Protocol: The effect of whole-grain dietary intake on non-communicable diseases: A systematic review, multivariate meta-analysis and dose-response of prospective cohorts, cross-sectional, case-control and intervention studies

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Abstract

The proposed protocol is for a systematic review and meta-analysis on the effects of whole-grains (WG) on non-communicable diseases such as type 2 diabetes, cardiovascular disease, hypertension and obesity. The primary objectives is to explore the mechanisms of WG intake on multiple biomarkers of NCDs such as fasting glucose, fasting insulin and many others. The secondary objective will look at the dose-response relationship between these various mechanisms. The protocol outlines the motive and scope for the review, and methodology including the risk of bias, statistical analysis, screening and study criteria.

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1 Background

1.1 The problem, condition or issue

Cereal grains contribute up to 300 million tons of world food supplies annually (eurostat, 2016). This has lead to a considerable interest in the effects of grains on human health, in particular whole-grains (WG). With non-communicable diseases (NCDs) such as diabetes, cardiovascular disease (CVD) and cancer accounting for 77% of burden of disease, WG consumption may mitigate the effects of NCDs (WHO, 2016). However, with a number of studies showing both a weak and strong association of WGs with NCDs, there is still speculation surrounding the effects of WG (McRae, 2016). Existing reviews mostly look at risk ratios not biomarkers of diseases. Although they provide valuable information, they often limit readers understanding, can be falsely interpreted, and do not provide information on underlying mechanisms (Knol et al, 2012). Most NCDs such as metabolic syndrome are diagnosed based on a cluster of biomarkers such as impaired glucose homeostasis, obesity and dyslipidemia (Alberti et al, 2005); Biomarkers may provide a more accurate way of assessing the effects of WG on NCDs.

Another reason for varying results may also be attributed to the definition of WG which varies in a number of regions (Van der Kamp et al, 2014; Ross et al, 2017). The proposed review not only aims to elucidate the overall effect of WGs but encourage governments to adopt similar definitions and set new targets for WG consumption in order to improve population health.

1.2 Whole-grain consumption and interventions

Most current interventions and cohorts consider WG intake as foods containing 25% or 30% WG weight depending on the definition adopted (Jacobs et al, 2007; Liu et al, 1999; Liu et al 2003). WGs are defined in all countries as containing all of the anatomical components of the grain, including the bran, germ and endosperm (Van der Kamp, 2014; Ross et al, 2017). Familiar grains such as rye, oats, wheat, barley, maize and rice are all considered WGs. While legumes and oilseeds are not (Van der Kamp, 2014). Over the years, WG consumption has been monitored in individuals with NCDs (e.g. diabetes) to assess the longitudinal effect of WG (Nimptsch et al, 2011). Similarly, there have been many interventions (e.g. random control trials) involving WG foods such as bread, cereals, or snacks in healthy individuals and individuals with NCDs (e.g. hypertension) (Kirwan et al, 2016). Cohorts attempt to measure total WG intake whereas interventions attempt to give WG specific food or a range of WG foods in order to mimic normal consumption. Participants tend to be either sex depending on the disease being investigated (e.g. men for prostate cancer and women for breast cancer) but most studies are randomly selected cases and/or healthy individuals from a population (Nimptsch et al, 2011; Mourouti et al, 2016). Studies mostly compare high WG intakes to low WG intakes. The lowest group in the interventions and cohorts normally consume the least WG or a placebo such as refined grains; both of which will be considered zero WG intake (Kirwan et al, 2016;
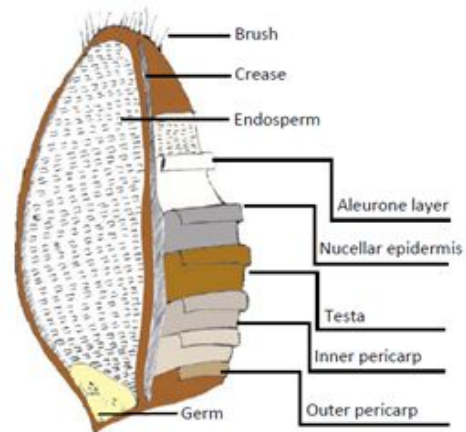
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Jacobs et al, 2007). There are many interventions that involve modified test foods such as WGs with added fiber which are not to be confused with regular WG intake (Liatis et al, 2009). Some studies also report all grains that are not separated into refined and WGs (Lewis et al, 2009; Deneo-Pellegrini et al, 1999). These are not considered as WG unless the intake for only WGs can be isolated from RGs.

1.3 How whole-grain foods reduce the risk of NCDs

WG foods are rich in dietary fibers, vitamins, minerals, protein and phytochemicals. These vary between grain types (Jonnalagadda et al, 2011).WGs retain the outer layers of the bran which makes WGs nutritionally more dense than RGs (Figure 1). Each nutrient has been shown to exhibit different effects on human health.

WGs are a rich source of dietary fibers which are found mainly in the bran (Slavin et al, 2004; Evers et al, 2002). They are well known for their ability to promote satiety, laxation, commensal gut microbiota in the large intestines, reduced blood glucose and cholesterol (Fuller et al, 2016). These may be the reasons for reductions in obesity and cancer cases found in WG cohorts (Lutsey et al, 2007; Skeie et al, 2014). Dietary fibers are chemically the most complex biomolecules in nature and each fiber behaves differently but have all been broadly characterised by these common effects (CFW, 2001).

Figure 1: Basic structure of a WG. The bran constitutes the inner and outer pericarp, testa, nucellar, epidermis and aleurone layer. The endosperm mostly consists of starch. The germ contains the plant embryo (Slavin et al, 2004; Evers et al, 2002).

WGs are rich in B vitamins including folate, thiamin, niacin, riboflavin and pyridoxine (Jonnalagadda et al, 2011; Pirronen et al, 2008). B vitamins have important roles in metabolic pathways. For instance, reductions in homocysteine concentrations have been observed after WG consumption, a marker of CVDs (Jang et al, 2001). This may attributed to folate which is necessary for the final enzymatic reaction in methionine metabolism (Gibney et al, 2009). Vitamin E and vitamin A (tocopherol and tocotrienol) are a fat soluble antioxidant found in the bran and germ layers of WGs (Bartłomiej et al, 2012; Lampi et al, 2008). When consumed, vitamin E is incorporated into the membrane of cells where it is able to retrieve reactive oxygen species (ROS); Molecules responsible for oxidative stress from a range of NCDs (Gibney et al, 2009). Vitamin A (retinoids and carotenoids) has important roles in cell gene expression and vision (Gibney et al, 2009). It has also been shown in animal models that high vitamin A intake have anti-obesity effects (Felipe et al, 2003; Berry et al, 2009). However, most of these studies used excess vitamin A doses so it is not known if the levels of vitamin A from WG are able to give similar effects.

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Phytochemicals are natural components of WGs which form part of the plants defence such as phytosterols and phenolic acids. Phytosterols are well documented for their ability to reduce serum cholesterol such as low-density lipoprotein (LDL) through inhibition of absorption in the small intestine (Nurmi et al, 2009; Rebello et al, 2014). Phenolic acids such as ferulic acid are also well known for their roles in regulating cholesterol levels and their aromatic ring with more than one hydroxyl group means that they can act as antioxidants (Borneo et al, 2012; Rebello et al, 2014; Li et al, 2008). Similar to vitamin A, E and dietary fibers, phytonutrients may be associated with reductions in cancers and obesity as shown in WG cohorts.

Despite these effects, some WG interventions have not presented compelling evidence for the association of WG with various biomarkers of NCDs. For instance, an intervention on body weight and inflammation did not show an effect on c-reactive protein (CRP) (a marker of inflammation) or LDL (a form of cholesterol) but observational studies (e.g. cohorts) have shown WG consumption leads to a decrease in body weight (Gaskins et al, 2010; Lutsey et al 2007). The same scenario can be applied to WG interventions on CVD, hypertension and diabetes which use similar biomarkers. Observational studies involve large sample sizes but interventions have a lot smaller sample sizes and are relatively short which means that the cumulative effect of WG on biomarkers may not be detected. An oatmeal intervention did not reduce fasting glucose levels after a 4 weeks but after a 12 week intervention with WG wheat and oat products a reduction was found (Tighe et al, 2010; Geliebter et al, 2014). Variations in WG definition and products used in interventions will vary in nutritional composition leading to variable outcomes.

1.4 Why is this review important?

To our knowledge, there are only a few systematic reviews which have tried to discuss a range of diseases. Aune et al (2016) have shown the effects of WG on incidence of CVD, cancer and all-cause-mortality. Similarly, Ye et al (2012) looked at the effects of WG on incidence of type 2 diabetes, CVD and weight gain. Both reviews suffered from significant heterogeneity in their model and they did not show the effects of WG specific foods meta-analytically. Ye et al (2012) attempted to look at biomarkers of NCDs such as fasting glucose but these were shown as weighted mean differences which appear to show WGs having significant effects. Even though many primary studies on biomarkers of WG have not shown significant improvements in biomarkers of NCDs. Pol et al (2013), Hollaender et al (2015), Harland et al (2008) and Kelly et al (2007) are the only reviews which look at the effects of biomarkers of body weight and CVD. These reviews fail to look at a range of diseases or biomarkers. Therefore, there is the need for the formation of a high quality systematic review and meta-analysis which a) adheres to campbells Methodological Expectations of Campbell Collaboration Intervention Reviews (MECCIR) and b) assesses the effect of WG on multiple mechanisms in the human body.

All reviews on the effects of WG use a standard univariate model and dose-response analysis (or meta-regression). Although, useful for assessing individual measurement, NCDs are complicated

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disorders that involve more than one measurement for complete diagnosis such as CVD and metabolic syndrome (Alberti et al, 2005). Multivariate meta-analyses have become increasingly popular which can be used to combine multiple biomarkers or measurements (Figure 2) (Riley et al, 2017). Multivariate meta-analysis are able to include a larger number of studies in the final models, reducing heterogeneity. This has been described as "borrowing strength" across effect sizes (Cheung et al, 2013; Riley et al, 2017).

The proposed review hopes to use these models as well as dose-response analysis (or meta-regression) to uncover the overall effect of WGs on NCDs and help inform a universal definition of WG.

2 Objectives

Our primary research questions are:

1. What is the cumulative effect of WG intake on non-communicable diseases (i.e. diabetes, CVD, obesity, cancer, mortality and hypertension)?
2. Can a more accurate assessment of the effects of WG be made by pooling biomarkers of NCD?

Our secondary research question is:

3. Can a dose-response analysis be used to provide better information on the relationship between multiple biomarkers of NCD risk and be used to support universal definitions of WG and WG-foods and set new dietary guidelines for WG intake?

3 Methodology

3.1 Criteria for including and excluding studies

Types of studies

Observational studies on total WG intake and WG specific foods including cross-sectional, case-control and cohorts will be included. Interventions such as randomised controlled trials (RCTs) on WG intake and WG specific foods (e.g. WG rye bread) will also be included.

Types of participants

Participants of either sex, all demographics and ages will be considered. Interventions that report healthy individuals (control) with individuals that are cases of the disease being investigated will be considered. Cohorts that provide a population with the least intake (control) and a population with the highest intake will be considered. Studies that do not report some form of control or reference category will be excluded.

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Types of interventions

Cohorts tend to involve total WG intake or total WG products consumed. Interventions tend to involve WG specific foods or a range of WG foods in order to mimic normal consumption. These are compared to either a low intake category or a placebo such as refined grains; Both of which will be considered zero WG intake (Kirwan et al, 2016; Jacobs et al, 2007). There are also a few studies that involve modified test foods such as added fiber these are not to be confused with normal WG intake and should be excluded. Some studies also report WGs as "grains" when this may imply both RGs and WGs (Lewis et al, 2009; Deneo-Pellegrini et al, 1999). These studies should be excluded unless WG consumption can be isolated from RGs.

Types of outcome measures

Biomarkers and measurements such as dietary intake, serum fasting glucose, fasting insulin, cholesterol (i.e.low-density-lipoprotein and high-density-lipoprotein), triaclyglycerols, inflammation (e.g. C-reactive protein, interleukins, tumor necrosis factor and a-amyloid), homeostatic model of assessment (HOMA), quantitative insulin sensitivity index (QUICKI), homocysteine, body fat mass, fat free mass, body mass index, waist circumference and systolic and diastolic blood pressure will be considered as primary outcomes for a range of NCD such as obesity, diabetes, CVD and hypertension. The meta-analysis will adopt a "barrow of strength" approach where biomarkers of one disease can help predict others (Riley et al, 2017). However, caution must be made when interpreting the final outcomes. To avoid misinterpretation outcomes will be stratified according to study topics (e.g. diabetes) and shown with and without a multivariate model. Secondary outcomes will include summary measures such as risk ratios, hazard ratios, odd ratios or incident ratios for diabetes, cancers, CVD and all-cause-mortality. These will be collected for the main NCD outlined earlier but are especially important for NCDs such as cancer where biomarkers are not readily available.

Duration of follow-up

All follow-up lengths will be considered. Interventions on WG consumption range between 2-16 weeks and cohorts can be anywhere from 7 to 20+ years. To reduce variation and duplicating data only studies that report the most up to date follow-up length will be included. An example of this is the Nurses Health study which has had numerous publications (He et al, 2010, Liu et al, 1999). Interventions will be stratified by length based on previous suggestions (McRae et al, 2016; Rebello et al, 2014). 2-11 week interventions will be separated from 12+ week interventions.

3.2 Search strategy

A sample of journal articles will be sourced from a single database (Medline, pubMed or web of science) and common phrases will be picked from titles to form initial search terms (Table 1). These search terms will then be used with boolean operators in three databases; Medline, pubMed and Web of Science. The search terms will be refined throughout the searches if necessary.

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Table 1. Example of search terms that will be used

Field	Search term(s)
All	(whole AND grain) OR (whole AND grains) OR wholegrain OR wholegrains OR (Cereal AND fibre) OR (cereal AND fiber) OR (wheat AND fibre) OR (wheat AND fiber) OR (rye AND fibre) OR (rye AND fibre) OR (wheat AND bran) OR (rye AND bran) OR (oat AND fibre) OR (oat AND fiber) OR (oat AND bran)
AND	
All	(cardiovascular disease OR heart OR stroke OR myocardial infarction OR blood pressure OR health OR diabetes OR inflammation OR Insulin resistance OR cholesterol OR endothelial function OR vascular function OR homocysteine OR body weight)

Searches will not be restricted by years, title or language. This will allow all studies that report WG to be collected and studies that are not specifically related to WG but do describe WG to be found.

Key authors will be contacted for latest publications and their existing publications will be searched for relevant articles. Studies included in the latest meta-analyses and systematic reviews will also be retrieved.

3.3 Search screening

Articles will initially be screened by title and abstract. Articles that do not specifically have "WG" in the title or abstract but do have phrases such as "dietary fiber" or "cereals" will be evaluated fully. In past efforts, studies on dietary fiber and cereals have been shown to contain information on WG (Li et al, 2015). All studies that meet the initial screening will be organised and compiled in an Endnote library. Screening will be conducted by two authors (W.A.I. and A.S.) and any disputes will be discussed and resolved with the corresponding author (C.J.S).

3.4 Description of methods used in primary research

Observational studies such as cohorts and cross-sectional studies involve random sampling from a population that meet a specific eligibility criteria (Kasum et al, 2001; Steffen et al, 2003). For instance, the Iowa Women's health study involved a random sample of premenopausal women (Kasum et al, 2001). Cohorts and cross-sectional studies adopt food frequency questionnaires (FFQs) for collecting dietary intake as they are large epidemiological studies which endure a lot of cost. Therefore, FFQs provide a relatively inexpensive and fast method. FFQs are normally given at the beginning of the cohort (baseline) and at the end of follow-up. Other data collection may include

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ascertainment of events such as death and occurance of particular diseases. Cohorts may assess this by medical records at baseline and at the end of follow-up or contact participants by telephone. All cohorts will involve the collection of anthropometric data at baseline. Some cohorts also collect blood samples such as the MESA and Framingham cohorts (Lutsey et al, 2007; Mckeown et al, 2002).

RCTs imply that the sample of participants are randomly selected and are healthy based on a certain criteria or are in accordance with specific eligibility criteria for a particular disease. These involve giving participants a particular type (e.g. wholemeal rye bread) or group of foods (WG snacks) for a certain duration of time. RCTs may involve splitting the participants into two groups with one group receiving the intervention food (e.g. WG) and another a placebo or another food deprived of the intervention (e.g. RG). For instance, the WHOLEheart study included a control group that maintained their normal diet intake and the intervention group were asked to consume 60-70g WG food (three slices of WG bread per day) (Brownlee et al, 2010). RCTs may also choose not to split the participants into two groups by first giving participants the control food followed by the intervention food with a wash out period in between (Kirwan et al, 2016). RCTs can become more complex by crossing-over treatments between groups (Ampatzoglou et al, 2015). Most RCTs are blinded which means that the participants and/or investigators are unable to distinguish the intervention food from the placebo or know who is having the intervention food. RCTs involve the collection of blood samples and anthropometric data at the beginning of intervention and at the end.

Case-control studies like cohorts and cross-sectional studies are observational. These involve collecting data from a selection of healthy individuals that are not at risk of NCD (controls) and individuals that are at risk (cases). For instance, a study in Switzerland looked at WG consumption of healthy individuals and individuals with oral, esophageal and laryngeal cancers (Levi et al, 2000). WG case-control studies may involve collecting data on dietary intake using 24 hour recalls by interview, food diaries or FFQs. They may also involve the collection of blood samples and anthropometric measurements.

Critical appraisal

A risk of bias tool outlined in the cochrane handbook will be adopted to assess the strength of the evidence presented in studies (Higgins et al, 2011). The studies will be screened for selection, detection, attrition and reporting bias and labelled "high risk", "low risk" or "unclear" accordingly. These forms of bias may inform reasons for heterogeneity in effect sizes. However, it is important to understand that not all outcomes in a study will be affected by the same bias. For instance, reporting bias may be detected in interviews or food frequency questionnaires but this may not be applicable for data from analysis of blood samples. Therefore, risk of bias must be carefully judged across all outcomes included in studies.

Risk of bias will be accompanied by funnel plots to assess publication bias. However, it is not possible to use this for asymmetric plots as described in the cochrane handbook (Higgins et al, 2011).

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No studies will be excluded based on the critical appraisal assessment but this information will be taken into consideration in the data compiling stage.

3.5 Criteria for determination of independent findings

Intervention outcomes that use the same population as both the controls and cases will most likely be separated by a wash out period as previously described. The results before the wash out period are considered the control and after the washout period when the intervention is given, the final outcomes. Some interventions also take measurements at time points (e.g. at 2, 3 and 4 weeks). The outcomes reported at the beginning or before the intervention can be considered as the control and the final time point the outcomes (e.g. week 4). Similarly, cohorts involve the same population but these are grouped by quantile of intake with individual findings for each group. With the group that had the least intake (e.g. first quantile or quartile or tertile) acting as the reference group or control and the group with the highest intake acting as the intervention group (e.g. last quantile or quartile or tertile). It is important to note that no baseline values should not be considered as controls in cohorts.

Many studies also report the same populations such as the Nurses health study, as previously described. If the studies based on the same outcomes (e.g. diabetes) have more than one publication, the study with the latest follow-up time will be chosen and others excluded. This will avoid double accounting the same data.

3.6 Details of study coding categories

The following characteristics will be looked for in cohorts, case-control and interventions:
- Total WG food or WG specific food (e.g. wholemeal rye bread).
- Healthy and/or cases of NCD being investigated.
- Blood measurements for one or more of the following: fasting insulin,fasting glucose, cholesterol (total or LDL or HDL), TAG, HOMA, QUICKI, CRP, a-amyloid, Interleukins, tumour necrosis factor, leptin ,glycosylated haemoglobin, systolic blood pressure diastolic blood pressure and homocysteine.
- Anthropometric data for one or more of the following: total body weight, fat free mass, fat mass, body mass index and waist circumference.
- Dietary intake data.
- Summary measures such as odd ratios, relative risk ratios, hazard ratios, mortality ratios or incidence rate ratios.

3.7 Statistical procedures and conventions

Statistical analysis in this review will be noval for WG research as it is believed no previous WG review has adopted multivariate meta-analyses. All data collecting will be conducted in an excel sheet and will be sorted based on WG intake (either all or specific) and topic (e.g. diabetes). These will all be collated in a single excel sheet to begin with. Individual outcomes will be transferred to individual

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sheets e.g. insulin. In these sheets, data will be converted into common units. A bootstrapping procedure will be conducted in R to obtain standard errors for studies that do not report standard deviations (IQR), standard errors (SE), confidence intervals (CI) or interquartile ranges (IQR). Studies that do report SD, CI or IQR will be converted into standard errors using the following formulas (Figure 2) (Borenstein et al, 2009; Wan et al, 2014):

$$SE = SD\sqrt{n} \qquad \textbf{A}$$

$$SE = \sqrt{n}\frac{(LB+UB/2)-UB}{1.96} \qquad \textbf{B}$$

$$SE = \sqrt{n}\frac{q3-q1}{2\Phi(\frac{0.75n-0.125}{n+0.25})} \qquad \textbf{C}$$

Figure 2: Formula to estimate SE when given the SD (**A**). Formula to estimate the SE when given confidence intervals (**B**) Formula to estimate SE when given IQR (**C**) (Borenstein et al, 2009; Wan et al, 2014)

Random effect models, forest plots, meta-regression and funnel plots will be produced for standard mean differences (SMD) using the metafor package in the R statistical software. SMDs have been chosen over mean differences as this will convert outcomes in different units (e.g. insulin mU/l and glucose µ mol/l) into a common scale (z-score). This will prevent the likelihood of a negative definite matrix when conducting variance-covariance matrix for the multivariate statistics.

Univariate forest plots will be produced to show the SMD for each outcome with a univariate summary measure and multivariate summary. Heterogeneity between studies will be interpreted as I^2. The multivariate summary effect will require additional calculations to compute a variance-covariance matrix. Within study correlation between effect sizes will be estimated using the formula described by Crawley et al (2007) (Figure 3,A). Covariances between SMD will be estimated as described by Wei and Higgins (2012) (Figure 3,B). A borrow of strength value which describes the additional strength obtained from a multivariate meta-analysis over a univariate plot will be estimated as described by Jackson et al (2017) (Figure 3,C).

$$p = \frac{\sigma1 + \sigma2 - \sigma1 - \sigma2}{\sqrt{2\sigma1\sigma2}} \qquad \textbf{A}$$

$$\rho\left(\frac{n_{12c}}{n_{1c}n_{2c}} + \frac{n_{12t}}{n_{1t}n_{2t}}\right) + \frac{k_{12}}{\sqrt{k_1 k_2}}\rho^2\delta_1\delta_2 J(v_1)J(v_2)\sqrt{\left(\frac{v_1}{v_1-2} - \frac{1}{J(v_1)^2}\right)\left(\frac{v_2}{v_2-2} - \frac{1}{J(v_2)^2}\right)} \qquad \textbf{B}$$

$$BoS_r^{RV} = 1 - \frac{\text{var}(\hat{\beta}_{mv,r})}{\text{var}(\hat{\beta}_{uv,r})} \qquad \textbf{C}$$

Figure 3: Formula to estimate correlation coefficient between two SMD (**A**). Formula to estimate covariance between two SMD (**B**) Formula to estimate the borrow of strength (**B**).

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Forest plots will be produced for each study topic (e.g. diabetes) but the multivariate summary measure will incorporate all similar biomarkers from a range of studies on WG. For instance, for all diabetic studies fasting glucose values will be shown on a standard univariate forest plot but fasting glucose values from all other related NCDs (i.e. CVD, obesity and hypertension) will be included in the multivariate summary measure. Additional related biomarkers such as cholesterol, TAG and insulin will be combined to help predict the summary measure for each biomarker. However, it is not clear just how many biomarkers can be combined at present. This will depend on the number of studies that report a common set of biomarkers during the data extraction stage but it can be assumed that studies reporting fasting glucose will also report fasting insulin, cholesterol and TAG.

Random effects model and forest plots will be produced for ratios such as odds, relative risks, incident rate ratios and hazard rate ratios for each NCD (obesity, diabetes, CVD, hypertension and cancers). Studies that report separate summary ratios for male and female will be combined using a fixed-effect model before being compiled in a random effects model as described in previous reviews (Benisi-Kohansal et al, 2016).

Dietary intake values will be used to produce dose-response analyses for all biomarkers and ratios. These will be converted into a common unit (e.g. g/day). Ranges will be averaged to obtain an estimate for the median. When the highest bound is open ended it will be assumed that it is the same as the adjacent interval. When the lower bound is open ended it will be assumed that it begins from 0 (Benisi-Kohansal et al, 2016).

Statistical analysis will be conducted by two authors (G.S and W.I.) and the data extraction will be conducted by two authors (W.I. and A.S) and checked by another (C.J.S.).

3.8 Treatment of qualitative research

Qualitative information will be collected on dietary assessment method, age, sex, number of participants, duration of study and adjustments made to outcomes. A table will be produced for all studies that report biomarkers and another table for all studies that report ratios (Table 2).

Table 2: Example table for qualitative data

Author(s) and Year	[a]Topic	Location	WG definition	Duration	[b]WG type	[c]Sex	Participants (n)	Population	Measurements	Adjustments
Brownlee et al, 2010	CVD	UK		16 weeks	Total WG intake	M/F	266	WHOLEheart	Glucose, Insulin, Cholesterol (HDL & LDL), TAG, fat free mass, fat mass, CRP, QUICKI, systolic and diastolic blood pressure,	-

a CVD=cardiovascular disease, T2D= Type 2 diabetes, MS= Metabolic syndrome
b Total WG intake= A range of WG products were consumed.
c F=Female, M=Male

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Roles

Content: Chris Seal has written a number of articles on primary research of WGs and continues to strive towards elucidating the benefits and health effects of WGs to the public. Wasim Iqbal and Abigail Smith have recently worked on other research projects in relation to WGs and have shown a considerable interest in this area.

Systematic review methods: Gavin Stewart has considerable experience in the formation of systematic reviews and meta-analyses.

Statistical analysis: Gavin Stewart has considerable experience in statistical methods and is an expert in bayesian statistics. Wasim Iqbal has conducted relevant statistical analysis and is competent in R programming.

Information retrieval: Chris Seal, Wasim Iqbal and Abigail Smith are experienced in information retrieval and boolean searches.

Sources of support

Chris Seal will be responsible for updating and maintaining the review. Wasim Iqbal will provide Chris Seal with additional support to ensure that the review is updated on a yearly basis.

Declarations of interest

Chris Seal is a member of HEALTHGRAIN forum, is part of the board of trustees for the Nutrition Society, member of the Institute of Food Science and Technology (IFST) and the Association for the Study of Obesity.

Gavin Stewart is an editor for Peer J, research synthesis methods and Cochrane/Campbell collaborations.

Preliminary timeframe

Date you plan to submit a draft protocol: July 2018
Date you plan to submit a draft review: June 2019

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