats. To facilitate comparison and synthesis of findings, where possible all results will be converted to estimates of relative risk and associated 95% confidence intervals. In particular, where fitting of linear trends is appropriate, results will be presented in a standard format of odds ratio for a unit increase of exposure. This will be done using the methods attributable to Greenland and Longnecker and Chêne and Thompson[21,22]. Generally, the methods used for meta-analysis of observational studies will be the same as those used in the World Cancer Research Fund 2nd Expert Report "Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective", which contains the details[20]. This and the key methods on

which they were based were also referenced to detailed works by Greenland and Longnecker[21] and by Chêne and Thompson[22] and are described in more detail below. The methods will be implemented using Stata version 10.1, using the -glst- command[23] as subsequently updated[24]. Results using these methods have been validated against those obtained by other centres involved in the WCRF review on a test dataset.

10.1 Deriving estimates of dose-response in cohort studies

To enable comparison of different studies, the relative risk for a linear dose-response across the exposure will be estimated. Wherever possible this will be estimated using the methods of Greenland and Longnecker[21] based on mean exposures for each category of exposure. However, this information is frequently not presented in papers and a number of approaches may be taken in order to derive the information required.

These will be applied in the following order of priority:

1) Where the exposure is 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) is not given in the text, these will be estimated using the methods of Greenland and Longnecker[21] using the mean exposure in each category given in the paper. No additional assumptions are required.
3) Greenland and Longnecker's method requires the total numbers of cases and non-cases to be known, and starting estimates for the number of cases in each category. Where these are not presented, values will be estimated based on the ratio of cases to non cases, the basis for any categorisation into quantiles (whether based on the whole population or just controls), or on the information contained in each category estimated from the width of the confidence intervals.
4) Where the mean exposure for each category is rarely given, so the methods of Chene and Thompson[22]were used to estimate the means for use in the Greenland and Longnecker technique. 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 and Longnecker technique.
6) Where no confidence intervals are 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 and Longnecker's method will then be applied using means given in the paper or derived assuming normality, based on these derived confidence intervals.
7) Where the above methods can not be used, the methods of Chene and Thompson[22] will be applied to derive the dose-response estimate directly through a weighted logistic regression.
8) Using the methods of Chene and Thompson, we can also derive an estimate of the dose-response slope from the mean exposure for cases and controls, alongside the numbers of each and a measure of variability such as standard deviation.
9) Where these fail, a comparison based on the extreme categories can be used to estimate the dose-response, ignoring the information from categories in-between. This still requires information to quantify the exposure so the mean exposure in each category can be estimated.

Where linear trends are not appropriate, comparison of the most extreme exposure categories will be considered. However, comparison of extreme categories, which has been used in other systematic reviews of carbohydrate-based foods and cardiovascular disease risk factors[13,25] can introduce further heterogeneity into the pooled estimate of risk since exposure levels within the comparison groups may vary markedly between studies. It is common for some studies, particularly older ones or poorer quality ones, not to present sufficient information to derive a dose-response trend. This could easily be as many as half the relevant studies identified. Whilst they cannot be included in meta-analysis of a linear dose-response trend (even if it were appropriate), they will be included in tables and the narrative overview.

To facilitate this, data abstraction of selected articles will include detailed information such as numbers of patients at each level of exposure, exact cut-offs for each of the exposure categories, numbers in each group developing or not developing the outcome, percentages where quoted, and other details that could allow relative risks to be derived where they are not quoted in the text. These will be tabulated and considered for formal meta-analysis.

10.1.1 Log transformation

The decision whether to log-transform will be made on an exposure by exposure basis. This will be based on previous experience of similar exposure distributions, and on the estimated means derived for use in the Greenland and Longnecker method for deriving dose-response estimates. Where data are presented as arithmetic means and standard deviations for cases and controls, then the mean and standard deviation of the log-transformed variable will be estimated using the method of Quan and Zhang[26].

10.2 Choice of increment for relative risk

For many exposures the SI units represent very small increments when compared to usual exposure. The relative risk for such small increments is often 1.00 (95% CI: 1.00 to 1.00), providing little useful information. We intend to present estimates of relative risk for more meaningful increments representing an achievable change in exposure relative to usual exposure. For example, rather than presenting a pooled estimate for each 1 g/day of non-starch polysaccharide, we may present estimates for each 5 g/day. This allows the reader to more easily assess the magnitude of the apparent effect and uncertainty in its estimate.

10.3 Meta-analysis

For each specific exposure a decision will be made whether or not to proceed to formal meta-analysis based on the number of useable studies. We will only consider pooling estimates using meta-analysis, where there are at least 3 cohort studies or 3 randomised controlled trials with identical outcomes and exposures, and where there is not excessive heterogeneity. Summary estimates will be prepared for each study design separately, and these will be displayed on separate forest plots. Fixed effects meta-analysis will be used for randomised controlled trials, with additional random effects meta-analysis presented for observational studies because of the large potential for between-study heterogeneity with these designs[25,27]. All analyses will be performed in Stata 10[28,29]. Results will be interpreted and reported in a manner interpretable by non-statisticians familiar with the subject matter.

10.3.1 Inclusion of cohort results in meta-analyses

All cohort studies extracted will be considered for inclusion in a meta-analysis if we consider that the dietary exposure and outcome of interest are the same as those reported in at least 2 further studies. The following guidelines will be applied:

- Where more than one paper has been published from the same study, the one containing the larger number of cases will be used. This is often the most recent paper.
- Where the same exposure has been analysed in more than one way with different levels of adjustment, the best model will be taken to be the one with the most appropriate adjustment for confounding. This is often the maximally adjusted analysis, or the one with the narrower confidence intervals. However, the best model is not always the maximally adjusted one and sometimes a model with less adjustment may more appropriate because it avoids over-adjustment.
- Where an exposure is presented for all study participants, and by subgroup, the analysis of all study participants will be used.

- Where an exposure is presented only by subgroup, the subgroups will be included in the meta-analysis separately and labelled by subgroup. This maintains the independence of observations included, and is essentially equivalent to including the overall estimate.
- Where a paper presents results from two separate studies and includes a mega-analysis pooling the two different studies (e.g. the Nurses Health Study and the Health Professionals Follow-up Study), then the studies will be included separately and the mega-analysis will not be included. This maintains the independence of observations included. Where necessary the mega-analysis will be described in the text of the overview.

Cohort studies have to present enough information for the dose-response to be estimated from one of the above approaches. To be included, they need one of the following combinations of pieces of information to be derivable or at least approximately estimable:

- Dose-response slope and measure of uncertainty, i.e. standard error or confidence interval.
- Mean exposure in each category, the total number of cases and non cases, estimated relative risks for each category, a way of quantifying uncertainty around these estimates, e.g. confidence intervals.
- Range of exposure for each category, the total number of cases and non-cases, estimated relative risks for each category, a way of quantifying uncertainty around these estimates, e.g. confidence intervals.
- Mean and number of cases and non-cases, along with a measure of uncertainty in the mean, e.g. standard deviation or standard error.

The main reasons for not being able to include results from some studies are likely to be related to lack of necessary information outlined above:

- No way of quantifying the exposure. Neither the mean nor range of exposure are given for each category. It is therefore impossible to estimate a dose-response, when the level of that dose of exposure is unknown. In addition it is impossible to plot the exposure on a dose-response graph. Where the means for cases and for non-cases are used to estimate the dose-response, and there is no measure of uncertainty given with these means, i.e. standard deviation, standard error or confidence intervals, and these cannot be derived from other information in the paper.
- The exposure is grouped into just two categories. If, as is often the case, the lower limit of exposure is not given, then the mean exposure can not be estimated for each category. Where there are three categories, but one is a "never" category, then there are only two remaining categories on which to base the estimates and the same problem emerges. For nutrient data this is rarely an issue, since everyone consumes all nutrients to some degree. This might be a potential issue for some food-group exposures where there is zero consumption category for e.g. sugar-sweetened beverages.
- No confidence intervals are given and there is no way of deriving the confidence interval or measure of uncertainty in the estimate.

10.3.2 Meta-analysis of intervention trials

Where results from studies can be quantitatively combined, and provided 3 studies are includable, a meta-analysis of the intervention trial data will be undertaken. For dichotomous data (such as number of events – e.g. heart attack or stroke) an odds ratio will be derived, and for continuous data a weighed mean difference will be calculated (weighted by the inverse of the variance). To aid interpretation and inclusion in meta-analysis, where possible the results of studies will be converted to the same SI units of outcome assessment. The standard mean difference will be used if trials report the same outcome but assessed in different ways e.g. different methods of measuring flow mediated dilation[30].

10.4 Assessment of Heterogeneity

Heterogeneity will be explored by both qualitative and quantitative methods. Where possible, given the number and variety of studies, the qualitative approach will involve consideration of forest plots after stratification on study and individual characteristics. These will be tailored to the particular exposure and outcome, but may include detail of exposure definition, range and length of exposure, nature of the population sampled, age, sex ratio, years of follow-up, geographical area, and measures of study quality such as sample size, dietary assessment method, adjustment for the tabulated possible confounders and correction for measurement error. Where meta-analysis is performed, one forest plot for each study type will be included in the report, because it is generally not appropriate to pool different study types.

Heterogeneity will be formally tested using the methods of DerSimonian and Laird[31,32] presented alongside the more useful proportion of total variation in study estimates that is due to heterogeneity (I^2)[33]. Whilst we recognise some potential weaknesses in the approach, we prefer to quantify heterogeneity using estimates of I^2 rather than testing, which depends on the number of studies, lacking power for small meta-analyses, and finding small amounts of heterogeneity statistically significant for large meta-analyses. It is common to interpret I^2 (the proportion of the total variation in study estimates that is due to between-study heterogeneity) as being excessive where the I^2 is in excess of 30% - 50%. We choose to use 50% as our cut off. Any heterogeneity will be formally described by extending the random effects meta-analysis to estimate the extent to which study-level covariates (listed above) explain heterogeneity in the exposure effects (meta-regression). This will also be performed within Stata 10[29,34]. Where possible, given the number and variety of studies, meta-regression will be performed separately within each study type.

Where there is substantial heterogeneity associated with the dietary assessment tool, then odds ratios for a one standard deviation increase in exposure will be considered in addition to the odds ratio for a one unit increase. Where there is any excessive heterogeneity, indicated by I^2 greater than 50%, pooled estimates and meta-analysis will be inappropriate and will not be presented.

11.0 Reporting

In preparing the report, we will keep in mind guidelines for presenting systematic literature reviews provided by the PRISMA statement (http://www.prisma-statement.org/) as described by Moher *et al.*[35,36]. Summaries of the evidence for each exposure/outcome will be prepared taking into consideration the ESRC report Guidance on the Conduct of Narrative Synthesis in Systematic Review. Required information will be displayed in SACN style tables and a narrative synthesis of the results from all the included studies will be provided without interpretation of data, conclusions or opinions.

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Appendix 1. Draft MEDLINE search strategy for dietary carbohydrate and cardio-metabolic health

1. exp cohort studies/
2. cohort$.tw.
3. controlled clinical trial.pt.
4. epidemiologic methods/
5. or/1-4
6. randomized controlled trial.pt.
7. controlled clinical trial.pt.
8. randomized.ab.
9. placebo.ab.
10. drug therapy.fs.
11. randomly.ab.
12. trial.ab.
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. (animals not (humans and animals)).sh.
15. 13 or 5
16. 15 not 14
17. exp dietary carbohydrates/
18. carbohydrat$.ab,ti.
19. ((glucose or fructose or lactose or maltose or sucrose) adj3 (diet$ or intake$)).tw.
20. sugar$.ab,ti.
21. sucrose/
22. exp starch/
23. starch$.tw.
24. polysaccharide$.tw.
25. monosaccharide$.tw.
26. disaccharide$.tw.
27. oligosaccharide$.tw.
28. polysaccharides/
29. inulin$.tw.
30. inulin/
31. alginates/
32. cellulose/
33. carageenan/
34. lignin/
35. methylcellulose/
36. carboxymethylcellulose/
37. isomaltose/
38. maltose/
39. mannans/
40. exp oligosaccharides/

41. pectins/
42. plant gums/
43. gum arabic/
44. karaya gum/
45. tragacanth/
46. chitin/
47. dietary fiber/
48. dietary fiber$.tw.
49. dietary fibre$.tw.
50. "guar gum".tw.
51. psyllium/
52. psyllium$.tw.
53. "beta glucan$".tw.
54. beta-glucans/
55. cereals/
56. cereal$.tw.
57. wheat$.tw.
58. (oat$ or porridge).tw.
59. rye$.tw.
60. barley.tw.
61. grain$.tw.
62. rice.tw.
63. bread/
64. bread$.tw.
65. wholegrain$.tw.
66. potato$.tw.
67. "whole grain$".tw.
68. (whole adj3 grain$).tw.
69. "refined grain".tw.
70. candy/
71. pasta/
72. ((cake$ or biscuit$ or cookie$ or confectionery) adj3 (diet or intake)).tw.
73. fabaceae/
74. legume$.tw.
75. bean$.tw.
76. carbonated beverages/
77. ((soda or carbonated or sweet$ or sugar$) adj3 beverage$).tw.
78. ((soda or carbonated or sweet$ or sugar$) adj3 drink$).tw.
79. "soft drink".tw.
80. glycemic index/
81. ((index or load) adj3 glyc?emic).tw.
82. ((diet$ or low or high) adj3 GI).tw.

83. exp cardiovascular diseases/
84. "cardiovascular disease$".tw.
85. stroke.ab,ti.
86. "acute coronary syndrome".tw.
87. STEMI.tw.
88. NSTEMI.tw.
89. angina.tw.
90. (transient isch?emic adj3 (accident or incident)).tw.
91. exp coronary diseases/
92. exp heart diseases/
93. (heart adj3 disease$).tw.
94. (coronary adj3 disease$).tw.
95. (CHD or CVD).tw.
96. (myocardial adj3 infarction).tw.
97. exp myocardial infarction/
98. exp myocardial ischemia/
99. myocardial isch?emia.tw.
100. hypertensi$.tw.
101. (blood adj3 pressure$).tw.
102. exp blood pressure/
103. exp cardiovascular system/
104. (arterial adj3 (stiffness or distensibility or elasticity)).tw.
105. "flow mediated dilation".tw.
106. (pulse wave adj3 (velocity or analysis)).tw.
107. (endothelial adj3 (function or dysfunction)).tw.
108. endothelium, vascular/ph
109. exp Vascular Resistance/
110. atherosclerosis.tw.
111. Cholesterol/bl [Blood]
112. Cholesterol, LDL/
113. Cholesterol, HDL/
114. (low adj3 density adj3 lipoprotein$).tw.
115. (high adj3 density adj3 lipoprotein$).tw.
116. LDL-C.tw.
117. HDL-C.tw.
118. Hyperlipidemias/bl [Blood]
119. Hyperlipidemia$.tw.
120. Hypercholesterolemia/bl, ep [Blood, Epidemiology]
121. Hypercholesterolemia$.tw.
122. Dyslipidemias/bl, ep [Blood, Epidemiology]
123. Dyslipidemia$.tw.
124. Triglycerides/bl [Blood]

125. Lipids/bl [Blood]
126. Apolipoproteins/bl [Blood]
127. Apolipoprotein$.tw.
128. (APOB or APO B).tw.
129. inflammation/bl
130. exp C-Reactive Protein/
131. "C reactive protein".tw.
132. CRP.tw.
133. exp fibrinogen/
134. fibrinogen$.tw.
135. Serum Amyloid A Protein/
136. "serum amyloid A".tw.
137. tumor necrosis factor-alpha/
138. "tumor necrosis factor alpha".tw.
139. (TNFalpha or TNF-alpha).tw.
140. interleukin-1alpha/
141. "interleukin 1".tw.
142. interleukin-6/
143. "interleukin 6".tw.
144. intercellular adhesion molecule-1/
145. "intercellular adhesion molecule-1".tw.
146. "ICAM-1".tw.
147. vascular cell adhesion molecule-1/
148. "vascular cell adhesion molecule-1".tw.
149. "VCAM-1".tw.
150. Diabetes Mellitus, Type 2/
151. Metabolic Syndrome X/
152. blood glucose/
153. Insulin/bl [Blood]
154. insulin resistance/
155. hyperglycemia/
156. hyperinsulinism/
157. carbohydrate metabolism/
158. ((resistance or sensitivi$ or control$ or fasting) adj3 insulin).tw.
159. "blood glucose".tw.
160. Hemoglobin A, Glycosylated/
161. HbA1c.tw.
162. exp obesity/
163. exp weight gain/
164. exp weight loss/
165. exp body weight/
166. exp body composition/

167. exp body mass index/

168. skinfold thickness/

169. intra-abdominal fat/

170. waist-hip ratio/

171. obes$.tw.

172. (weight adj3 (cyc$ or reduc$ or maint$ or watch$ or control$ or gain or loss or chang$)).tw.

173. (body adj3 (weigh$ or size or fat or mass)).tw.

174. BMI.tw.

175. (skinfold adj3 (thick$ or measur$)).tw.

176. (waist adj3 hip adj3 ratio).tw.

177. (waist adj3 circumference$).tw.

178. (hip adj3 circumference$).tw.

179. fat$ distribut$.tw.

180. (ectopic adj3 (fat or adipose)).tw.

181. intramyocellular lipid.tw.

182. intrahepatocellular lipid.tw.

183. (drug or diagnos$ or prognos$ or therap$ or surg$).ti.

184. or/17-82

185. or/83-182

186. 16 and 184 and 185

187. 186 not 183

188. limit 187 to english language

189. limit 188 to yr="1990 -Current"

190. limit 189 to (addresses or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or interactive tutorial or interview or lectures or legal cases or legislation or letter or newspaper article or patient education handout or portraits or "review")

191. 189 not 190

192. limit 191 to (cats or cattle or chick embryo or dogs or goats or guinea pigs or hamsters or horses or mice or rabbits or rats or sheep or swine)

193. 191 not 192

Appendix 2. Draft MEDLINE search strategy for dietary carbohydrate and energy intake and satiety

1. exp cohort studies/

2. cohort$.tw.

3. controlled clinical trial.pt.

4. epidemiologic methods/

5. or/1-4

6. randomized controlled trial.pt.

7. controlled clinical trial.pt.

8. randomized.ab.
9. placebo.ab.
10. drug therapy.fs.
11. trial.ab.
12. Cross-Over Studies/
13. repeated measures.tw.
14. within subject$.tw.
15. or/6-14
16. 5 or 15
17. exp dietary carbohydrates/
18. carbohydrat$.ab,ti.
19. ((glucose or fructose or lactose or maltose or sucrose) adj3 (diet$ or intake$)).tw.
20. sugar$.ab,ti.
21. sucrose/
22. exp starch/
23. starch$.tw.
24. polysaccharide$.tw.
25. monosaccharide$.tw.
26. disaccharide$.tw.
27. oligosaccharide$.tw.
28. polysaccharides/
29. inulin$.tw.
30. inulin/
31. alginates/
32. cellulose/
33. carageenan/
34. lignin/
35. methylcellulose/
36. carboxymethylcellulose/
37. isomaltose/
38. maltose/
39. mannans/
40. exp oligosaccharides/
41. pectins/
42. plant gums/
43. gum arabic/
44. karaya gum/
45. tragacanth/
46. chitin/
47. dietary fiber/
48. dietary fiber$.tw.
49. dietary fibre$.tw.

50. "guar gum".tw.
51. psyllium/
52. psyllium$.tw.
53. "beta glucan$".tw.
54. beta-glucans/
55. cereals/
56. cereal$.tw.
57. wheat$.tw.
58. (oat$ or porridge).tw.
59. rye$.tw.
60. barley.tw.
61. grain$.tw.
62. rice.tw.
63. bread/
64. bread$.tw.
65. wholegrain$.tw.
66. potato$.tw.
67. "whole grain$".tw.
68. (whole adj3 grain$).tw.
69. "refined grain".tw.
70. candy/
71. pasta/
72. ((cake$ or biscuit$ or cookie$ or confectionery) adj3 (diet or intake)).tw.
73. fabaceae/
74. legume$.tw.
75. bean$.tw.
76. carbonated beverages/
77. ((soda or carbonated or sweet$ or sugar$) adj3 beverage$).tw.
78. ((soda or carbonated or sweet$ or sugar$) adj3 drink$).tw.
79. "soft drink".tw.
80. glycemic index/
81. ((index or load) adj3 glyc?emic).tw.
82. ((diet$ or low or high) adj3 GI).tw.
83. satiation/
84. energy intake/
85. satiety response/
86. hunger/
87. appetite/
88. appetite regulation/
89. hunger.tw.
90. satiety.tw.
91. appetite.tw.

92. energy intake.tw.

93. or/17-82

94. or/83-92

95. 16 and 93 and 94

96. limit 95 to english language

97. limit 96 to yr="1990 -Current"

98. limit 97 to (addresses or bibliography or biography or case reports or classical article or clinical conference or comparative study or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interactive tutorial or interview or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or overall or patient education handout or periodical index or portraits or "review" or "scientific integrity review" or technical report)

99. 97 not 98

100. limit 99 to (cats or cattle or chick embryo or dogs or goats or guinea pigs or hamsters or horses or mice or rabbits or rats or sheep or swine)

101. 99 not 100

Appendix II:

Guidelines for Article Relevancy

Article Not Relevant

Reject if you can determine from the title and/or abstract:

- Study published before 1990
- Study is not published in English
- Participants outside age range 5-80 years
- Study includes animals only
- The reference is not an original research article (e.g. news, letter, review)
- The study is not a cohort or an RCT (e.g. case study, cross-sectional study)
- The study does not relate to carbohydrate intake at all (e.g. Meat, Soy etc)
- All participants have a pre-existing health condition, are pregnant or have an eating disorder (e.g. Polycystic Ovary Syndrome/Cancer Patients/ Type1Diabetes/ Type2Diabetes/ Hypertension/ CVD/ Angina etc)
- The study does not relate carbohydrate intake to a clinical outcome e.g. a survey of intakes
- The study relates to exercise and dietary components cannot be separated from the exercise.
- The study is clearly not relevant to the review (e.g. study of cancer treatment or surgical procedure)
- The study does not include satiety-related outcomes and intervention duration is 1 day or less

Potentially Relevant

Allow if you cannot reject on the above criteria:

- Anything which appears to be relevant or where insufficient information is available to make a decision that it is ‘article not relevant’ or ‘population not relevant’
- Studies which appear to be relevant even if the duration is too short to be formally included at a later stage.

Appendix III:

Inclusion/Exclusion Form

Dietary Carbohydrates and Cardio-Metabolic Health and Disease

Assessor name……..…….. Date: / /2010

Citation Details

First Author	
Ref Manager ID	
Publication Year	
Journal Details	

Status of Study (circle one):

Excluded Code……	Included Code……	Pending	Status/Code Updated in RefMan? ✔ ☐

Population: Potentially non relevant? Give Detail ……
……
……

If included, mark this study as PA, PB, PC or PD to denote the population difference

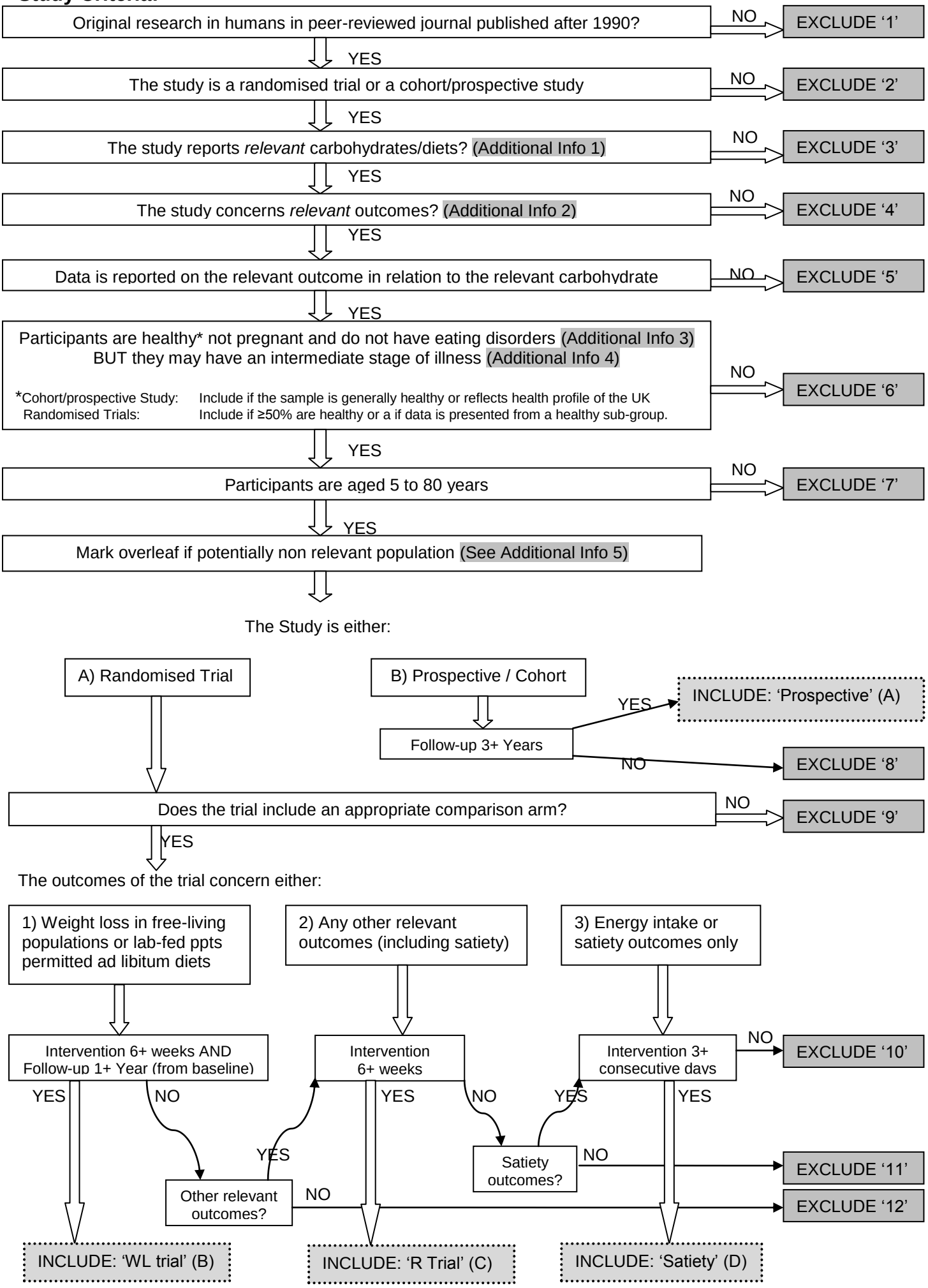
If included:

		RefMan Updated ✔	Date Updated
Determine study type (see flow chart)			
Decide Study name			

If included as a trial, circle as appropriate

Was the allocation sequence adequately generated?	Bias	No bias	Unclear
Was allocation adequately concealed?	Bias	No bias	Unclear
Were participants blinded to treatment status?	Bias	No bias	Unclear
Were assessors blinded to treatment status?	Bias	No bias	Unclear
Were incomplete outcome data adequately addressed?	Bias	No bias	Unclear
Was the study free of suggestion of selective outcome reporting?	Bias	No bias	Unclear
Was the study free of other problems that could cause bias?	Bias	No bias	Unclear

Study Criteria:



Appendix IV:

Inclusion/ Exclusion Additional Info 1: Carbohydrates

Relevant Exposures:

Carbohydrates	
Carbohydrate, total (grams/day)	Modified starches
Carbohydrate, total (% energy)	Resistant starch
Sugars, total (g/d)	Dietary Fibre, unspecified
Sugars, total (% energy)	Non-starch polysaccharide
Monosaccharides, total	NSP density (g/MJ)
Glucose	Cellulose
Fructose	Hemicellulose
Galactose	Glucomannans
Disaccharides, total	Methylcellulose
Sucrose	Carboxymethlycellulose
Lactose	Dextrins
Maltose	Maltodextrins
Isomaltose	Pectin
Trehalose	Arabinoxylans
Oligosaccharides (3–9), total	Beta glucans
Maltooligosaccharides (a-glucans)	Mannans
Non-a-glucan oligosaccharides	Chitin
Raffinose	Inulin
Stachyose	AOAC fibre
Fructooligosaccharides	Fibre density (g/MJ)
Galacto oligosaccharides	Southgate fibre
Mannanoligosaccharides	Fibre density (g/MJ)
A-galactosides	Fibre from fruit
Polysaccharides (>10), unspecified	Fibre from vegetables
Starch, total	Fibre from cereals
Amylose	Fibre from legumes
Amylopectin	Lignin

Characteristics of carbohydrates
Glycaemic index
"High GI" foods
"Low GI" foods
Glycaemic load
High GI diet
Low GI diet

Dietary sources of carbohydrates	
Cereals, total	Starchy roots, tubers and plantains, total
Total wholegrain foods	Potatoes
Wholegrains, FDA definition	Other starchy roots, tubers and plantains
Wholegrains, non-FDA	Legumes/Fabaceae (excluding soy),
Total refined grain foods	Snacks and confectionary, total
Breakfast cereals, unspecified	Savoury starch-based snacks
Bread, unspecified	Potato-based snacks
Wholewheat bread	Sweet snack foods, nonspecific
White bread	Biscuits
Other wheat foods	Buns and pastries
Wheat bran	Cakes
Bulgar wheat	Non milk based puddings and desserts
Oats and oat products, total	Non-chocolate confectionary/candy
Whole and rolled oats	Table sugar
Oat cereal/porridge	Jam and preserves
Oatmeal	Other extrinsic sugars (syrups)
Barley, total	High fructose corn syrup (HFCS)
Barley kernels	Sugar-sweetened beverages, total
Barley porridge	Full-calorie sugar sweetened beverages (SSB's)
Rice, total	Mixed sugar and artificial sweetner beverages
Brown rice	Fructose sweetened beverages
White rice	Fibre isolates
Rice bran	Gum arabic
Rye and rye products, total	Karaya Gum
Whole rye	Alginates
Rye Bread	Carageenan
Rye flour	Psyllium
Corn, and corn products, total	Mucilages
Corn bran	Oat gum/bran
Popcorn	Tragacanth
Maize meal	

NOT to include:

- Diets with distinct features where effects of carbohydrates cannot be separated out (diets with a high proportion of plant sterols, soy, viscous fibres, nuts or oily fish etc):
    - Portfolio diets
    - Combination diets
    - Mediterranean diet
    - Diets containing Soy and Soy Isolates
- Crude Fibre only
- Chocolate

Inclusion/ Exclusion Additional Info 2: Relevant Outcomes

Cardiovascular disease

- Incidence of fatal CVD
  - Fatal myocardial infarction
  - Fatal stroke

- Incidence of non-fatal CVD
  - Acute coronary syndrome (ACS) including:
    - acute myocardial infarction (AMI),
    - ST elevation myocardial infarction (STEMI),
    - non-ST elevation myocardial infarction (NSTEMI),
    - troponin +ve ACS, troponin –ve ACS,
    - unstable angina.

  - Ischaemic heart disease (IHD) including:
    - Angina/ chronic stable angina,
    - coronary artery bypass grafting (CABG),
    - percutaneous coronary intervention (PCI)/ angioplasty.

  - Stroke disease including:
    - haemorrhagic and thrombotic stroke,
    - transient ischaemic accident (TIA).

- Markers of CVD
  - Incident metabolic syndrome or syndrome X
  - Incident hypertension, and blood pressure as a continuous variable
  - Markers of vascular function:
    - Arterial stiffness
    - Endothelial dysfunction
    - Flow mediated dilation
    - Nitric oxide metabolites and enzymes

  - Blood lipids (fasting and random):
    - Total cholesterol
    - LDL cholesterol (including small dense LDL particles, VLDL)
    - HDL cholesterol
    - Triglycerides
    - Apo lipoprotein A/B
    - Hyperlipidemia
    - LDL containing apolipoprotein C-III
    - Homocysteine
    - Interleukin 6

  - Markers of inflammation:
    - C-reactive protein (CRP, hsCRP)
    - Fibrinogen
    - Serum amyloid A
    - Cytokines eg IL-6, IL-1, TNFα
    - Adhesion molecules eg ICAMs, VCAMs
    - White blood cells, subtypes, derivatives and counts

Diabetes Mellitus

- Incidence of diabetes mellitus (type II)
- Incidence of impaired glucose tolerance
- Incidence of impaired fasting glucose
- Markers relating to impaired glucose tolerance / insulin resistance
    - Glycaemic control/ Hyperglycaemia
        - Glycated haemoglobin (Hba1c/ A1c/ Hb1c/ Hga1c)
        - Blood Glucose
        - Leptin
        - Fructosamine
    - Insulin control/ Hyperinsulinaemia
        - Insulin resistance/sensitivity, (HOMA, IV GTT, ITT, IST)
        - C-peptide
        - Insulin
        - Glucagon
        - Acute Insulin Response (AIR)

Obesity

- Incidence of overweight and obesity
- Markers of obesity
    - Markers of weight and weight changes
    - Markers of body composition
        - BMI, other weight adjusted for height measures,
        - weight,
        - skinfold measurements,
        - other measures such as DEXA/ bio-impedance,
        - change in body composition
    - Markers of distribution of fat
        - Waist/ hip circumference/ waist to hip ratio
        - skinfolds ratio
        - other measures such as CT/ ultrasound
        - Ectopic Fat/
- Energy intake and satiety
    - Appetite
    - Appetite hormones
    - Food Intake
    - Energy Intake
    - Hunger
    - Satiety-related scores

Inclusion/ Exclusion Additional Info 3: Illness/disease list

Exclude study if >50% of participants have any illness (see list below) or where data for healthy participants is not presented separately. Participants may have a combination of illnesses, providing the sample contains at least 50% who are free of any one illness.

Exclude also if >50% are taking medication which would influence relevant outcomes

- Diabetes
- CHD/CVD
- Hypertension
- Hyperlipidaemia
- Ischaemic heart disease (IHD)
- Acute Coronary Syndrome
- Stroke (transient ischaemic accident /TIA)
- Angina
- Acute myocardial infarction (AMI)
- (Non) ST elevation myocardial infarction (STEMI/NSTEMI)
- Angioplasty
- Coronary artery bypass grafting (CABG)
- Percutaneous coronary intervention (PCI)

Inclusion/ Exclusion Additional Info 4: Illness thresholds

Include if participants are classified as being 'mildly glucose intolerant' or 'slightly hyperglycaemic' etc. providing thresholds for the following markers are not exceeded by the trial participants at baseline:

- Diabetes thresholds

	mg/dl	mmol/L
Fasting plasma glucose*	126	7.0
Plasma glucose OGTT (75g/120mins)*	200	11.1
Whole blood glucose (fasting)*	110	6.1
Whole blood glucose OGTT (75g/120mins)*	180	10.0
Random plasma glucose	200	11.1
Glycosylated haemoglobin (HbA1c) – only used in USA	Above 6.0%	

*Based on WHO diabetes definition (1999)

- Hypertension: Max BP = 140/90 mmHg

- Hypercholesterolemia/ Hyperlipidaemia thresholds

	mg/dl	mmol/L
Total cholesterol**	240	6.2
LDL**	160	4.1
HDL** (Exclude lower than…)	F: <40 M: <50	F: <1.0 M:< 1.3
Triglyceride**	200	2.3

** American Heart Association thresholds for being classified as 'High Risk for Heart Disease/High cholesterol level'. Source: http://www.americanheart.org/presenter.jhtml?identifier=183

N.B. The conversion for mg/dl into mmol/l is different for each outcomes is dependent upon the molecular weight of substance in question. Conversion factors are as follows: LDL/HDL- factor of 39/ Triglyceride- factor of 89/ Glucose- factor of 18.

Appendix V:

Data extraction fields within the access database

The following information was extracted for all study types:

Country	Country the study took place in
Ethnicity	Ethnicity of the participants
Nationality	Nationality of the participants
% male	Proportion of participants that were male
Age mean/range/description	Mean age of study participants was entered if reported. The range or description was used if the mean was not reported.
Method of assessing dietary compliance: *Is dietary data reported? *Dietary assessment method *Dietary assessment technique issues	 *Tick-box for yes *Drop down menu that could be added to if necessary *Free text to capture any issues that would influence assessment of dietary compliance

Quality of dietary assessment methods

Was more than one method used?	Drop down menu for yes, no, unsure
Number of times diet assessed	Free text
How was the tool administered?	Drop down menu for self administered, self administered plus check, interview, not reported/unsure
Who provided dietary data?	Drop down menu for subject, next of kin, other proxy, combined proxy, combined subject/proxy, not reported
Period assessment refers to?	Free text
Is a validation study referenced?	Drop down menu for yes, no, unsure
Name of FFQ?	Drop down menu with extensive list of known FFQs.
Number of FFQ items?	Free text

RCT descriptive characteristics

BMI mean/range/description	Mean BMI of study participants was entered if reported. The range or description was used if the mean was not reported
Subject inclusion criteria	Inclusion criteria applied to participants at entry into the study.
Dietary intervention type	Drop down menu: • Supplement • Substitution • All food provided • Free living diet plan • Not stated
Design type	Drop down menu: • Parallel • Cross-over • Factorial

Randomisation	Drop down menu: • Yes • No • Not reported
Blinding	Drop down menu: • Double • Single • Open • Not reported
Follow up periods	It was possible to enter as many follow up periods as needed in weeks, months or years. It was also possible to enter as an average if this was how it was reported e.g. an average of 5 months follow-up.
Is the trial industry funded?	Tick-box for yes
Risk of bias: *Allocation sequence ok? *Allocation concealed? *Patients blind? *Researchers blind? *Incomplete outcomes dealt with? *Free of selective outcomes reporting? *Free of other problems?	Drop down menu for each of these questions (see appendix VI for more detail): • Bias • No bias • Unclear
Total sample size	Free text
Number of intervention arms	Free text
Intervention arms: *Intervention arm name *Length of intervention *Exposure *Detailed description *Response rate *N for this intervention group *Wash out *Intended diet	This field could be replicated to accommodate any number of intervention arms *Free text to enter the name the authors assigned to each arm *Could be entered in days, weeks, months or years *Drop down menu of preselected exposures (see appendix IV). This could be added to if the exposure reported did not fit under the preselected exposures *Free text to fully describe the exposure details *Percentage of original group still participating at follow-up *Number of participants assigned to intervention arm *Period between intervention periods. Filled in for cross-over trials only *Tick box for if dietary characteristics reported were the intended diet. If actual diet was reported this was extracted in priority to intended diet.
Arm dietary characteristics: *Energy KJ/day or Kcal/day *CHO %/day or g/day *Protein %/day or g/day *Fat %/day or g/day *Fibre g/day	Dietary characteristics were extracted for the arms or more specifically for supplements, where this data was provided.
Weight change within each arm	Drop down menu • Increase • Decrease • No change • Not reported
Age mean/range/description	Mean age of study participants in each intervention arm was

	entered if reported. The range or description was used if the mean was not reported.
BMI mean/range/description	Mean BMI of study participants in each intervention arm was entered if reported. The range or description was used if the mean was not reported.

RCTs Result extraction

Outcome levels 1, 2, 3 and 4.	Four separate drop down menus for the 4 different outcome levels. Level 1 is cardiovascular disease, markers of cardiovascular disease, markers of inflammation, diabetes and glycaemia and obesity. Level 2 and 3 give further detail and are specific to each outcome level 1 list. Outcome level 4 captures methodological details.
Outcome assessed blind	Drop down menu for bias, no bias, unclear
How are the results presented?	Tick box for either difference between arms or intervention arms separately
Is this a sub group analysis	Tick box for yes
Subgroup description	Drop down menus of an extensive list. This list could be added to if necessary
Results for which follow up	Drop down menu for the follow-up periods already selected fro this trial
Per protocol analysis	Tick box for yes
Adjustments	There was an unlimited number of drop down menus of an extensive list. This list could be added to if necessary. There was also space to add extra details relating to the adjustments if necessary.
Model type: Maximally adjusted Minimally adjusted Unadjusted Best model for subgroup Best model	Tick box for yes
Results table	This results section allowed the research team to enter data for when results were presented in intervention arms separately and when the difference between arms was presented. Data on N, means, SE, SD, CIs, IQ ranges, p-values, outcome units and frequencies were extracted.

Cohort descriptive characteristics

Subject specific study characteristics	There was an unlimited number of drop down menus from an extensive list. This list could be added to if necessary (e.g. no T2DM)
Size of Cohort	Initial number of participants
Length to follow-up	Could be entered in days, weeks, months or years
Length follow description	Was used if the follow-up was described rather than stated.
Average/max length follow up	Drop down menu for whether the follow-up was an average, minimum or maximum
Loss to follow-up	Free text for percentage loss to follow-up
How cohort formed	Drop down menu for community cohort, occupational cohort, population sampled cohort or volunteers

Cohorts result extraction

Exposure	Drop down menu of preselected exposures (see appendix A). This could be added to if the exposure reported did not fit under the preselected exposures
Additional details	Free text to fully describe the exposure details
How are the results presented?	Tick box for either quantiles, categories, continuous, mean exposure cases vs. Controls, regression analysis
No. Quantiles/categories	Free text
Adjustments table	There was an unlimited number of drop down menus of an extensive list. This list could be added to if necessary. There was also space to add extra details if necessary.
Model type: Maximally adjusted Minimally adjusted Unadjusted Best model for subgroup Best model	Tick box for yes
Is this a sub group analysis	Tick box for yes
Subgroup description	Drop down menus of an extensive list. This list could be added to if necessary
N for cases	Free text
N for controls	Free text
N Total	Free text
Outcome levels 1, 2, 3 and 4	Four separate drop down menus for the 4 different outcome levels. Level 1 is cardiovascular disease, markers of cardiovascular disease, markers of inflammation, diabetes and glycaemia and obesity. Level 2 and 3 give further detail and are specific to each outcome level 1 list. Outcome level 4 captures methodological details.
Group used to calculate quantiles	Drop down menu for whole study, just controls, just controls separated for men and women, other cases, not reported
Results table	This results section allowed the research team to enter data for when results were presented as quartiles, categories, continuously, as mean exposure in cases and controls or as regression analysis. Data on N of cases and controls, means, SE, SD, CIs, p-values, quantile/category descriptions, event rates, relative risks, beta co-efficient, outcome units and frequencies were extracted.

Appendix VI

Further information on risk of Bias

Dietary Carbohydrates and Cardio-Metabolic Health and Disease

Criteria for risk of bias

1. **Sequence generation criteria**

Examples of Yes, free of bias	Examples of No, suspected bias
Referring to a random number table	Sequence generated by odd or even date of birth
Using a computer random number generator	Sequence generated by rule based on date of admission
Coin tossing, shuffling cards, throwing dice	Sequence generated by some rule based on record number
minimization	Allocation by judgement or preference or availability of the intervention

Example of unclear: if insufficient information about the sequence generation process to permit judgement of yes or no.

2. **Allocation concealment**

Examples of Yes, free of bias	Examples of No, suspected bias
Central allocation	Open random allocation schedule
Sequentially numbered containers or envelopes of identical appearance	Alternation or rotation or date of birth or record number

Example of unclear: if insufficient information to permit judgement of yes or no. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. **Blinding of participants, personnel and outcome assessors**

Examples of Yes, free of bias	Examples of No, suspected bias
No blinding, but outcome and outcome measurement are not likely to be influenced by lack of blinding	No blinding, and outcome or outcome measurement likely to be influenced by lack of blinding
Blinding used and unlikely to have been broken	Blinding likely to have been broken
Outcome assessment was blinded and non-blinding of others unlikely to introduce bias	Some personnel were not blinded and likely to introduce bias

Example of unclear: Insufficient information to permit judgement of yes or no or the study did not address this outcome.

4. **Incomplete outcome data**

Examples of Yes, free of bias	Examples of No, suspected bias
No missing outcome data	Reason for missing outcome data likely to be related to outcome, either imbalance in numbers or reasons for missing data across intervention groups
Reasons for missing outcome data unlikely to be related to outcome	For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce relevant bias in intervention effect estimate

Missing outcome data balanced in numbers across intervention groups with similar reasons for missing data across groups	For continuous outcome data, plausible effect size among missing outcomes enough to induce clinically relevant bias in observed effect size
For continuous outcome data, plausible effect size among missing outcomes not enough to have relevant impact on observed effect size	As-treated analysis done with substantial departure of the intervention received from that assigned at randomization
Missing data imputed	Inappropriate application of simple imputation

Example of unclear: Insufficient reporting of attrition/exclusions to permit judgement of yes or no (e.g. number randomised not stated, no reasons for missing data provided) or the study did not address this outcome.

5. Selective outcome reporting

Examples of Yes, free of bias	**Examples of No, suspected bias**
Protocol available and all of study's pre-specified outcomes of interest have been reported in pre-specified way	Not all study's pre-specified primary outcomes have been reported
Protocol not available but clear that published reports include all expected outcomes, including those pre-specified	One or more primary outcomes reported using measurements, analysis methods or subsets of the data that were not pre-specified
	Outcomes reported that were not pre-specified or no results reported for key outcome
	Outcomes reported incompletely so cannot be entered in a meta-analysis

Example of unclear: Insufficient information to permit judgement of yes or no. It is likely that the majority of studies will fall into this category.

6. Other potential threats to validity

Examples of Yes, free of bias	**Examples of No, suspected bias**
The study appears to be free of other sources of bias	Potential source of bias
	Stopped early due to some data-dependent process
	Extreme baseline balance
	Other problems reported

Example of unclear: There may be a risk of bias, but there is either: insufficient information to assess whether an important risk of bias exists; or insufficient rationale or evidence that an identified problem will introduce bias.