BMJ Open

The association of industry sponsorship with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality: Systematic review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022912
Article Type:	Research
Date Submitted by the Author:	14-Mar-2018
Complete List of Authors:	Chartres, Nicholas; The University of Sydney, Faculty of Pharmacy Fabbri, Alice; The University of Sydney McDonald, Sally ; The University of Sydney Turton, Jessica; The University of Sydney Allman-Farinelli, Margaret; University of Sydney, Faculty of Science McKenzie, Joanne; Monash University Bero, Lisa; University of Sydney Faculty of Health Sciences, Pharmacy
Keywords:	NUTRITION & DIETETICS, STATISTICS & RESEARCH METHODS, PUBLIC HEALTH

The association of industry sponsorship with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality: Systematic review and Meta-analysis

Chartres N, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia, PhD Candidate

Fabbri A, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia, Postdoctoral Research Fellow

McDonald S, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Research Assistant

Turton J, The University of Sydney, University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia

Allman-Farinelli M, The University of Sydney, D17, The Hub, 4th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia, Professor

McKenzie J E, Monash University, 553 St Kilda Road, Melbourne, VIC, 3004, Australia, Senior Research Fellow

Bero L, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia, Professor

Corresponding author: Prof. Lisa Bero, email lisa.bero@sydney.edu.au; Telephone +612 8627 1881

Keywords: Nutrition, Industry Sponsorship, Conflict of Interest, Bias, Food Industry

Word Count: 4264

Abstract

Objective: To determine if the presence of food industry sponsorship or author conflicts of interest with the food industry (COI) (industry ties) in primary nutrition studies examining the association of wholegrain foods with cardiovascular disease outcomes is associated with statistical significance of results, effect size or conclusions that favour the study sponsor. To determine whether studies with industry ties differ in their risk of bias compared with studies with no industry ties.

Design: Systematic review and meta-analysis of observational studies.

Data sources: We searched 8 databases from 1997-2017 and hand searched the reference lists of included studies.

Eligibility Criteria for selecting studies: Primary observational studies that quantitatively examined the association of wholegrains or wholegrain foods with cardiovascular disease outcomes in healthy adults or children.

Results: 21 of the 22 studies had a serious or critical risk of bias. Studies with industry ties were more likely to have favourable results than those with no industry ties, RR= 1.44 (95% CI 0.88-2.35), although the difference was not statistically significant. The same association was found for study conclusions. We did not find an important difference in effect size (magnitude of RRs) between studies with industry ties, RR = 0.77 (95% CI 0.58-1.01) and studies with no industry ties, RR = 0.85 (95% CI 0.73-1.00) (P=0.50) I2 0%. These results were comparable for studies that measured the magnitude using hazard ratios; industry ties HR=0.82 (95% CI 0.76-0.88) vs. no industry ties HR=0.86 (95% CI 0.81-0.91) (P=0.34) I2 0%.

Conclusions: These findings suggest, but do not establish, that the presence of food industry sponsorship or authors with a COI with the food industry, may be associated with both results and conclusions that favour industry sponsors. Our findings support international reforms to improve the disclosure and management of the conflicts of interest in nutrition research.

Systematic review registration: PROSPERO ID CRD42017055841

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to evaluate the association of industry sponsorship and author conflicts of interest (COI) with the results, conclusions and risk of bias of primary nutrition studies examining the effect of wholegrain foods on cardiovascular disease outcomes.
- We conducted a comprehensive search and followed explicit and well-defined inclusion and exclusion criteria for the included studies.
- Although our sample was small, we searched several databases and reference lists of included studies.
- We did not attempt to contact the authors of studies lacking a COI disclosure statement, thus, we may be underestimating the number of articles that had authors with conflicts of interest.
- Our assessment of risk of bias in the included studies was based on a tool that is under development, but changes to the tool are unlikely to affect the risk of bias ratings.

Background

Dietary guidelines are designed to promote wellbeing and reduce the risk of non-communicable diseases. Recent evaluations of the development of dietary guidelines have identified concerns with the methods of the systematic reviews and how evidence from these reviews is synthesised into final recommendations.[1-3] Several countries, including the United Kingdom, United States, and Australia have dietary guidelines offering recommendations around the consumption of wholegrain foods.[4-6] These recommendations are supported by recent systematic reviews and meta-analyses of prospective cohort studies, which have found a consistent, inverse relationship between wholegrain intake and cardiovascular disease (CVD) risk and mortality .[7-9]

Dietary guidelines use a variety of methods to assess bias in primary research studies, but these do not assess one potential source of bias – financial conflicts of interest.[10] Across a variety of research areas, industry sponsorship and author conflicts of interest (COI) have been found to be associated with outcomes that favour the study sponsor. [11-13] Even when controlling for methodological biases, industry sponsored studies are more likely to have results that favour the sponsor's product than those studies with no or other sources of sponsorship.[11] Industry sponsors may bias research via the questions they ask (research agenda), how they design and conduct a study, the selection of results they report and through 'spin' on conclusions. [14-17]

A systematic review of methodological studies that compared food industry sponsored studies with those that had no or other sources of sponsorship found that food industry sponsored studies were more likely to have favourable conclusions than non-industry sponsored studies. [18] However, there were insufficient data to quantitatively assesses the association of sponsorship with study results. Only one methodological study examined the association of author COI and conclusions, and found a statistically significant association between them.[19]

Funding sources and author COI may be a risk of bias in studies of wholegrain consumption as these studies could test formulated or processed wholegrain products, such as breakfast cereals. Industry sponsors may gain financially from finding that these types of products have health benefits that can be used to market their products. There has been no assessment of the association of food industry sponsorship and author COI with the food industry and the statistical significance of results, effect sizes, conclusions and risk of bias of observational studies examining the cardiovascular health benefits of wholegrain consumption. The primary objective of this review is to determine whether:

- Primary studies examining the association of wholegrain foods with cardiovascular disease with food industry sponsorship and / or authors with COI with the food industry are more likely to have results and/ or conclusions that are favourable to industry than those with no industry ties.

- This review also examines whether any differences between industry and non-industry sponsored studies could be related to their methods or interpretation of results.

The secondary objectives of this review are to determine whether:

- Studies with food industry sponsorship and / or authors with COI with the food industry differ in their risk of bias compared with studies with no industry ties.

- Studies with food industry sponsorship and / or authors with COI with the food industry have a higher level of discordance between study results and conclusions, with the conclusions more likely to be favourable compared to the results.

METHODS

We conducted a systematic review of observational studies examining the association of wholegrain consumption with cardiovascular disease.

Literature search strategy

The search was based on the Process Manual used in the development of the 2013 Australian Dietary Guidelines[20] and the advice of an information specialist. We searched the following databases from January 1997-October 2017: MEDLINE; CINAHL; PubMed; PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy we used for Ovid MEDLINE is shown in Supplementary file 1. We adapted this strategy for the other databases. We also hand searched the references lists of identified studies and reviews. The search also included terms for randomized control trials to identify relevant trials for a future systematic review.

Eligibility Criteria

This review included primary nutrition studies of cohort or case control designs that quantitatively examined the benefits or harms of wholegrain consumption related to cardiovascular disease outcomes in healthy children and/or adults.

We included studies that defined wholegrains in any way, as defined by the author. If total wholegrain consumption had been assessed in the study, we included this as our only exposure. If total wholegrain consumption as an exposure was not available, we included any type of wholegrain consumption (i.e. wholegrain cereal, breakfast cereal, bread, rice etc) as our exposure. We included studies that compared wholegrain food to other foods or compared various levels of wholegrain consumption. We included the result representing the effect of the highest level of wholegrain consumption compared to the lowest level of wholegrain consumption (e.g., 'yes' to wholegrain consumption vs. 'no' to wholegrain consumption, tertile 3 vs. tertile 1, quartile 4 vs. quartile 1, quintile 5 vs. quintile 1). If our pre-specified rules for selection did not uniquely identify one exposure for inclusion in the meta-analysis, we randomly selected one result.

We included studies that had a clinical outcome measure related to cardiovascular disease, defined as mortality related to specific cardiovascular events, and/or cardiovascular events, (e.g., first myocardial infarction, total stroke etc.). If 'cardiovascular disease mortality/death/s' (verbatim) had been assessed, we included this as our only outcome. If not, we included any type of cardiovascular disease mortality (e.g., coronary heart disease mortality, stroke mortality etc.) as our outcome. If there were no mortality outcomes assessed in the study, we included

any cardiovascular disease event as our outcome. If a study assessed subgroups of cardiovascular disease deaths and events (e.g., intracerebral haemorrhages, ischaemic stroke) and also assessed them collectively (e.g., cerebrovascular diseases), we took the result that had assessed them collectively. If our pre-specified rules for selection did not uniquely identify one outcome for inclusion in the meta-analysis, we randomly selected one result.

We excluded conferences presentations, opinion pieces and letters to the editor. We had no language restrictions.

Types of Outcome Measures

Primary Outcomes

We hypothesized that studies with food industry sponsorship and/or authors with a COI with the food industry would be more likely to have favourable findings than those with no industry ties. We assessed three primary outcomes:

1. Statistical significance of results favourable to the sponsor

Favourable results were defined as results that were favourable to the sponsor's product(s), either indicating greater health benefits or less harm than the comparator. Specifically, for studies of health benefits of wholegrains, favourable results were defined as those that were statistically significant at the 0.05 level. For studies of harms of wholegrains, favourable results were defined as those where harms were not statistically significant at the 0.05 level or there

were a statistically significant higher number of harms in the comparator group. Otherwise, results were classified as unfavourable.

2. Effect size of results

Effect size was defined as the risk ratio of the association between whole grains and a clinical outcome of cardiovascular disease. We compared the magnitude of the pooled effect estimates in studies with food industry sponsorship and/or authors with a COI compared with studies with no industry ties.

3. Conclusions

Conclusions that suggested that the wholegrain intervention being studied was beneficial to health and / or safe were considered favourable to the study sponsor. Otherwise, the conclusions were considered unfavourable.

Secondary Outcomes

We assessed two secondary outcomes:

1. The risk of bias of the included studies

We hypothesized that studies with industry sponsorship and/or authors with a COI with the food industry would have the same overall risk of bias as those with no industry ties.

2. Concordance between study results and conclusions

We hypothesized that studies with industry sponsorship and/or authors with a COI would be more likely to have discordant results and conclusions, with results not favouring the sponsor and conclusions favouring the sponsor, than those with no industry ties.

Selection of studies

Three investigators (NC, SMc & JT, working in pairs) independently screened the titles and abstracts of all retrieved records for obvious exclusions. Full text of potentially eligible studies was then retrieved, and three investigators (NC, SMc & JT) assessed these against our inclusion criteria. Agreement was reached by consensus.

Data Collection and analysis

Three assessors (NC, SMc & JT) independently extracted the following data from each included study. Discrepancies in data extraction were resolved by consensus. If agreement could not be reached, a fourth assessor (LB) adjudicated the outcome.

From each study we extracted:

- Year of publication
- Study design (cohort or case control)
- Sample size of study
- Age of participants
- Intervention or observation period
- How the study defined wholegrain (verbatim)
- Level of wholegrain content in wholegrain foods
- Disclosure of funding source (no disclosure, yes and there is a sponsor, the authors state they received no funding for their work)
- Name of the funders of the study (verbatim)
- Role of the funders (role of the sponsor not mentioned, sponsor not involved in study design and analyses, sponsor involved, N/A)
- Disclosure of author COI (no disclosure, yes, the authors state they had no conflicts of interest to declare)
- Authors COI statement (verbatim)
- Outcomes assessed in the study (any cardiovascular disease death and/or event)

- The numerical results of the study (eg., OR, HR)

We stored all extracted data from the included studies in REDcap, a secure web-based application for the collection and management of data.[21]

Classification of industry sponsorship and author conflicts of interest

Sponsorship was categorized as 1) industry or 2) non-industry. We defined industry sponsored studies as those declaring any sponsorship from the food industry, including if the study received 'mixed funding' from the food industry, non-profit organizations or other industries (i.e. pharmaceutical). Any study with an author with any disclosed financial tie to the food industry was classified as having a conflict of interest (COI). Author COI were categorized as 1) presence of a COI with the food industry or 2) no COI. Any studies that did not contain an author COI disclosure statement were classified as no COI. We contacted the authors of one paper [22] for clarification on their disclosure of funding source.

Assessment of risk of bias in included studies

We used an adapted version of the Cochrane Collaboration's 'Risk of Bias in Non-Randomized Studies-of Interventions' (ROBINS-I)[23] tool to measure the risk of bias of included observational studies. The tool assesses bias across seven domains. Each domain is assessed at a low, moderate, serious or critical risk of bias, or no information. The domain rating with the highest risk of bias determines the overall risk of bias rating for the study. For example, if a study is rated as being at a serious risk of bias in one domain, the overall risk of bias rating is 'serious.'

Analysis

We report frequencies and percentages of study characteristics across all studies, and separately, by funding source. We visually depict the overall risk of bias rating and the ratings for each domain by study.

We calculated risk ratios (and 95% confidence intervals) to quantify the association between food industry sponsorship and / or authors with COI with the food industry and favourable results, favourable conclusions and the overall study risk of bias rating. For the risk of bias rating analysis we dichotomised the overall risk of bias ratings as low (low or moderate) or high (serious or critical). We had planned to calculate a RR for level of concordance, however since in all studies there was concordance between the results and conclusions, we did not undertake this analysis.

We used meta-analysis to examine whether food industry sponsorship and / or authors with COI with the food industry modified the magnitude of association between whole grains and cardiovascular disease outcomes. Specifically, we undertook a subgroup analysis within a random effects meta-analysis model that compared the pooled associations across subgroups defined by industry sponsorship. The associations were pooled using inverse variance weighting and DerSimonian and Laird's method of moments estimator was used to estimate between study heterogeneity. Separate meta-analyses were fitted for studies that had measured the association using hazard ratios and those that had used either risk ratios or odds ratios. Given cardiovascular events were rare, the odds ratios approximated risk ratios. We quantified

heterogeneity for subgroup differences using the I^2 statistic [24] and tested for heterogeneity using the Chi2 test. Review Manager 5.3 was used to analyse the data. [25]

Protocol Registration

The protocol is published in PROSPERO [26] ID CRD42017055841. (Supplementary file 2)

Patient Involvement

No patients were involved in the completion of this review.

RESULTS

Search results

We identified 6818 references for screening, from which, 22 studies met the inclusion criteria (Figure 1). See Supplementary file 3 for 'List of excluded Studies' and reasons for exclusion.

Characteristics of included Studies

All studies were published between 1998 and 2015. Three of the studies were case control and 19 were cohort design. All studies contained a sponsorship disclosure. Five studies disclosed food industry sponsorship, but only one of these had a statement describing the role of the sponsor. Five studies contained an author with a COI with the food industry. Ten studies did not

contain a disclosure statement. Nine studies contained either food industry sponsorship or had an author with a COI.

A greater proportion of industry sponsored studies (67%) than non-industry sponsored studies (31%) used a definition of wholegrain as greater than 25%, and most of these examined breakfast cereals (Table 1). Industry sponsored studies were also more likely than non-industry studies to focus on a specific food (44%) than total wholegrain intake (23%) (Table 1). Non-industry sponsored studies (85%) had a greater proportion of studies with a serious or critical risk of bias in classification of exposures than industry sponsored studies (56%). Other characteristics were similarly distributed across industry vs. non-industry sponsored studies. Details of each individual study are in Supplementary file 4.

Table 1. Characteristics of the included studies by sponsorship and author COI

		Funding Source, n (%[1])		
Characteristic	Category	Total N = 22	Industry/COI N = 9	Non-Industry/No COI N = 13
Sex	Male	4 (18)	3 (33)	0 (0)
	Female	6 (27)	1 (11)	6 (46)
	Both	12 (55)	5 (56)	7 (54)
Sample Size, quartiles	<5000	6 (27)	2 (22)	4 (31)
	5000-50,000	10 (45)	4 (44)	5 (38)
	>50,000	6 (27)	3 (33)	4 (31)
Length of Follow up	N/A*	3 (14)	1 (11)	2 (15)
	<10 years	4 (18)	1 (11)	0 (0)
	10-15 years	9 (41)	4 (44)	8 (62)
	>15	6 (27)	3 (33)	3 (23)

Percent Wholegrain	Not defined	12 (55)	3 (33)	9 (69)
	>25%**	10 (45)	6 (67)	4 (31)
Type of Wholegrain	Only Wholegrain Intake	15 (68)	5 (56)	10 (77)
	Individual Wholegrain Food***	7 (32)	4 (44)	3 (23)
Primary Outcome	Favourable to Wholegrains	16 (73)	8 (89)	8 (62)
	Unfavourable to Wholegrains	6 (27)	1 (11)	5 (38)
Conclusions	Favourable to Wholegrains	16 (73)	8 (89)	8 (62)
	Unfavourable to Wholegrains	6 (27)	1 (11)	5 (38)
Risk of Bias Assessment				
	Serious/Critical Bias due to confounding	21 (95)	9 (100)	12 (92)
	Serious/Critical Bias in selection of participants into the study	3 (14)	1 (11)	2 (15)
	Serious/Critical Bias in classification of exposures	16 (73)	5 (56)	11 (85)
	Serious/Critical Bias due to deviations from exposures	7 (32)	3 (33)	4 (31)
	Serious/Critical Bias due to missing data	0 (0)	0 (0)	0 (0)
	Serious/Critical Bias in measurement of outcomes	1 (5)	1 (11)	0 (0)
	Serious/Critical Bias in selection of reported results	0 (0)	0 (0)	0 (0)
	Serious/Critical overall risk of bias	21 (95)	9 (100)	12 (92)

[1] Percentages may not add to 100 due to rounding

* Case control studies were not followed up

**Any part of the wholegrain consumption was defined as >25%, including breakfast cereal

***Individual foods included wholegrain cereal, breakfast cereal, bread & brown rice

Risk of bias in included studies

One study[27] was assessed as having an overall moderate risk of bias, four as having a serious risk of bias and 17 as having critical risk of bias (Figure 2). The majority of studies had a critical risk of bias in the confounding domain. All but one study was assessed at a low risk of bias on the outcome measurement domain. For all domains, except classification of exposure, the risk of bias ratings were similarly distributed across industry vs. non-industry sponsored studies (Table 1).

Favourable results - Statistical significance: Industry sponsored versus non-industry sponsored

The risk of reporting favourable outcomes was 44% higher in studies with industry sponsorship and/or authors with a COI with the food industry RR= 1.44 (95% CI 0.88-2.35). However, the confidence interval was wide and included differences in risks that were unimportant or operating in the opposite direction as plausible estimates. When we compared only industry sponsored (n=5) and non-industry sponsored studies (n=17), the risk was smaller RR = 1.13 (95% CI 0.66-1.94).

Favourable results - Effect size: Industry sponsored versus non-industry sponsored studies

There was no important difference in the magnitude of RRs (measuring the association between wholegrains and cardiovascular disease outcomes) between studies with industry sponsorship and/or authors with a COI with the food industry RR = 0.77 (95% CI 0.58-1.01) and those studies with no industry sponsorship or author COI RR = 0.85 (95% CI 0.73-1.00) (subgroup test P=0.50,

I^2 = 0%) (Figure 3). For studies that had measured the association using hazard ratios there was also no important difference found in the magnitude of HRs between studies with industry sponsorship and/or authors with a COI with the food industry HR=0.82 (95% CI 0.76-0.88) and studies with no industry sponsorship or author COI HR=0.86 (95% CI 0.81-0.91) (subgroup test P=0.34, I^2 = 0%) (Figure 4).

Our analysis comparing studies with industry sponsorship RR 0.63 (95% CI 0.28-1.39) and those with no industry sponsorship RR 0.85 (95% CI 0.74-0.97) (subgroup test P=0.46, I^2 = 0%), showed no important difference in the magnitude of RRs. This was again comparable between industry sponsored HR 0.82 (95% CI 0.77-0.87) and non-industry sponsored studies HR 0.85 (95% CI 0.81-0.90) (subgroup test P=0.29), I^2=12.2%) that measured the association using hazard ratios.

Favourable conclusions: Industry sponsored versus non-industry sponsored

As there was concordance between the results and conclusions of every included study, the same associations were found for conclusions as for the statistical significance of results. Studies with industry sponsorship and/or authors with a COI with the food industry were more likely to have favourable conclusions compared to those with no industry sponsorship or author COI RR= 1.44 (95% CI 0.88-2.35), however the confidence interval was wide. When studies were compared only by industry sponsorship, the risk was again smaller RR = 1.13 (95% CI 0.66-1.94).

Risk of Bias Assessment

Studies with industry sponsorship and/or authors with a COI with the food industry were less likely (0/9) to have an overall low risk of bias rating compared to those studies with no industry sponsorship or author COI (1/13), RR = 0.47 (95% CI 0.02 -10.32), however there was large uncertainty in the association.

DISCUSSION

Although observational studies examining the effect of wholegrain consumption on cardiovascular disease outcomes that were sponsored by the food industry and / or had authors with a COI with the food industry more often had favourable results than research not tied to the food industry, the difference was not statistically significant. We found no evidence of a difference in the magnitude of effect between industry sponsored and non-industry sponsored studies. It is difficult to detect differences in effect size by sponsorship as many study design features, such as dose and duration of exposures, and specific cardiovascular disease outcomes, vary across studies and may influence the effect size. In previous assessments of drug studies that have demonstrated that industry funded studies are more likely to have results that favour the study sponsors, there was no statistically significant difference found in effect sizes between industry and non-industry sponsored studies. [11]

Although all the included studies had a sponsorship disclosure, almost half were missing disclosures about author COI. Nondisclosed COIs in nutrition research are a concern.[48] Larger samples of industry funded studies and studies with disclosed author COI could make it possible to establish the association of sponsorship with research outcomes.

Studies that were sponsored by the food industry and / or had authors with a COI with the food industry more often had favourable conclusions than studies with no industry ties, although there was uncertainty in this relationship. There was absence of spin in the included studies as all the results agreed with the conclusions.

The overall risk of bias in every study, other than one non-industry sponsored study [27], was classified as high (either serious or critical). The overall risk of bias rating was based on the domain with the highest/worst risk of bias rating within each study, and most of the studies had a risk of bias related to confounding. Across each domain, we found little difference in the risk of bias between industry sponsored and non-industry sponsored studies.

Strengths and limitations of this review

Our review was registered in PROSPERO [26]. We conducted a comprehensive search and followed explicit and well-defined inclusion and exclusion criteria for the included studies. Although our sample was small, we searched several databases and reference lists of included studies. Authors of the studies for which we required clarification on funding source were also contacted, but we did not attempt to contact the authors of studies lacking a COI disclosure statement. Thus, we may be underestimating the number of articles that had authors with conflicts of interest. Our assessment of risk of bias in the included studies was based on a tool that is under development, but changes to the tool are unlikely to affect the risk of bias ratings.[23]

Agreements and disagreements with other studies or reviews

The relationship that we identified between food industry sponsorship and authors with a COI and favourable study outcomes towards the study sponsor has been previously demonstrated in an assessment of a broad range of nutrition research.[18] Only one study has reported an association of food industry funding with effect sizes.[49] Of studies examining the association between soft drink consumption and adverse health outcomes, food industry sponsored studies reported significantly smaller effects than non-food industry sponsored studies. Compared to our study, this study examined studies with a homogeneous population of industry funders, sugar sweetened beverage companies, which may have a more consistent influence on study outcomes than the diverse pool of food industry sponsors in our study.

There was also no difference in the level of risk of bias between industry sponsored and non-industry sponsored studies. This is consistent with previous assessments of pharmaceutical, tobacco and nutrition research that has shown industry-sponsored studies are of equal or better quality than non–industry-sponsored studies.[11 18 50-52]

Implications for clinicians, policy makers and future research

The recent critiques to reform the methods used in the development of dietary guidelines have proposed steps to improve the transparency of how evidence is evaluated and synthesized into recommendations. [1 2] However, until the influence of industry sponsorship in primary nutrition studies has been further explored and measured with larger samples of industry sponsored

studies, this bias may still be unaccounted for in dietary guidelines. Although there was uncertainty around the differences in the results and conclusions that we observed between industry and non-industry studies, the differences are unlikely to be explained by methodological risks of bias in these studies.

There are ways that study sponsorship can influence outcomes other than through the design of research. Bias may also be introduced in the way industry sponsored studies code events and analyse data, [53 54] through the selective reporting of study outcomes and through publication bias. [55] It has been demonstrated in other areas of medical research that there is a greater propensity to publish studies with statistically significant results. [56] Therefore, selective publication of study results or studies in their entirety, may limit the availability of all relevant nutrition data and can skew results that are used in dietary guideline development.[57] Publication bias could be minimized with the introduction of study registries for nutrition research, as has been established in pharmaceutical research. [58] The association of food industry sponsorship with the reporting of nutrition research still needs to be assessed.

Almost half of the studies included in this review had authors that did not disclose if they had a COI with the food industry or not. Compliance with COI disclosure policies is now well documented across many domains of research. [59-64] Recent examinations of the levels of disclosure in research assessing the effects of artificially sweetened beverages on weight outcomes found similarly poor disclosure rates.[50] Several solutions have been proposed to increase transparency and disclosure rates, including the use of different databases and

additional resources to identify conflicted authors, and the introduction of mandatory disclosure requirements in all journals, with the use of penalties for those who do not adhere to the stated policies. [18 50]

This research further strengthens calls for stricter policies relating to the disclosure and management of conflicts of interest in nutrition research. These findings suggest, but do not establish, that the presence of food industry sponsorship or authors with a conflict of interest with the food industry, may be associated with both the results and conclusions that favour industry sponsors.

Figure 1. Study Flow Diagram

Figure 2. Risk of Bias of Included Studies

Figure 3: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Risk Ratio

Figure 4: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Hazard Ratio

References

1. National Academies of Sciences Engineering, and Medicine. Redesigning the process for establishing the dietary guidelines for Americans 2017 [Available from: https://www.nap.edu/catalog/24883/redesigning-the-process-for-establishing-the-dietary-guidelines-for-americans (accessed Nov 2017)].
2. National Academies of Sciences Engineering, and Medicine. Optimizing the process for establishing the Dietary Guidelines for Americans: the selection process 2017 [Available from: https://www.nap.edu/catalog/24637/optimizing-the-process-for-establishing-the-dietary-guidelines-for-americans (accessed Nov 2017)].
3. Bero L. Developing reliable dietary guidelines. *BMJ* 2017;**359**.
4. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition December 2015 [Available from: https://health.gov/dietaryguidelines/2015/guidelines/(accessed Dec 2017)].
5. National Health and Medical Research Council: Department of Health and Ageing. Australian Dietary Guidelines. Canberra, Commonwealth of Australia: NHMRC, 2013.
6. Public Health England. The Eatwell Guide 2017 [Available from: https://www.gov.uk/government/publications/the-eatwell-guide(accessed Dec 2017)].
7. Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2016;**353**.
8. Benisi-Kohansal S, Saneei P, Salehi-Marzijarani M, et al. Whole-Grain Intake and Mortality from All Causes, Cardiovascular Disease, and Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. *Adv Nutr* 2016;**7**(6):1052-65.

9. Zhang B, Zhao Q, Guo W, et al. Association of whole grain intake with all-cause, cardiovascular, and cancer mortality: a systematic review and dose-response meta-analysis from prospective cohort studies. *Eur J Clin Nutr* 2017.

10. Blake P, Durao S, Naude CE, et al. An analysis of methods used to synthesize evidence and grade recommendations in food-based dietary guidelines. *Nutr Rev* 2018.

11. Lundh A, Lexchin J, Mintzes B, et al. Industry sponsorship and research outcome. *Cochrane Database Syst Rev* 2017;**2**:Mr000033.

12. Huss A, Egger M, Hug K, et al. Source of funding and results of studies of health effects of mobile phone use: systematic review of experimental studies. *Cienc Saude Colet* 2008;**13**(3):1005-12.

13. Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. *JAMA* 1998;**279**(19):1566-70.

14. Lexchin J. Those who have the gold make the evidence: how the pharmaceutical industry biases the outcomes of clinical trials of medications. *Sci Eng Ethics* 2012;**18**(2):247-61.

15. Sismondo S. How pharmaceutical industry funding affects trial outcomes: causal structures and responses. *Soc Sci Med* 2008;**66**(9):1909-14.

16. Boutron I, Dutton S, Ravaud P, et al. Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. *JAMA* 2010;**303**(20):2058-64.

17. Odierna DH, Forsyth SR, White J, et al. The cycle of bias in health research: a framework and toolbox for critical appraisal training. *Account Res* 2013;**20**(2):127-41.

18. Chartres N, Fabbri A, Bero LA. Association of industry sponsorship with outcomes of nutrition studies: A systematic review and meta-analysis. *JAMA Intern Med* 2016;**176**(12):1769-77.

19. Diels J, Cunha M, Manaia C, et al. Association of financial or professional conflict of interest to research outcomes on health risks or nutritional assessment studies of genetically modified products. *Food Policy* 2011;**36**(2):197-203.

20. Dietitians Association of Australia. A review of the evidence to address targeted questions to inform the revision of the Australian dietary guidelines 2009: Process Manual, 2011.

21. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;**42**(2):377-81.

22. Holmberg S, Thelin A, Stiernstrom EL. Food choices and coronary heart disease: a population based cohort study of rural Swedish men with 12 years of follow-up. *Int J Environ Res Public Health* 2009;**6**(10):2626-38.

23. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;**355**.

24. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

25. Review Manager Version 5.3 [program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

26. National Institute for Health Research. International Prospective Register for Sytematic Reviews. 2015 [Available from: http://www.crd.york.ac.uk/PROSPERO/].

27. Wu H, Flint AJ, Qi Q, et al. Association between dietary whole grain intake and risk of mortality: two large prospective studies in US men and women. *JAMA Intern Med* 2015;**175**(3):373-84.

28. Djousse L, Gaziano JM. Breakfast cereals and risk of heart failure in the physicians' health study I. *Arch Intern Med* 2007;**167**(19):2080-5.

29. Huang T, Xu M, Lee A, et al. Consumption of whole grains and cereal fiber and total and cause-specific mortality: prospective analysis of 367,442 individuals. *BMC Medicine* 2015;**13**(1):59.

30. Jacobs Jr DR, Meyer KA, Kushi LH, et al. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: The Iowa women's health study. *Am J Clin Nutr* 1998;**68**(2):248-57.

31. Jacobs DR, Jr., Meyer KA, Kushi LH, et al. Is whole grain intake associated with reduced total and cause-specific death rates in older women? The Iowa Women's Health Study. *Am J Public Health* 1999;**89**(3):322-9.

32. Jacobs DR, Jr., Meyer HE, Solvoll K. Reduced mortality among whole grain bread eaters in men and women in the Norwegian County Study. *Eur J Clin Nutr* 2001;**55**(2):137-43.

33. Jacobs Jr DR, Andersen LF, Blomhoff R. Whole-grain consumption is associated with a reduced risk of noncardiovascular, noncancer death attributed to inflammatory diseases in the Iowa Women's Health Study. *Am J Clin Nutr* 2007;**85**(6):1606-14.

34. Jensen MK, Koh-Banerjee P, Hu FB, et al. Intakes of whole grains, bran, and germ and the risk of coronary heart disease in men. *Am J Clin Nutr* 2004;**80**(6):1492-99.

35. Li Y, Hruby A, Bernstein AM, et al. Saturated Fats Compared With Unsaturated Fats and Sources of Carbohydrates in Relation to Risk of Coronary Heart Disease: A Prospective Cohort Study. *J Am Coll Cardiol* 2015;**66**(14):1538-48.

36. Liu S, Stampfer MJ, Hu FB, et al. Whole-grain consumption and risk of coronary heart disease: Results from the Nurses' Health Study. *Am J Clin Nutr* 1999;**70**(3):412-19.

37. Liu S, Manson JE, Stampfer MJ, et al. Whole grain consumption and risk of ischemic stroke in women: A prospective study. *JAMA* 2000;**284**(12):1534-40.

38. Liu S, Sesso HD, Manson JE, et al. Is intake of breakfast cereals related to total and cause-specific mortality in men? *Am J Clin Nutr* 2003;**77**(3):594-9.

39. Lockheart MS, Steffen LM, Rebnord HM, et al. Dietary patterns, food groups and myocardial infarction: a case-control study. *Br J Nutr* 2007;**98**(2):380-7.

40. Mizrahi A, Knekt P, Montonen J, et al. Plant foods and the risk of cerebrovascular diseases: a potential protection of fruit consumption. *Br J Nutr* 2009;**102**(7):1075-83.

41. Muraki I, Wu H, Imamura F, et al. Rice consumption and risk of cardiovascular disease: results from a pooled analysis of 3 U.S. cohorts. *Am J Clin Nutr* 2015;**101**(1):164-72.

42. Nettleton JA, Steffen LM, Loehr LR, et al. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc* 2008;**108**(11):1881-7.

43. Sahyoun NR, Jacques PF, Zhang XL, et al. Whole-grain intake is inversely associated with the metabolic syndrome and mortality in older adults. *Am J Clin Nutr* 2006;**83**(1):124-31.

44. Sonestedt E, Hellstrand S, Schulz CA, et al. The association between carbohydrate-rich foods and risk of cardiovascular disease is not modified by genetic susceptibility to dyslipidemia as determined by 80 validated variants. *PLoS One* 2015;**10**(4):e0126104.

45. Steffen LM, Jacobs DR, Jr., Stevens J, et al. Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Clin Nutr* 2003;**78**(3):383-90.

46. Tavani A, Bosetti C, Negri E, et al. Carbohydrates, dietary gylcaemic load and glycaemic index, and risk of acute myocardial infarction. *Heart* 2003;**89**(7):722-26.

47. Tavani A, Bertuzzi M, Gallus S, et al. Risk factors for non-fatal acute myocardial infarction in Italian women. *J Prev Med* 2004;**39**(1):128-34.

48. Nestle M. Corporate Funding of Food and Nutrition Research: Science or Marketing? *JAMA Intern Med* 2016;**176**(1):13-4.

49. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health* 2007;**97**(4):667-75.

50. Mandrioli D, Kearns CE, Bero LA. Relationship between Research Outcomes and Risk of Bias, Study Sponsorship, and Author Financial Conflicts of Interest in Reviews of the Effects of Artificially Sweetened Beverages on Weight Outcomes: A Systematic Review of Reviews. *PLoS One* 2016;**11**(9):e0162198.

51. Barnes DE, Bero LA. Industry-funded research and conflict of interest: an analysis of research sponsored by the tobacco industry through the Center for Indoor Air Research. *J Health Polit Policy Law* 1996;**21**(3):515-42.

52. Cho MK, Bero LA. The quality of drug studies published in symposium proceedings. *Ann Intern Med* 1996;**124**(5):485-9.

53. Psaty BM, Prentice RL. Minimizing bias in randomized trials: the importance of blinding. *JAMA* 2010;**304**(7):793-4.

54. Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. *JAMA* 2008;**299**(15):1813-7.

55. Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *BMJ* 2012;**344**.

56. Hopewell S, Loudon K, Clarke MJ, et al. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev* 2009(1):Mr000006.

57. Misakian AL, Bero LA. Publication bias and research on passive smoking: comparison of published and unpublished studies. *JAMA* 1998;**280**(3):250-3.

58. Dickersin K, Rennie D. The evolution of trial registries and their use to assess the clinical trial enterprise. *JAMA* 2012;**307**(17):1861-4.

59. Forsyth SR, Odierna DH, Krauth D, et al. Conflicts of interest and critiques of the use of systematic reviews in policymaking: an analysis of opinion articles. *Syst Rev* 2014;**3**:122.

60. Ruff K. Scientific journals and conflict of interest disclosure: what progress has been made? *Environ Health* 2015;**14**:45.

61. Resnik DB. Science and money: problems and solutions. *J Microbiol Biol Educ* 2014;**15**(2):159-61.

62. Roseman M, Milette K, Bero LA, et al. Reporting of conflicts of interest in meta-analyses of trials of pharmacological treatments. *JAMA* 2011;**305**(10):1008-17.

63. Bero L. Addressing bias and conflict of interest among biomedical researchers. *JAMA* 2017;**317**(17):1723-24.

64. Grundy Q, Dunn AG, Bourgeois FT, et al. Prevalence of disclosed conflicts of interest in biomedical research and associations with journal impact factors and altmetric scores. *JAMA* 2018;**319**(4):408-09.

Contributors: NC, AF, SMc, MA-F and LB designed and wrote the review protocol. NC wrote the search strategy and undertook the literature search. NC, SMc and JT conducted the title and abstract screening and full article screening for final study inclusion. NC, SMc and JT conducted data collection and cleaning, LB supervised. NC and JMc undertook all data analysis. LB advised on methods, statistical analyses, and interpretation of findings. All authors contributed to the final manuscript. NC and LB are guarantors.

Funding: This work was funded by National Health and Medical Research Council Grant #APP1139997. Nicholas Chartres is a recipient of the James Millner PhD Scholarship in Pharmacy from the University of Sydney. Sally McDonald is a scholarship recipient (Charles Perkins Centre summer scholarship) from the University of Sydney. Jessica Turton is a scholarship recipient (Charles Perkins Centre summer scholarship) from the University of Sydney.

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf. No support was received from any organisation for the submitted work. The authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. The authors report no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval: Not required

Transparency declaration: The authors affirm that this manuscript is a honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Data Sharing: Available from The University of Sydney data repository. DOI to be determined.

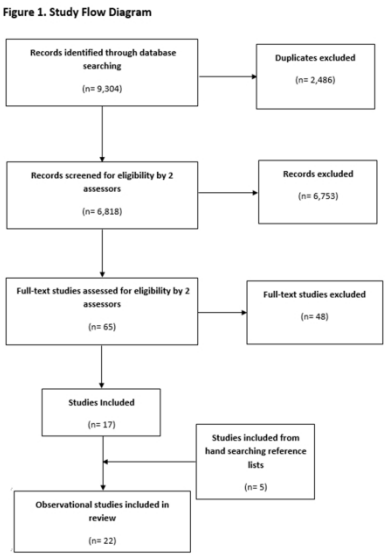

Figure 1. Study Flow Diagram

338x190mm (300 x 300 DPI)

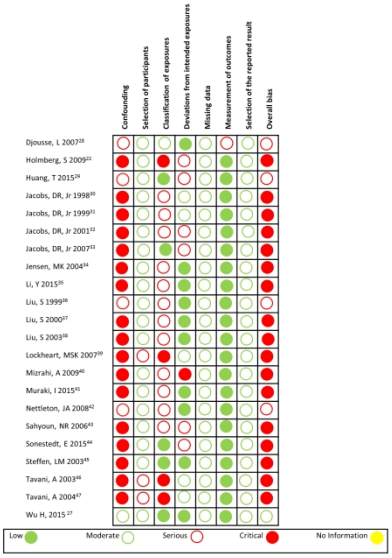

Figure 2. Risk of Bias Table

338x190mm (300 x 300 DPI)

Figure 3: Effect Size - Industry Sponsored &/OR Author COI versus Non-Industry Sponsored & No Author COI, RR

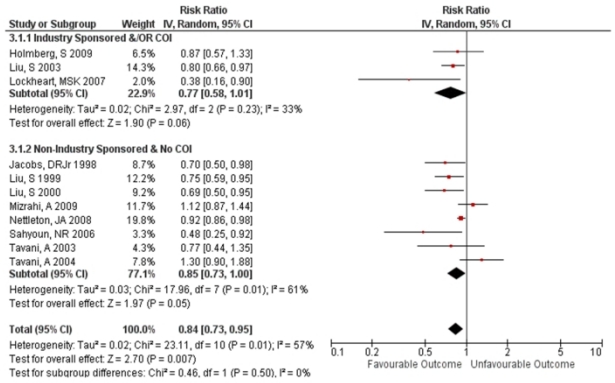

Figure 3. Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Risk Ratio

338x190mm (300 x 300 DPI)

Figure 4: Effect Size - Industry Sponsored &/OR Author COI versus Non-Industry Sponsored & No Author COI, HR

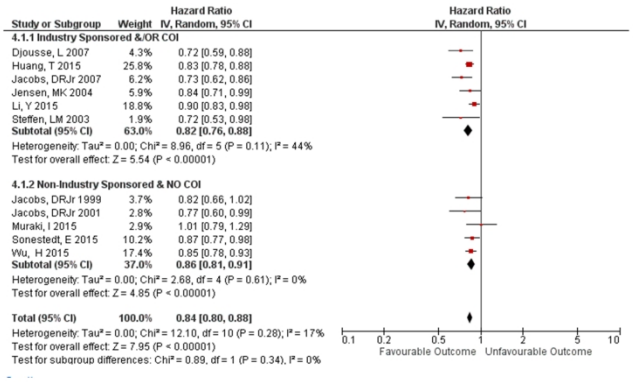

Figure 4: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Hazard Ratio

338x190mm (300 x 300 DPI)

Supplementary File 1: Search Strategy

OVID Medline: wholegrain & CVD

1. Randomized controlled trial*.sh.
2. experimental design.tw.
3. intervention*.tw.
4. (RCT* or rct*).tw.
5. random* control* trial*.tw.
6. clinical trial*.sh.
7. field trial*.tw.
8. community trial*.tw.
9. controlled clinical trial*.tw.
10. pragmatic trial*.tw.
11. observational study.sh.
12. cohort study.tw.
13. prospective cohort*.tw.
14. retrospective cohort*.tw.
15. case control*.sh.
16. ecological study.tw.
17. time series analys?s.tw.
18. before-after study.tw.
19. pre-post study.tw.

20. follow up stud*.sh.

21. comparative stud*.sh.

22. evaluation stud*.sh.

23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. Edible Grain/ae, me [Adverse Effects, Metabolism]

25. grain*.tw.

26. Dietary Carbohydrates/ or Edible Grain/ or Bread/ or Dietary Fiber/

27. whole grain*.tw.

28. partially processed grains.tw.

29. whole wheat.tw.

30. wholemeal.tw.

31. rice*.tw.

32. oat*.tw.

33. barley*.tw.

34. wheat*.tw.

35. Amaranthus/ae, me [Adverse Effects, Metabolism]

36. amaranth.tw.

37. Millets/me [Metabolism]

38. millet*.tw.

39. Sorghum/me [Metabolism]

40. sorghum*.tw.

41. maize*.tw.

42. spelt*.tw.

43. buckwheat*.tw.

44. Triticale/me [Metabolism]

45. triticale*.tw.

46. fonio*.tw.

47. emmer.tw.

48. einkorn*.tw.

49. kamut*.tw.

50. canary seed*.tw.

51. Bread/ae, an, me [Adverse Effects, Analysis, Metabolism]

52. bread*.tw.

53. breakfast cereal*.tw.

54. pasta*.tw.

55. noodle*.tw.

56. Flour/ae, an, st [Adverse Effects, Analysis, Standards]

57. flour*.tw.

58. polenta*.tw.

59. semolina*.tw.

60. bran.tw.

61. corn.tw.

62. wheat germ*.tw.

63. corn cake*.tw.

64. scone*.tw.

65. couscous.tw.

66. crumpet*.tw.

67. dietary fiber.tw.

68. dietary carbohydrate*.tw.

69. glycemic index.tw.

70. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 64 or 65 or 66 or 67 or 68 or 69

71. Coronary Disease/ or Cardiovascular Diseases/ or Hypertension/ or Atherosclerosis/

72. cardiovascular disease*.tw.

73. coronary*.tw.

74. heart*.tw.

75. cardia*.tw.

76. myocard*.tw.

77. isch?em*.tw.

78. angina*.tw.

79. ventric*.tw.

80. tachycardi*.tw.

81. pericard*.tw.

82. endocardi*.tw.

83. atrial fibrillat*.tw.

84. arrhythmi*.tw.

85. athero*.tw.

86. arterio*.tw.

87. HDL.tw.

88. LDL.tw.

89. VLDL.tw.

90. lipid*.tw.

91. lipoprotein*.tw.

92. triacylglycerol*.tw.

93. hyperlipid*.tw.

94. hypercholesterol*.tw.

95. hypercholester?emia*.tw.

96. hypertriglycerid?emia*.tw.

97. Cholesterol/

98. Stroke/

99. Cerebrovascular Disorders/

100. vascular accident*.tw.

101. TIA.tw.

102. Thrombosis/

103. thrombosis.tw.

104. Embolism/ or Pulmonary Embolism/

105. apoplexy.tw.

106. (brain adj2 accident*).tw.

107. ((brain* or cerebral or lacunar) adj2 infarct*).tw.

108. Blood Pressure/ or Hypertension/

109. systolic blood pressure.tw.

110. diastolic blood pressure.tw.

111. Peripheral Vascular Diseases/ or Peripheral Arterial Disease/

112. (coronar$ adj5 (bypas$ or graft$ or disease$ or event$)).tw.

113. (cerebrovasc$ or cardiovasc$ or mortal$ or angina$ or stroke or strokes).tw.

114. (myocardi$ adj5 (infarct$ or revascular$ or ischaemi$ or ischemi$)).tw.

115. (morbid$ adj5 (heart$ or coronar$ or ischaem$ or ischem$ or myocard$)).tw.

116. (vascular$ adj5 (peripheral$ or disease$ or complication$)).tw.

117. (heart$ adj5 (disease$ or attack$ or bypass$)).tw.

118. Mortality/

119. mortality.tw.

120. Diabetes Mellitus, Type 2/

121. Hyperglycemia/

122. hyperglycemi*.tw.

123. (glucose adj2 intoleran*).tw.

124. Insulin Resistance/

125. (metabolic adj3 syndrome adj3 x).tw.

126. metabolic cardiovascular syndrome.tw.

127. dysmetabolic syndrome x.tw.

128. HbA1c.tw.

129. (glyc?emic adj3 control).tw.

130. 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129

131. 23 and 70 and 130

132. limit 131 to (humans and yr="1997 -Current")

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for
Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
The association of industry sponsorship with outcomes of studies examining the effect of intake of wholegrain foods with cardiovascular disease and mortality: protocol

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
28/11/2016

4 Anticipated completion date
Give the date by which the review is expected to be completed.
31/05/2017

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Mr Chartres

7 Named contact email
Enter the electronic mail address of the named contact.
ngar0960@uni.sydney.edu.au

8 Named contact address
Enter the full postal address for the named contact.
THE UNIVERSITY OF SYDNEY D17, The Hub, 6th floor, Charles Perkins Centre| The University of Sydney | NSW | 2006

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
02 8627 4328

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed

as 'None' if the review is not affiliated to any organisation.
THE UNIVERSITY OF SYDNEY

Website address:
sydney.edu.au

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Mr	Nicholas	Chartres	The Hub, 6th floor, Charles Perkins Centre, The University of Sydney
Dr	Alice	Fabbri	The Hub, 6th floor, Charles Perkins Centre, The University of Sydney
Miss	Sally	McDonald	The Hub, 6th floor, Charles Perkins Centre, The University of Sydney
Miss	Jessica	Turton	The Hub, 6th floor, Charles Perkins Centre, The University of Sydney
Professor	Margaret	Allman-Farinelli	Charles Perkins Centre, The University of Sydney
Professor	Lisa	Bero	D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
Nicholas Chartres is a scholarship recipient (James Milner PhD scholarship in Pharmacy) from the University of Sydney. Alice Fabbri is a PhD student. She is recipient of a scholarship from the Italian Ministry of Education, Universities and Research. Sally McDonald is a scholarship recipient (Charles Perkins Centre summer scholarship) from the University of Sydney. Jessica Turton is a scholarship recipient (Charles Perkins Centre summer scholarship) from the University of Sydney.

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
The objective of this study is to determine if the presence of food industry sponsorship in primary nutrition studies examining the association of wholegrain foods with cardiovascular outcomes is associated with effect sizes, statistical significance of results and/ or conclusions that are favorable to the sponsor.

We will also determine whether industry sponsored primary nutrition studies assessing the association of wholegrain foods with cardiovascular outcomes differ in their risk of bias compared with studies with no or other sources of sponsorship.

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
We will search the following databases from 1997-2016: Ovid MEDLINE; CINAHL; PubMed; PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC.

17 URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
No

18 Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
public health - nutrition

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
studies of adults and / or children were eligible for inclusion Inclusion Criteria • The study quantitatively measure the effects of wholegrain consumption in humans • The study involves or considers research with healthy children and/or adults with BMI 25% wholegrain, which may be whole, partially processed, ground or milled grain products in which every part of the grain is present in proportions that represent those present in the whole grain • The study has an outcome measure related to cardiovascular disease. • The study evaluates clinical outcomes (e.g. risk ratio/hazard ratio/odds ratio (RR/HR/OR) of cardiovascular mortality, nonfatal heart attack, stroke, etc.) and/or the surrogate outcomes of Blood Pressure (mmHg), LDL cholesterol, or HbA1c. • If the study examines mixed interventions (e.g. nutritional and educational) we will include them only if data related to wholegrain consumption are reported separately or can be obtained from the authors • In case of multiple reports from the same study, we will use the most complete and/or recently reported data Exclusion Criteria • Cross sectional studies, reviews and meta-analysis, commentaries. • The study examines dietary patterns only (e.g. the “Mediterranean diet”) • The study examines nutrients in an altered state (i.e. cereal fibre supplements or bran fortification) • The study examines total grain intake without differentiating between wholegrains and refined grains, or includes significant refined grain products in the wholegrain category. • The study examines only refined grain products, including cereal products containing high added fat or sugar (e.g. cakes, biscuits, pastries). • The study examines intake of supplemented or enriched foods (e.g. with the addition of bran) and not intake of wholegrain foods.

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Wholegrain vs Wholegrain (different doses) Wholegrain vs Wholegrain (different grains) Wholegrain vs no Wholegrain Wholegrain vs Refined grain Wholegrain vs Other food Other (mixed intervention)

22 Types of study to be included
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Inclusion: RCT/ cluster RCT Controlled Trial/ pseudo-randomized Cohort Case-control Pre/Post Exclusion: Cross sectional studies reviews and meta-analysis commentaries.

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 Primary outcome(s)
Give the most important outcomes.
a. Primary Outcome 1 and 2 (Results and effect size) - Statistical significance of results - Effect size of outcomes b. Primary Outcome 3 (Conclusions) For this study, we will use clinical outcomes only for observational studies and both clinical and surrogate outcomes for interventional studies. We define as clinically relevant cardiovascular outcomes as mortality related to specific cardiovascular events, and/or number of cardiovascular events (including myocardial infarction, stroke). We define relevant surrogate outcomes as blood pressure (mmHg), lipid marker (LDL cholesterol),

or HbA1c. Our rationale for including only these outcomes is that these were used to measure cardiovascular disease risk factors in the development of the Australian Dietary Guidelines We will define favorable results and conclusions as those showing a statistically significant association of wholegrain consumption and decreased cardiovascular disease risk. For each study we will record the stated hypothesis for the study, including the stated outcomes to be measured. If primary outcomes are not stated we will take mortality (related to specific cardiovascular events) as the primary outcome to be measured. In the absence of mortality outcomes, we will take number of cardiovascular events (including non-fatal myocardial infarction and stroke) as the primary outcome. In the absence of these, blood pressure, LDL cholesterol, or HbA1C as risk factors will be used as the primary outcome.

Give information on timing and effect measures, as appropriate.
variable

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
Secondary Outcome 1 (Methodological risk of bias) Secondary Outcome 2 (Concordance between results and conclusions) Risk of Bias Assessment We will use the Cochrane Risk of Bias tool for randomised studies to measure the methodological quality of randomized controlled trials. The tool assesses bias across 7 domains and each of these will be reported separately. To measure methodological quality in observational studies we will use the ROBINS-E tool for non-randomized studies (ROBINS-E), which also measures bias across 7 domains. We will classify concordance between study results and conclusions as 'yes' if the authors' conclusions are supported by all outcomes. This will include the reporting of all significant and non-significant results. Otherwise, concordance will be classified as 'no'.

Give information on timing and effect measures, as appropriate.
variable

26

Supplementary File 3: List of Excluded Studies

Author: Year	Title	Reason For Exclusion
Ahn, Y 2013[1]	Rice-eating pattern and the risk of metabolic syndrome especially waist circumference in Korean Genome and Epidemiology Study (KoGES)	No wholegrain rice group on its own. Only mixed meals
Alonso, A 2006[2]	Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort	Fiber from cereals was not exclusively from wholegrain products
Altorf-van der Kuil, W 2012[3]	Sources of dietary protein and risk of hypertension in a general Dutch population	The study does not specify grain source of protein is from wholegrains
Appleby, PN 1999[4]	The Oxford Vegetarian Study: an overview	No analysis of wholegrains, only dietary fiber
Assmann, KE 2015[5]	A Healthy Dietary Pattern at Midlife, Combined with a Regulated Energy Intake, Is Related to Increased Odds for Healthy Aging	Dietary pattern assessment only. No separate analysis of wholegrains
Bae, JM 2002[6]	A nested case-control study on the high-normal blood pressure as a risk factor of hypertension in Korean middle-aged men	No measurement of wholegrain intake, only total dietary fiber
Bazzano, LA 2003[7]	Dietary fiber intake and reduced risk of coronary heart disease in US men and women: the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study	No separate analysis of dietary fiber from wholegrains
Bernstein, AM 2011[8]	Cereal fiber and coronary heart disease: a comparison of modeling approaches for repeated dietary measurements, intermediate outcomes, and long follow-up	No separate analysis of cereal fiber from wholegrains
Bertoia, ML 2014[9]	Mediterranean and Dietary Approaches to Stop Hypertension dietary patterns and risk of sudden cardiac death in postmenopausal women	Dietary pattern assessment only. No separate analysis of wholegrains

Bingham, CM 2012[10]	Food choices and health during military service: increases in sugar- and fibre-containing foods and changes in anthropometric and clinical risk factors	Cross sectional analysis only of diet. No measurement of whole grain foods
Buil-Cosiales, P 2014[11]	Fiber intake and all-cause mortality in the Prevención con Dieta Mediterránea (PREDIMED) study	Participants did not meet the inclusion criteria
Burger, KN 2011[12]	Dietary glycemic load and glycemic index and risk of coronary heart disease and stroke in Dutch men and women: the EPIC-MORGEN study	No measurement of wholegrain intake
Burke, V 2005[13]	Predictors of body mass index and associations with cardiovascular risk factors in Australian children: a prospective cohort study	No measurement of wholegrain intake
Chuang, S-C 2012[14]	Fiber intake and total and cause-specific mortality in the European Prospective Investigation into Cancer and Nutrition cohort	No separate analysis of cereal fiber from wholegrains
Crowe, FL 2012[15]	Dietary fibre intake and ischaemic heart disease mortality: the European Prospective Investigation into Cancer and Nutrition-Heart study	No separate analysis of cereal fiber from wholegrains
Djoussé, L 2009[16]	Relation between modifiable lifestyle factors and lifetime risk of heart failure	No separate analysis of cereal from wholegrains
Eshak, ES 2014[17]	Rice consumption is not associated with risk of cardiovascular disease morbidity or mortality in Japanese men and women: a large population-based, prospective cohort study	No separate analysis of brown/unrefined rice
Flint, AJ 2009[18]	Whole grains and incident hypertension in men	No clinical CVD outcome measured

Guo, J 2013[19]	Influence of dietary patterns on the risk of acute myocardial infarction in China population: the INTERHEART China study	Only 'Grains' measured for association with risk of MI. No separate analysis for wholegrains
Hansen-Krone, IJ 2012[20]	Heart healthy diet and risk of myocardial infarction and venous thromboembolism. The Tromso Study	Dietary pattern assessment only. No separate analysis of wholegrains
Iso, H 2007[21]	Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC)	No separate analysis of brown/unrefined rice
Jacobs, DR Jr 2000[22]	Fiber from whole grains, but not refined grains, is inversely associated with all-cause mortality in older women: the Iowa women's health study	Fiber from cereals was not exclusively from whole grain products for the high wholegrain fiber group (29% from refined grain)
Jansen, MC 1999[23]	Dietary fiber and plant foods in relation to colorectal cancer mortality: the seven countries study	No clinical CVD outcome measured
Johnsen, NF 2015[24]	Whole-grain products and whole-grain types are associated with lower all-cause and cause-specific mortality in the Scandinavian HELGA cohort	No combined data for men and woman
Kanda, A 1999[25]	Association of lifestyle parameters with the prevention of hypertension in elderly Japanese men and women: a four-year follow-up of normotensive subjects	No separate analysis of brown/unrefined rice No clinical CVD outcome measured
Kochar, J 2012[26]	Breakfast cereals and risk of hypertension in the Physicians' Health Study I	No clinical CVD outcome measured
Kokubo, Y 2011[27]	Dietary fiber intake and risk of cardiovascular disease in the Japanese population: the Japan Public Health Center-based study cohort	No separate analysis of fiber from wholegrains
Larsson, SC 2016[28]	Dietary Approaches to Stop Hypertension Diet and Incidence of Stroke: Results From 2 Prospective Cohorts	Dietary pattern assessment only. No separate analysis of wholegrains
Li, S 2014[29]	Dietary fiber intake and mortality among survivors of myocardial infarction: prospective cohort study	Participants did not meet the inclusion criteria

Liang, W 2010[30]	White rice-based food consumption and ischemic stroke risk: a case-control study in southern china	No separate analysis of brown rice/wholegrains
Liu, S 2000[31]	A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women	No clinical CVD outcome measured
Mozaffarian, D 2003[32]	Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals	No separate analysis of cereal fiber from wholegrains
Negri, E 2003[33]	Fiber intake and risk of nonfatal acute myocardial infarction	No separate analysis of cereal fiber from wholegrains
Oh, K 2005[34]	Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women	No separate analysis of cereal fiber from wholegrains
Pan, A 2012[35]	Red meat consumption and mortality: results from 2 prospective cohort studies	No analysis of whole grain intake and CVD outcomes
Park, Y 2011[36]	Dietary fiber intake and mortality in the NIH-AARP diet and health study	No separate analysis of cereal fiber from wholegrains. No combined data for men and woman
Pierucci, P 2012[37]	Diet and myocardial infarction: a nested case-control study in a cohort of elderly subjects in a Mediterranean area of southern Italy	No analysis of wholegrains
Rebello, SA 2014[38]	Amount, type, and sources of carbohydrates in relation to ischemic heart disease mortality in a Chinese population: a prospective cohort study	No combined data for men and woman
Rodriguez-Campello, A 2014[39]	Dietary habits in patients with ischemic stroke: a case-control study	No separate analysis of breaded foods from wholegrains
Shi, Z 2012[40]	Rice intake, weight change and risk of the metabolic syndrome development among Chinese adults: the Jiangsu Nutrition Study (JIN)	No analysis of wholegrain intake and CVD outcomes
Steffen, LM 2005[41]	Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white adults: the Coronary Artery Risk	No clinical CVD outcome measured

	Development in Young Adults (CARDIA) Study	
Streppel, MT 2008[42]	Dietary fiber intake in relation to coronary heart disease and all-cause mortality over 40 y: the Zutphen Study	No separate analysis of bread and cereal fiber from wholegrains
Threapleton, DE 2013[43]	Dietary fibre and cardiovascular disease mortality in the UK Women's Cohort Study	No separate analysis of total and breakfast cereal fiber from wholegrains
Threapleton, DE 2015[44]	Dietary fibre intake and risk of ischaemic and haemorrhagic stroke in the UK Women's Cohort Study	No separate analysis of total and breakfast cereal fiber from wholegrains
Wang, L 2007[45]	Whole- and refined-grain intakes and the risk of hypertension in women	No clinical CVD outcome measured
Wolk, A 1999[46]	Long-term intake of dietary fiber and decreased risk of coronary heart disease among women	No separate analysis of fiber from wholegrains
Yu, D 2014[47]	Adherence to dietary guidelines and mortality: a report from prospective cohort studies of 134,000 Chinese adults in urban Shanghai	Dietary pattern assessment only. No separate analysis of wholegrains
Yu, D 2016[48]	Dietary glycemic index, glycemic load, and refined carbohydrates are associated with risk of stroke: a prospective cohort study in urban Chinese women	No analysis of wholegrains

1. Ahn Y, Park SJ, Kwack HK, et al. Rice-eating pattern and the risk of metabolic syndrome especially waist circumference in Korean Genome and Epidemiology Study (KoGES). *BMC Public Health* 2013;**13**:61.

2. Alonso A, Beunza JJ, Bes-Rastrollo M, et al. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res* 2006;**37**(6):778-86.

3. Altorf-van der Kuil W, Engberink MF, Geleijnse JM, et al. Sources of dietary protein and risk of hypertension in a general Dutch population. *Br J Nutr 2012*;**108**(10):1897-903.

4. Appleby PN, Thorogood M, Mann JI, et al. The Oxford Vegetarian Study: an overview. *Am J Clin Nutr* 1999;**70**(3 Suppl):525S-31S.

5. Assmann KE, Lassale C, Andreeva VA, et al. A Healthy Dietary Pattern at Midlife, Combined with a Regulated Energy Intake, Is Related to Increased Odds for Healthy Aging. *J Nutr* 2015;**145**(9):2139-45.

6. Bae JM, Ahn YO. A nested case-control study on the high-normal blood pressure as a risk factor of hypertension in Korean middle-aged men. *J Korean Med Sci* 2002;**17**(3):328-36.

7. Bazzano LA, He J, Ogden LG, et al. Dietary fiber intake and reduced risk of coronary heart disease in US men and women: the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Arch Intern Med* 2003;**163**(16):1897-904.

8. Bernstein AM, Rosner BA, Willett WC. Cereal fiber and coronary heart disease: a comparison of modeling approaches for repeated dietary measurements, intermediate outcomes, and long follow-up. *Eur J Epidemiol* 2011;**26**(11):877-86.

9. Bertoia ML, Triche EW, Michaud DS, et al. Mediterranean and Dietary Approaches to Stop Hypertension dietary patterns and risk of sudden cardiac death in postmenopausal women. *Am J Clin Nutr* 2014;**99**(2):344-51.

10. Bingham CM, Lahti-Koski M, Absetz P, et al. Food choices and health during military service: increases in sugar- and fibre-containing foods and changes in anthropometric and clinical risk factors. *Public Health Nutr* 2012;**15**(7):1248-55.

11. Buil-Cosiales P, Zazpe I, Toledo E, et al. Fiber intake and all-cause mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. *Am J Clin Nutr* 2014;**100**(6):1498-507.

12. Burger KN, Beulens JW, Boer JM, et al. Dietary glycemic load and glycemic index and risk of coronary heart disease and stroke in Dutch men and women: the EPIC-MORGEN study. *PLoS One* 2011;**6**(10):e25955.

13. Burke V, Beilin LJ, Simmer K, et al. Predictors of body mass index and associations with cardiovascular risk factors in Australian children: a prospective cohort study. *Int J Obes* 2005;**29**(1):15-23.

14. Chuang S-C, Norat T, Murphy N, et al. Fiber intake and total and cause-specific mortality in the European Prospective Investigation into Cancer and Nutrition cohort. *Am J Clin Nutr* 2012;**96**(1):164-74.

15. Crowe FL, Key TJ, Appleby PN, et al. Dietary fibre intake and ischaemic heart disease mortality: the European Prospective Investigation into Cancer and Nutrition-Heart study. *Eur J Clin Nutr* 2012;**66**(8):950-6.

16. Djoussé L, Driver JA, Gaziano JM, et al. Relation between modifiable lifestyle factors and lifetime risk of heart failure. *JAMA* 2009;**302**(4):394-400.

17. Eshak ES, Hiroyasu I, Kazumasa Y, et al. Rice consumption is not associated with risk of cardiovascular disease morbidity or mortality in Japanese men and women: a large population-based, prospective cohort study. *Am J Clin Nutr* 2014;**100**(1):199-207.

18. Flint AJ, Hu FB, Glynn RJ, et al. Whole grains and incident hypertension in men. *Am J Clin Nutr* 2009;**90**(3):493-98.

19. Guo J, Li W, Wang Y, et al. Influence of dietary patterns on the risk of acute myocardial infarction in China population: the INTERHEART China study. *Chin Med J* 2013;**126**(3):464-70.

20. Hansen-Krone IJ, Enga KF, Njolstad I, et al. Heart healthy diet and risk of myocardial infarction and venous thromboembolism. The Tromso Study. *Thromb Haemost* 2012;**108**(3):554-60.

21. Iso H, Kubota Y. Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pacific journal of cancer prevention: *APJCP* 2007;**8 Suppl**:35-80.

22. Jacobs DR, Pereira MA, Meyer KA, et al. Fiber from whole grains, but not refined grains, is inversely associated with all-cause mortality in older women: the Iowa women's health study. *J Am Coll Nutr* 2000;**19**(3 Suppl):326S-30S.

23. Jansen MC, Bueno-de-Mesquita HB, Buzina R, et al. Dietary fiber and plant foods in relation to colorectal cancer mortality: the Seven Countries Study. *Int J Cancer* 1999;**81**(2):174-9.

24. Johnsen NF, Frederiksen K, Christensen J, et al. Whole-grain products and whole-grain types are associated with lower all-cause and cause-specific mortality in the Scandinavian HELGA cohort. *Br J Nutr* 2015;**114**(4):608-23.

25. Kanda A, Hoshiyama Y, Kawaguchi T. Association of lifestyle parameters with the prevention of hypertension in elderly Japanese men and women: a four-year follow-up of normotensive subjects. *Asia Pac J Public Health* 1999;**11**(2):77-81.

26. Kochar J, Gaziano JM, Djousse L. Breakfast cereals and risk of hypertension in the Physicians' Health Study I. *Clin Nutr* 2012;**31**(1):89-92.

27. Kokubo Y, Iso H, Saito I, et al. Dietary fiber intake and risk of cardiovascular disease in the Japanese population: the Japan Public Health Center-based study cohort. *Eur J Clin Nutr* 2011;**65**(11):1233-41.

28. Larsson SC, Wallin A, Wolk A. Dietary Approaches to Stop Hypertension Diet and Incidence of Stroke: Results From 2 Prospective Cohorts. *Stroke* 2016;**47**(4):986-90.

29. Li S, Flint A, Pai JK, et al. Dietary fiber intake and mortality among survivors of myocardial infarction: prospective cohort study. *BMJ* 2014;**348**:g2659.

30. Liang W, Lee AH, Binns CW. White rice-based food consumption and ischemic stroke risk: a case-control study in southern china. *J Stroke Cerebrovasc Dis* 2010;**19**(6):480-84.

31. Liu S, Manson JE, Stampfer MJ, et al. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health* 2000;**90**(9):1409-15.

32. Mozaffarian D, Kumanyika SK, Lemaitre RN, et al. Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. *JAMA* 2003;**289**(13):1659-66.

33. Negri E, La Vecchia C, Pelucchi C, et al. Fiber intake and risk of nonfatal acute myocardial infarction. *Eur J Clin Nutr* 2003;**57**(3):464-70.

34. Oh K, Hu FB, Cho E, et al. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. *Am J Epidemiol* 2005;**161**(2):161-9.

35. Pan A, Sun Q, Bernstein AM, et al. Red meat consumption and mortality: results from 2 prospective cohort studies. *Arch Intern Med* 2012;**172**(7):555-63.

36. Park Y, Subar AF, Hollenbeck A, et al. Dietary fiber intake and mortality in the NIH-AARP diet and health study. *Arch Intern Med* 2011;**171**(12):1061-8.

37. Pierucci P, Misciagna G, Ventura MT, et al. Diet and myocardial infarction: a nested case-control study in a cohort of elderly subjects in a Mediterranean area of southern Italy. *Nutr Metab Cardiovasc Dis* 2012;**22**(9):727-33.

38. Rebello SA, Hiromi K, Chen C, et al. Amount, type, and sources of carbohydrates in relation to ischemic heart disease mortality in a Chinese population: a prospective cohort study. *Am J Clin Nutr* 2014;**100**(1):53-64.

39. Rodriguez-Campello A, Jimenez-Conde J, Ois A, et al. Dietary habits in patients with ischemic stroke: a case-control study. *PLoS One* 2014;**9**(12):e114716.

40. Shi Z, Taylor AW, Hu G, et al. Rice intake, weight change and risk of the metabolic syndrome development among Chinese adults: the Jiangsu Nutrition Study (JIN). *Asia Pac J Clin Nutr* 2012;**21**(1):35-43.

41. Steffen LM, Kroenke CH, Yu X, et al. Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr* 2005;**82**(6):1169-77; quiz 363-4.

42. Streppel MT, Ocké MC, Boshuizen HC, et al. Dietary fiber intake in relation to coronary heart disease and all-cause mortality over 40 y: the Zutphen Study. *Am J Clin Nutr* 2008;**88**(4):1119-25.

43. Threapleton DE, Greenwood DC, Burley VJ, et al. Dietary fibre and cardiovascular disease mortality in the UK Women's Cohort Study. *Eur J Epidemiol* 2013;**28**(4):335-46.

44. Threapleton DE, Burley VJ, Greenwood DC, et al. Dietary fibre intake and risk of ischaemic and haemorrhagic stroke in the UK Women's Cohort Study. *Eur J Clin Nutr* 2015;**69**(4):467-74.

45. Wang L, Gaziano JM, Liu S, et al. Whole- and refined-grain intakes and the risk of hypertension in women. *Am J Clin Nutr* 2007;**86**(2):472-79.

46. Wolk A, Manson KE, Stampfer MJ, et al. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *JAMA* 1999;**281**(21):1998-2004.

47. Yu D, Zhang X, Xiang Y-B, et al. Adherence to dietary guidelines and mortality: a report from prospective cohort studies of 134,000 Chinese adults in urban Shanghai. *Am J Clin Nutr* 2014.

48. Yu D, Zhang X, Shu XO, et al. Dietary glycemic index, glycemic load, and refined carbohydrates are associated with risk of stroke: a prospective cohort study in urban Chinese women. *Am J Clin Nutr* 2016;**104**(5):1345-51.

Supplementary File 4: Characteristics of Included Studies

Study ID	Study Deign	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to wholegrain foods)	Comparison (lowest tertile/quartile/quintile or 'no' to wholegrain foods)	Outcomes Measured	Funding Source	Disclosed author conflicts of interest
Djousse, L 2007	Cohort	19.6 years (average)	21,376	53.7 ±9.5 years	Wholegrain Breakfast Cereal ≥ 7 (1 serving=1 cup [250 mL]) servings/week	Wholegrain Breakfast Cereal 0 servings/week	Heart Failure	Non-Industry[1]	Yes[a]
Holmberg, S 2009	Cohort	12 years	1,752	50.2 years	Whole meal bread (wholegrain rye bread and crisp/hard bread)	White or Rye bread	Coronary Heart Disease Death or Event (death or hospitalization)	Industry[2]	No disclosure
Huang, T 2015	Cohort	14 years (average)	367,442	61.7 years	Wholegrain 1.20 oz eq/day	Wholegrain 0.13 oz eq/day	Cardiovascular Disease Death	Industry[3]	Yes[b]
Jacobs, DRJr 1998	Cohort	10 years	34,492	55–69 years	Wholegrain 22.5 servings/week (median)	Wholegrain 1.5 servings/week (median)	Ischemic Heart Disease Death	Non-Industry[4]	No disclosure
Jacobs, DRJr 1999	Cohort	10 years	38,740	61.5 years	Wholegrain 22.5 servings/week (median)	Wholegrain 1.5 servings/week (median)	Cardiovascular Disease Death (all cardiovascular disease)	Non-Industry[5]	No disclosure
Jacobs, DRJr 2001	Cohort	Baseline 1977-83, followed through to 1994	33,848	35-56 years	Wholegrain Bread Score (2.25-5.40) *	Wholegrain Bread Score (0.05-0.60) *	Cardiovascular Disease Death (total cardiovascular disease)	Non-Industry[6]	No disclosure
Jacobs, DRJr 2007	Cohort	17 years	27, 312	55–69 years	Wholegrain ≥ 19 servings/week	Wholegrain 0–3.5 servings/week	Cardiovascular Disease Death	Industry[7]	No[c]
Jensen, MK 2004	Cohort	14 years	42,850	40-75 years	Wholegrain 42.4 g/day (median)	Wholegrain 3.5 g/day (median)	Coronary Heart Disease Death or Event (non-fatal MI infarction & fatal CHD)	Industry[8]	No[d]
Li, Y 2015	2 Cohorts	30 years & 24 years	127,536	NHS 30-55 years	Wholegrain 4.6 % of total Energy Intake	Wholegrain 0.4 % of total Energy Intake	Coronary Heart Disease Death or	Non-Industry[9]	Yes[e]

				HPFS 40-75 years			Event (non-fatal MI & CHD deaths)		
Liu, S 1999	Cohort	10 years	75,521	38-63 years	Wholegrain 2.70 servings/day (median)	Wholegrain 0.13 servings/day (median)	Coronary Heart Disease Death or Event (non-fatal MI & fatal CHD)	Non-Industry[10]	No disclosure
Liu, S 2000	Cohort	12 years	75,521	38-63 years	Wholegrain 2.70 servings/day (median)	Wholegrain 0.13 servings/day (median)	Ischemic Stroke Death or Event	Non-Industry[11]	No disclosure
Liu, S 2003	Cohort	5.5 years (average)	86,190	40–84 years	Wholegrain Breakfast Cereal 1 servings/day	Rarely	Cardiovascular Disease Deaths	Non-Industry[12]	Yes[f]
Lockheart, MSK 2007	Case Control		211	Case 62·5 ± 7·7 Control 62·2 5 ± 7·7	Wholegrain Breakfast Cereal 36 g/day (median) & Wholegrain breads 240 g/day (median)	0 94 g/day	Myocardial Infarction (first MI)	Industry[13]	No Disclosure
Mizrahi, A 2009	Cohort	24 years	3,932	40–74 years	Wholegrain Men 280–1321 g/day (range) Women 195–963 g/day (range)	Wholegrain Men 0–139 g/day (range) Women 0–89 g/day (range)	Cerebrovascular Disease Death or Event (total strokes, including all acute strokes, subarachnoidal haemorrhages and other, undefined strokes; ischaemic stroke and intracerebral haemorrhage)	Non-Industry[14]	No[g]
Muraki I, 2015	3 Cohorts	26 years, 20 years & 24 years	207,556	Not available	Brown Rice ≥ 5 servings/week	Brown Rice < 1 servings/week	Cardiovascular Disease Death or Event (nonfatal MI, fatal CAD, and stroke (nonfatal or fatal))	Non-Industry[15]	No[h]

Nettleton, JA 2008	Cohort	13.3 years (average)	14,153	45-64 years	Wholegrain 1.3 ± 0.01 servings/day	Wholegrain 1.1 ± 0.04 servings/day	Heart Failure Death or Event	Non-Industry[16]	No[i]
Sahyoun, NR 2006	Cohort	Baseline 1981-84, followed through to 1995	535	60–98 years	Wholegrain >1.94 servings/day	Wholegrain ≤0.56 servings/day	Cardiovascular Disease Death	Non-Indusry[17]	No[j]
Sonestedt, E 2015	Cohort	14 year (average)	26,445	44–74 years	Wholegrain 2.5 portions/day	Wholegrain 0 portions/day	Cardiovascular Disease Death or Event (Incident CVD events, Stroke events, CHD (fatal or non-fatal myocardial infarction or death due to ischemic heart disease), Ischemic stroke).	Non-Industry[18]	No Disclosure
Steffen, L M 2003	Cohort	11 years	11,940	45–64 years	Wholegrain 3.0 servings/day	Wholegrain 0.1 servings/day	Coronary Artery Disease Death or Event (the first definite or probable MI, silent MI by electrocardiography, definite CAD death, or coronary revascularization) & Ischemic Stroke Death or Event (first definite or probable cardioembolic or thrombotic brain infarction)	Non-Industry[19]	Yes[k]
Tavani, A 2003	Case Control		881	25–79 years	Wholegrain Bread Consumers	Wholegrain Bread Non-Consumers	Myocardial Infarction (first acute)	Non-Industry[20]	No Disclosure

Tavani, A 2004	3 Case Controls		1,602	17–79 years	Wholegrain >2 portions/per week	Wholegrain <2 portions/per week	Myocardial Infarction (first acute)	Non-Industry[21]	No Disclosure
Wu, H 2015	2 Cohort	26 years & 24 years	118,085	NHS 30-55 years HPFS 32-87 years	Wholegrain NHS 33 g/day (median) HPFS 47.8 g/day (median)	Wholegrain NHS 4.2 g/day (median) HPFS 5.9 g/day (median)	Cardiovascular Disease Death	Non-Industry[22]	No[l]

*Wholegrain bread score: slices eaten per day (question 1) times the percentage wholegrain flour used in bread. Q5 = 9 slices of bread usually eaten per day x

60% wholegrain flour. Q1 = 1 slice of bread per day x 5% wholegrain flour

Description of Funding Source (Verbatim)

1. The PHS is supported by grants CA-34944 and CA-40360 from the National Cancer Institute and grants HL-26490 and HL-34595 from the National Heart Lung and Blood Institute (NHLBI), Bethesda, Maryland. Dr Djousse´ is supported by grant K01 HL70444 from the NHLBI
2. This study was supported by grants from AFA Insurance, LRF Research Foundation, The Swedish Council for Working Life and Social Research and Kronoberg County Council
3. This study is funded by an unrestricted research fund from NutraSource.Dr. Qi was supported by grants from the National Heart, Lung, and Blood Institute (HL071981), the National Institute of Diabetes and Digestive and Kidney Diseases (DK091718), the Boston Obesity Nutrition Research Center (DK46200), and United States–Israel Binational Science Foundation Grant 2011036. Dr. Qi was a recipient of the American Heart Association Scientist Development Award (0730094 N). Funding from NutraSource. There were no other relationships or activities that could appear to have influenced the submitted work
4. Supported by the National Institutes of Health (research grant CA-39742)
5. This research was supported by grant CA-39742 from the National Institutes of Health
6. Institute for Nutrition Research, University of Oslo and National Health Screening Service, Oslo, Norway

7. RB was supported by grants from the Norwegian Research Council, The Johan Throne Holst Nutrition Research Foundation, and The Norwegian Cancer Society. DRJ was supported by the Norwegian Research Council and by a grant (RO1 CA39742) from the National Cancer Institute.
8. Supported by research grants HL35464 and CA55075 from the National Institutes of Health and a scholarship from the Danish Research Foundation (to MKJ). The Kellogg Company provided unrestricted funding of the development of the whole-grain database
9. The cohorts were supported by grants UM1 CA186107, R01 HL034594, R01 HL35464, R01 HL60712, and UM1 CA167552 from the National Institutes of Health.
10. Supported by research grants HL24074, HL34594, and CA40356 and by nutrition training grant T32DK07703 from the National Institutes of Health
11. The work reported in this article was supported by grants CA40356, HL24074, HL34594, and DK02767 from the National Institutes of Health
12. Supported by grants HL-42441 and DK02767 from the National Institutes of Health
13. The present study was supported by NIH NRSA T32HL007779. CVD Epidemiology and Prevention, American Heart Association, Greater Midwest Affiliate. Throne Holst's Foundation for Nutrition Research. The Norwegian Association of Margarine Producers. DeNoFa Fabriker A/S and Tine Norwegian Dairies

14. The present study received funds from the Social Insurance Institution, Finland.

15. Supported by NIH grants CA50385, CA87969, CA176726, CA167552, HL60712, HL034594, HL088521, and HL35464. QS was supported by a career development grant R00HL098459 sponsored by the National Heart, Lung, and Blood Institute. FI was supported by Medical Research Council Epidemiology Unit Core Support (MC_UU_12015/5)

16. This research was supported by the National Institutes of Health grant HL73366, training grant T32 HL07779, and contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01- HC-55022 from the National Heart, Lung, and Blood Institute.

17. Supported by the US Department of Agriculture, under agreement no. 58-1950-4-401

18. This study was supported by the Swedish Medical Research Council, the Swedish Heart and Lung Foundation, the Skåne University Hospital, the Albert Påhlsson Research Foundation, and the Crafoord Foundation

19. Supported by the National Heart, Lung, and Blood Institute (contract nos. N01-HC-55015, N01-HC-55016, HC-55018, N01-HC-55019, HC-55020,N01-HC-55021, and N01-HC-55022)

20. This study was partly supported by "Ministero della Salute" (contract No 177, RF 2001).

21. Partly supported by ''Ministero della Salute'' (Contract n.177, RF 2001) and by the Commission of the EuropeanCommunities (Contract No. QLK1-CT-2000-00069)

22. This work was supported by research grants R01 DK58845 (Dr Hu), P01 CA87969, R01 HL034594, UM1 CA167552 (DrWillett), R01 HL35464 (Dr Rimm), HL60712 (DrHu), U54CA155626 (Dr Hu), and CA055075 from the National Institutes of Health and Career Development Award R00HL098459 from the National Heart, Lung, and Blood Institute (Dr Sun)

Description of Author Disclosure Statement (Verbatim)

a) Dr Gaziano has received investigator-initiated research grants from BASF, DSM Pharmaceuticals, Wyeth Pharmaceuticals, McNeil Consumer Products, and Pliva as well as honoraria from Bayer and Pfizer for speaking engagements. He is a consultant for Bayer, McNeil Consumer Products, Wyeth Pharmaceuticals, Merck, Nutraquest, and GlaxoSmithKline

b) A Lee NutraSource (AWL), Royal Oak, MI 48073, USA. S Cho NutraSource (SSC), Clarksville, MD 21029, USA

c) None of the authors had a conflict of interest

d) None of the authors had any conflicts of interest

e) Dr. Hu has received honoraria from the Hass Avocado Board for participating in an academic symposium; and grant support from Metagenics and the California Walnut Commission

f) In 2001 SL received honoraria from General Mills Co for a presentation unrelated to this article

g) None of the authors had any personal or financial conflict of interest.

h) All authors reported no conflicts of interest related to the study.

i) The authors have no conflicts of interest to report

j) None of the authors had a conflict of interest

k) None of the authors had any conflicts of interest except for DRJ, who holds a research award from General Mills, Inc, Minneapolis

l) None reported

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	7
2	Hypothesis statement	10
3	Description of study outcome(s)	10-11
4	Type of exposure or intervention used	9-10
5	Type of study designs used	9
6	Study population	9
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	8
8	Search strategy, including time period included in the synthesis and key words	& Supp File 1
9	Effort to include all available studies, including contact with authors	8
10	Databases and registries searched	8
11	Search software used, name and version, including special features used (eg, explosion)	8
12	Use of hand searching (eg, reference lists of obtained articles)	8
13	List of citations located and those excluded, including justification	16 & Supplementary File 3
14	Method of addressing articles published in languages other than English	10
15	Method of handling abstracts and unpublished studies	10
16	Description of any contact with authors	14
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	9-10
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7 (according to published protocol Supp File 2)
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	13-14
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	14, (included in RoB assessment)
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	14 & 19
22	Assessment of heterogeneity	15-16
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	15-16
24	Provision of appropriate tables and graphics	17-18
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	21
26	Table giving descriptive information for each study included	17 & Supplementary

		File 4
27	Results of sensitivity testing (eg, subgroup analysis)	N/A
28	Indication of statistical uncertainty of findings	19-21

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	21
30	Justification for exclusion (eg, exclusion of non-English language citations)	N/A
31	Assessment of quality of included studies	21-23
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	21-22
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	21-22
34	Guidelines for future research	24-25
35	Disclosure of funding source	33

BMJ Open

The association of industry ties with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality: Systematic review and Meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-022912.R1
Article Type:	Research
Date Submitted by the Author:	20-Dec-2018
Complete List of Authors:	Chartres, Nicholas; The University of Sydney, Faculty of Pharmacy Fabbri, Alice; The University of Sydney McDonald, Sally ; The University of Sydney Turton, Jessica; The University of Sydney Allman-Farinelli, Margaret; University of Sydney, Faculty of Science McKenzie, Joanne; Monash University Bero, Lisa; University of Sydney Faculty of Health Sciences, Pharmacy
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Nutrition and metabolism, Public health
Keywords:	NUTRITION & DIETETICS, STATISTICS & RESEARCH METHODS, PUBLIC HEALTH

The association of industry ties with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality: Systematic review and Meta-analysis

Chartres N, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia, PhD Candidate

Fabbri A, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia, Postdoctoral Research Fellow

McDonald S, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Research Assistant

Turton J, The University of Sydney, University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia

Allman-Farinelli M, The University of Sydney, D17, The Hub, 4th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia, Professor

McKenzie J E, Monash University, 553 St Kilda Road, Melbourne, VIC, 3004, Australia, Senior Research Fellow

Bero L, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia, Professor

Corresponding author: Prof. Lisa Bero, email lisa.bero@sydney.edu.au; Telephone +612 8627 1881

Keywords: Nutrition, Industry Sponsorship, Conflict of Interest, Bias, Food Industry

Word Count: 4264

Abstract

Objective: To determine if observational studies examining the association of wholegrain foods with cardiovascular disease with food industry sponsorship and / or authors with conflicts of interest with the food industry are more likely to have results and/ or conclusions that are favourable to industry than those with no industry ties. To determine whether studies with industry ties differ in their risk of bias compared with studies with no industry ties.

Design: Systematic review and meta-analysis of observational studies.

Data sources: We searched 8 databases from 1997-2017 and hand searched the reference lists of included studies.

Eligibility Criteria for selecting studies: Cohort and case control studies that quantitatively examined the association of wholegrains or wholegrain foods with cardiovascular disease outcomes in healthy adults or children.

Results: 21 of the 22 studies had a serious or critical risk of bias. Studies with industry ties more often had favourable results compared to those with no industry ties, but the confidence interval was wide, RR= 1.44 (95% CI 0.88-2.35). The same association was found for study conclusions. We did not find a difference in effect size (magnitude of RRs) between studies with industry ties, RR = 0.77 (95% CI 0.58-1.01) and studies with no industry ties, RR = 0.85 (95% CI 0.73-1.00) (P=0.50) I^2 0%. These results were comparable for studies that measured the magnitude using hazard ratios; industry ties HR=0.82 (95% CI 0.76-0.88) vs. no industry ties HR=0.86 (95% CI 0.81-0.91) (P=0.34) I^2 0%.

Conclusions: We did not establish that the presence of food industry sponsorship or authors with a COI with the food industry was associated with results or conclusions that favour industry

sponsors. The association of food industry sponsorship or authors with a COI with the food industry and favourable results or conclusions is uncertain. However, our analysis was hindered by the low level of COI disclosure in the included studies. Our findings support international reforms to improve the disclosure and management of conflicts of interest in nutrition research. Without such disclosures, it will not be possible to determine if the results of nutrition research are free of food industry influences and potential biases.

Systematic review registration: PROSPERO ID CRD42017055841

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to evaluate the association of industry sponsorship and author conflicts of interest (COI) with the results, conclusions and risk of bias of primary nutrition studies examining the effect of wholegrain foods on cardiovascular disease outcomes.
- We conducted a comprehensive search and followed explicit and well-defined inclusion and exclusion criteria for the included studies.
- Although our sample was small, we searched several databases and reference lists of included studies.
- We did not attempt to contact the authors of studies lacking a COI disclosure statement, thus, we may be underestimating the number of articles that had authors with conflicts of interest.
- Our assessment of risk of bias in the included studies was based on a tool that is under development, but changes to the tool are unlikely to affect the risk of bias ratings.

Background

Dietary guidelines are designed to promote wellbeing and reduce the risk of non-communicable diseases. Recent evaluations of the development of dietary guidelines have identified concerns with the methods of the systematic reviews and how evidence from these reviews is synthesised into final recommendations.[1-3] Several countries, including the United Kingdom, United States, and Australia have dietary guidelines offering recommendations around the consumption of wholegrain foods.[4-6] The guidelines conclude that there is a probable association between whole grain consumption and a reduced risk of cardiovascular disease.[4-6] These recommendations are supported by recent systematic reviews and meta-analyses of prospective cohort studies, which have found a consistent, inverse relationship between wholegrain intake and cardiovascular disease (CVD) risk and mortality .[7-9] However, the beneficial effects of wholegrains on CVD when assessed in randomised controlled trials (RCTs) are uncertain. [10]

Wholegrain products can be defined in various ways, including by the species (e.g., wheat, oats), components (e.g., endosperm, bran, germ), and percentages (e.g., 25%-100%). While some food regulators use a definition of 100% retention of wholegrain content, the epidemiological literature typically uses 25% or more retained content. In the development of the Australian Dietary Guidelines, the most common definition for whole grain foods was those containing 25% or more of wholegrains.[11]

Dietary guidelines use a variety of methods to assess bias in primary research studies, but these do not assess one potential source of bias – financial conflicts of interest.[12] Across a variety of research areas, industry sponsorship and author conflicts of interest (COI) have been found to be associated with outcomes that favour the study sponsor. [13-15] Even when controlling for methodological biases, industry sponsored studies are more likely to have results that favour the sponsor's product than those studies with no or other sources of sponsorship.[13] Industry sponsors may bias research via the questions they ask (research agenda), how they design and conduct a study, the selection of results they report and through 'spin' on conclusions. [16-19]

A systematic review of methodological studies that compared food industry sponsored studies with those that had no or other sources of sponsorship found that food industry sponsored studies were more likely to have favourable conclusions than non-industry sponsored studies. [20] However, there were insufficient data to quantitatively assesses the association of sponsorship with study results. Only one methodological study examined the association of author COI and conclusions, and found a statistically significant association between them.[21]

Funding sources and author COI may be a risk of bias in studies of wholegrain consumption as these studies could test formulated or processed wholegrain products, such as breakfast cereals. Industry sponsors may gain financially from finding that these types of products have health benefits that can be used to market their products. There has been no assessment of the association of food industry sponsorship and author COI with the food industry and the statistical significance of results, effect sizes, conclusions and risk of bias of observational

studies examining the cardiovascular health benefits of wholegrain consumption. The primary objective of this review is to determine whether:

- Primary studies examining the association of wholegrain foods with cardiovascular disease with food industry sponsorship and / or authors with COI with the food industry are more likely to have results and/ or conclusions that are favourable to industry than those with no industry ties.
- This review also examines whether any differences between industry and non-industry sponsored studies could be related to their methods or interpretation of results.

The secondary objectives of this review are to determine whether:

- Studies with food industry sponsorship and / or authors with COI with the food industry differ in their risk of bias compared with studies with no industry ties.
- Studies with food industry sponsorship and / or authors with COI with the food industry have a higher level of discordance between study results and conclusions, with the conclusions more likely to be favourable compared to the results.

METHODS

We conducted a systematic review of observational studies examining the association of wholegrain consumption with cardiovascular disease.

Literature search strategy

The search was based on the Process Manual used in the development of the 2013 Australian Dietary Guidelines[22] and the advice of an information specialist. We searched the following databases from January 1997-October 2017: MEDLINE; CINAHL; PubMed; PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy we used for Ovid MEDLINE is shown in Supplementary file 1. We adapted this strategy for the other databases. We also hand searched the references lists of identified studies and reviews. The search also included terms for randomized control trials to identify relevant trials for a future systematic review.

Eligibility Criteria

The randomized controlled trials identified in our search were included in another review currently under development. We selected observational studies for this review. This review included primary nutrition studies of cohort or case control designs that quantitatively examined the benefits or harms of wholegrain consumption related to cardiovascular disease outcomes in healthy children and/or adults.

We included studies that defined wholegrains in any way, as defined by the author of the included study. If total wholegrain consumption had been assessed in the study, we included this as our only exposure. If total wholegrain consumption as an exposure was not available, we included any type of wholegrain consumption (i.e. wholegrain cereal, breakfast cereal, bread, rice etc) as our exposure. We included studies that compared wholegrain food to other foods

or compared various levels of wholegrain consumption. We included the result representing the effect of the highest level of wholegrain consumption compared to the lowest level of wholegrain consumption (e.g., 'yes' to wholegrain consumption vs. 'no' to wholegrain consumption, tertile 3 vs. tertile 1, quartile 4 vs. quartile 1, quintile 5 vs. quintile 1). If our pre-specified rules for selection did not uniquely identify one exposure for inclusion in the meta-analysis, we randomly selected one result.

We included studies that had a clinical outcome measure related to cardiovascular disease, defined as mortality related to specific cardiovascular events, and/or cardiovascular events, (e.g., first myocardial infarction, total stroke etc.). If 'cardiovascular disease mortality/death/s' (verbatim) had been assessed, we included this as our only outcome. If not, we included any type of cardiovascular disease mortality (e.g., coronary heart disease mortality, stroke mortality etc.) as our outcome. If there were no mortality outcomes assessed in the study, we included any cardiovascular disease event as our outcome. If a study assessed subgroups of cardiovascular disease deaths and events (e.g., intracerebral haemorrhages, ischaemic stroke) and also assessed them collectively (e.g., cerebrovascular diseases), we took the result that had assessed them collectively. If our pre-specified rules for selection did not uniquely identify one outcome for inclusion in the meta-analysis, we randomly selected one result.

We excluded conferences presentations, opinion pieces and letters to the editor. We had no language restrictions.

Types of Outcome Measures

Primary Outcomes

We hypothesized that studies with food industry sponsorship and/or authors with a COI with the food industry would be more likely to have favourable findings than those with no industry ties. We assessed three primary outcomes:

1. Statistical significance of results favourable to the sponsor

Favourable results were defined as results that were favourable to the sponsor's product(s), either indicating greater health benefits or less harm than the comparator. Specifically, for studies of health benefits of wholegrains, favourable results were defined as those that were statistically significant at the 0.05 level (two tailed). For studies of harms of wholegrains, favourable results were defined as those where harms were not statistically significant at the 0.05 level or there were a statistically significant higher number of harms in the comparator group. Otherwise, results were classified as unfavourable.

2. Effect size of results

Effect size was defined as the risk ratio, hazard ratio or odds ratio of the association between whole grains and a clinical outcome of cardiovascular disease. We compared the magnitude of the pooled effect estimates in studies with food industry sponsorship and/or authors with a COI compared with studies with no industry ties.

3. Conclusions

Conclusions that suggested that the wholegrain intervention being studied was beneficial to health and / or safe were considered favourable to the study sponsor. Otherwise, the conclusions were considered unfavourable.

Secondary Outcomes

We assessed two secondary outcomes:

1. The risk of bias of the included studies

We hypothesized that studies with industry sponsorship and/or authors with a COI with the food industry would have the same overall risk of bias as those with no industry ties.

2. Concordance between study results and conclusions

We hypothesized that studies with industry sponsorship and/or authors with a COI would be more likely to have discordant results and conclusions, with results not favouring the sponsor and conclusions favouring the sponsor, than those with no industry ties.

Selection of studies

Three investigators (NC, SMc & JT, working in pairs) independently screened the titles and abstracts of all retrieved records for obvious exclusions. Full text of potentially eligible studies

was then retrieved, and three investigators (NC, SMc & JT) assessed these against our inclusion criteria. Agreement was reached by consensus.

Data Collection and analysis

Three assessors (NC, SMc & JT) independently extracted the following data from each included study. Discrepancies in data extraction were resolved by consensus. If agreement could not be reached, a fourth assessor (LB) adjudicated the outcome.

From each study we extracted:

- Year of publication
- Study design (cohort or case control)
- Sample size of study
- Age of participants
- Exposure duration or observation period
- How the study defined wholegrain (verbatim)
- Level of wholegrain content in wholegrain foods
- Disclosure of funding source (no disclosure, yes and there is a sponsor, the authors state they received no funding for their work)
- Name of the funders of the study (verbatim)
- Role of the funders (role of the sponsor not mentioned, sponsor not involved in study design and analyses, sponsor involved, N/A)

- Disclosure of author COI (no disclosure, yes, the authors state they had no conflicts of interest to declare)
- Authors COI statement (verbatim)
- Outcomes assessed in the study (any cardiovascular disease death and/or event)
- The numerical results of the study (eg., OR, HR)

We stored all extracted data from the included studies in REDcap, a secure web-based application for the collection and management of data.[23]

Classification of industry sponsorship and author conflicts of interest

Sponsorship was categorized as 1) industry or 2) non-industry. We defined industry sponsored studies as those declaring any sponsorship from the food industry, including if the study received 'mixed funding' from the food industry, non-profit organizations or other industries (i.e. pharmaceutical). Any study with an author with any disclosed financial tie to the food industry was classified as having a conflict of interest (COI). Author COI were categorized as 1) presence of a COI with the food industry or 2) no COI. Any studies that did not contain an author COI disclosure statement were classified as no COI. We contacted the authors of one paper [24] for clarification on their disclosure of funding source.

Assessment of risk of bias in included studies

We used an adapted version of the Cochrane Collaboration's 'Risk of Bias in Non-Randomized Studies-of Interventions' (ROBINS-I)[25] tool to measure the risk of bias of included observational

studies. The tool assesses bias across seven domains. Each domain is assessed at a low, moderate, serious or critical risk of bias, or no information. The domain rating with the highest risk of bias determines the overall risk of bias rating for the study. For example, if a study is rated as being at a serious risk of bias in one domain, the overall risk of bias rating is 'serious.'

Analysis

We report frequencies and percentages of study characteristics across all studies, and separately, by funding source. We visually depict the overall risk of bias rating and the ratings for each domain by study.

We calculated risk ratios or hazard ratios (and 95% confidence intervals) to quantify the association between food industry sponsorship and / or authors with COI with the food industry and favourable results, favourable conclusions and the overall study risk of bias rating. For the risk of bias rating analysis we dichotomised the overall risk of bias ratings as low (low or moderate) or high (serious or critical). We had planned to calculate a RR for level of concordance, however since in all studies there was concordance between the results and conclusions, we did not undertake this analysis.

We used meta-analysis to examine whether food industry sponsorship and / or authors with COI with the food industry modified the magnitude of association between whole grains and cardiovascular disease outcomes. Specifically, we undertook a subgroup analysis within a random effects meta-analysis model that compared the pooled associations across subgroups

defined by industry sponsorship. The associations were pooled using inverse variance weighting and DerSimonian and Laird's method of moments estimator was used to estimate between study heterogeneity. Separate meta-analyses were fitted for studies that had measured the association using hazard ratios and those that had used either risk ratios or odds ratios. Given cardiovascular events were rare, the odds ratios approximated risk ratios. We quantified heterogeneity for subgroup differences using the I^2 statistic [26] and tested for heterogeneity using the Chi2 test. Review Manager 5.3 was used to analyse the data. [27]

Protocol Registration

The protocol is published in PROSPERO [28] ID CRD42017055841. (Supplementary file 2)

Patient Involvement

No patients were involved in the completion of this review.

RESULTS

Search results

We identified 6818 references for screening, from which, 22 studies met the inclusion criteria (Figure 1). See Supplementary file 3 for 'List of excluded Studies' and reasons for exclusion.

Characteristics of included Studies

All studies were published between 1998 and 2015. Three of the studies were case control and 19 were cohort design. All studies contained a sponsorship disclosure. Five studies disclosed food industry sponsorship, but only one of these had a statement describing the role of the sponsor. Five studies contained an author with a COI with the food industry. Ten studies did not contain an author conflict of interest disclosure statement. Nine studies contained either food industry sponsorship or had an author with a COI.

A greater proportion of industry sponsored studies (67%) than non-industry sponsored studies (31%) used a definition of wholegrain as greater than 25%, and most of these examined breakfast cereals (Table 1). Industry sponsored studies were also more likely than non-industry studies to focus on a specific food (44%) than total wholegrain intake (23%) (Table 1). Industry sponsored studies were less likely (56%) to have a serious or critical risk of bias in classification of exposures than non-industry sponsored studies (85%). Other characteristics were similarly distributed across industry vs. non-industry sponsored studies. Details of each individual study are in Supplementary file 4.

Table 1. Characteristics of the included studies by sponsorship and author COI

		Funding Source, n (%[1])		
Characteristic	Category	Total N = 22	Industry/COI N = 9	Non-Industry/No COI N = 13
Sex	Male	4 (18)	3 (33)	0 (0)
	Female	6 (27)	1 (11)	6 (46)

	Both	12 (55)	5 (56)	7 (54)
Sample Size, quartiles	<5000	6 (27)	2 (22)	4 (31)
	5000-50,000	10 (45)	4 (44)	5 (38)
	>50,000	6 (27)	3 (33)	4 (31)
Length of Follow up	N/A*	3 (14)	1 (11)	2 (15)
	<10 years	4 (18)	1 (11)	0 (0)
	10-15 years	9 (41)	4 (44)	8 (62)
	>15	6 (27)	3 (33)	3 (23)
Percent Wholegrain	Not defined	12 (55)	3 (33)	9 (69)
	>25%**	10 (45)	6 (67)	4 (31)
Type of Wholegrain	Only Wholegrain Intake	15 (68)	5 (56)	10 (77)
	Individual Wholegrain Food***	7 (32)	4 (44)	3 (23)
Primary Outcome	Favourable to Wholegrains	16 (73)	8 (89)	8 (62)
	Unfavourable to Wholegrains	6 (27)	1 (11)	5 (38)
Conclusions	Favourable to Wholegrains	16 (73)	8 (89)	8 (62)
	Unfavourable to Wholegrains	6 (27)	1 (11)	5 (38)
Risk of Bias Assessment				
	Serious/Critical Bias due to confounding	21 (95)	9 (100)	12 (92)
	Serious/Critical Bias in selection of participants into the study	3 (14)	1 (11)	2 (15)
	Serious/Critical Bias in classification of exposures	16 (73)	5 (56)	11 (85)
	Serious/Critical Bias due to deviations from exposures	7 (32)	3 (33)	4 (31)
	Serious/Critical Bias due to missing data	0 (0)	0 (0)	0 (0)
	Serious/Critical Bias in measurement of outcomes	1 (5)	1 (11)	0 (0)
	Serious/Critical Bias in selection of reported	0 (0)	0 (0)	0 (0)

	results			
	Serious/Critical overall risk of bias	21 (95)	9 (100)	12 (92)

[1] Percentages may not add to 100 due to rounding

* Case control studies were not followed up

**Any wholegrain foods defined as >25%

***Individual foods included wholegrain cereal, breakfast cereal, bread & brown rice

Risk of bias in included studies

One study[29] was assessed as having an overall moderate risk of bias, four as having a serious risk of bias and 17 as having a critical risk of bias (Figure 2). The majority of studies had a critical risk of bias in the confounding domain. For example, a confounder was fruit and vegetable intake. If this was not appropriately controlled for when assessing the effect of wholegrain intake on a cardiovascular disease outcome, the study was rated as having a risk of bias for confounding. All but one study was assessed at a low risk of bias on the outcome measurement domain. For all domains, except classification of exposure, the risk of bias ratings were similarly distributed across industry vs. non-industry sponsored studies (Table 1).

Favourable results - Statistical significance: Industry sponsored versus non-industry sponsored

The risk of reporting favourable outcomes was 44% higher in studies with industry sponsorship and/or authors with a COI with the food industry RR= 1.44 (95% CI 0.88-2.35). However, the confidence interval was wide and included differences in risks that were unimportant or operating in the opposite direction as plausible estimates**.** When we compared only industry

sponsored (n=5) and non-industry sponsored studies (n=17), the risk was smaller RR = 1.13 (95% CI 0.66-1.94).

Favourable results - Effect size: Industry sponsored versus non-industry sponsored studies

There was no difference in the magnitude of RRs (measuring the association between wholegrains and cardiovascular disease outcomes) between studies with industry sponsorship and/or authors with a COI with the food industry RR = 0.77 (95% CI 0.58-1.01) and those studies with no industry sponsorship or author COI RR = 0.85 (95% CI 0.73-1.00) (subgroup test P=0.50, I^2 = 0%) (Figure 3). For studies that had measured the association using hazard ratios there was also no difference found in the magnitude of HRs between studies with industry sponsorship and/or authors with a COI with the food industry HR=0.82 (95% CI 0.76-0.88) and studies with no industry sponsorship or author COI HR=0.86 (95% CI 0.81-0.91) (subgroup test P=0.34, I^2 = 0%) (Figure 4).

Our analysis comparing studies with industry sponsorship RR 0.63 (95% CI 0.28-1.39) and those with no industry sponsorship RR 0.85 (95% CI 0.74-0.97) (subgroup test P=0.46, I^2 = 0%), showed no important difference in the magnitude of RRs. This was again comparable between industry sponsored HR 0.82 (95% CI 0.77-0.87) and non-industry sponsored studies HR 0.85 (95% CI 0.81-0.90) (subgroup test P=0.29), I^2=12.2%) that measured the association using hazard ratios.

Favourable conclusions: Industry sponsored versus non-industry sponsored

As there was concordance between the results and conclusions of every included study, the same associations were found for conclusions as for the statistical significance of results. Studies with industry sponsorship and/or authors with a COI with the food industry were more likely to have favourable conclusions compared to those with no industry sponsorship or author COI RR= 1.44 (95% CI 0.88-2.35), however the confidence interval was wide. When studies were compared only by industry sponsorship, the risk was again smaller RR = 1.13 (95% CI 0.66-1.94).

Risk of Bias Assessment by Industry Ties

Studies with industry sponsorship and/or authors with a COI with the food industry were less likely (0/9) to have an overall low risk of bias rating compared to those studies with no industry sponsorship or author COI (1/13), RR = 0.47 (95% CI 0.02 -10.32), however there was large uncertainty in the association.

DISCUSSION

Observational studies examining the effect of wholegrain consumption on cardiovascular disease outcomes that were sponsored by the food industry and / or had authors with a COI with the food industry more often had favourable results than research not tied to the food industry. However, this finding was inconclusive with respect to the association between industry ties and favorable results, as the relative risk could be as high as 2.35 or as low as 0.88. We found no evidence of a difference in the magnitude of effect between industry sponsored and non-industry sponsored studies. It is difficult to detect differences in effect size by

sponsorship as many study design features, such as dose and duration of exposures, and specific cardiovascular disease outcomes, vary across studies and may influence the effect size. In previous assessments of drug studies that have demonstrated that industry funded studies are more likely to have results that favour the study sponsors, there was no statistically significant difference found in effect sizes between industry and non-industry sponsored studies. [13]

Although all the included studies had a sponsorship disclosure, almost half were missing disclosures about author COI. Nondisclosed COIs in nutrition research are a concern.[30] Larger samples of industry funded studies and studies with disclosed author COI could make it possible to establish the association of sponsorship with research outcomes.

Studies that were sponsored by the food industry and / or had authors with a COI with the food industry more often had favourable conclusions than studies with no industry ties, although there was uncertainty in this relationship. There was absence of spin in the included studies as all the results agreed with the conclusions.

The overall risk of bias in every study, other than one non-industry sponsored study, [29] was classified as high (meaning either serious or critical). The overall risk of bias rating was based on the domain with the highest risk of bias rating within each study, and most of the studies had a risk of bias related to confounding. Across each domain, we found little difference in the risk of bias between industry sponsored and non-industry sponsored studies.

Strengths and limitations of this review

Our review was registered in PROSPERO .[28] We conducted a comprehensive search and followed explicit and well-defined inclusion and exclusion criteria for the included studies. Although our sample was small, we searched several databases and reference lists of included studies. Authors of the studies for which we required clarification on funding source were also contacted, but we did not attempt to contact the authors of studies lacking a COI disclosure statement. Thus, we may be underestimating the number of articles that had authors with conflicts of interest. Our assessment of risk of bias in the included studies was based on a tool that is under development, but changes to the tool are unlikely to affect the risk of bias ratings.[25]

Agreements and disagreements with other studies or reviews

The relationship that we identified between food industry sponsorship and authors with a COI and favourable study outcomes towards the study sponsor has been previously demonstrated in an assessment of a broad range of nutrition research.[20] Only one study has reported an association of food industry funding with effect sizes.[31] Of studies examining the association between soft drink consumption and adverse health outcomes, food industry sponsored studies reported significantly smaller effects than non-food industry sponsored studies. Compared to our study, this study examined studies with a homogeneous population of industry funders, sugar sweetened beverage companies, which may have a more consistent influence on study outcomes than the diverse pool of food industry sponsors in our study.

There was also no difference in the level of risk of bias between industry sponsored and non-industry sponsored studies. This is consistent with previous assessments of pharmaceutical, tobacco and nutrition research that has shown industry-sponsored studies are of equal or better quality than non–industry-sponsored studies.[13 20 32-34]

Implications for clinicians, policy makers and future research

The recent critiques to reform the methods used in the development of dietary guidelines have proposed steps to improve the transparency of how evidence is evaluated and synthesized into recommendations. [1 2] However, until the influence of industry sponsorship in primary nutrition studies has been further explored and measured with larger samples of industry sponsored studies, or studies that have author disclosure statements, this bias may still be unaccounted for in dietary guidelines. Although there was uncertainty around the differences in the results and conclusions that we observed between industry and non-industry studies, the differences are unlikely to be explained by methodological risks of bias in these studies.

There are ways that study sponsorship can influence outcomes other than through the design of research. Bias may also be introduced in the way industry sponsored studies code events and analyse data, [35 36] through the selective reporting of study outcomes and through publication bias. [37] It has been demonstrated in other areas of medical research that there is a greater propensity to publish studies with statistically significant results. [38] Therefore, selective publication of study results or studies in their entirety, may limit the availability of all relevant nutrition data and can skew results that are used in dietary guideline development.[39]

Publication bias could be minimized with the introduction of study registries for nutrition research, as has been established in pharmaceutical research. [40] The association of food industry sponsorship with the reporting of nutrition research still needs to be assessed.

Almost half of the studies included in this review had authors that did not disclose if they had a COI with the food industry or not. Compliance with COI disclosure policies is now well documented across many domains of research. [41-46] Recent examinations of the levels of disclosure in research assessing the effects of artificially sweetened beverages on weight outcomes found similarly poor disclosure rates.[32] Several solutions have been proposed to increase transparency and disclosure rates, including the use of different databases and additional resources to identify conflicted authors, and the introduction of mandatory disclosure requirements in all journals, with the use of penalties for those who do not adhere to the stated policies. [20 32]

Conclusion

We did not establish that the presence of food industry sponsorship or authors with a COI with the food industry was associated with results or conclusions that favour industry sponsors. The association of food industry sponsorship or authors with a COI with the food industry and favourable results or conclusions is uncertain. However, our analysis was hindered by the low level of COI disclosure in the included studies. This research further strengthens calls for stricter policies relating to the disclosure and management of conflicts of interest in nutrition research.

Without such disclosures, it will not be possible to determine if the results of nutrition research are free of food industry influences and potential biases.

Figure 1. Study Flow Diagram

Figure 2. Risk of Bias of Included Studies

Figure 3: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Risk Ratio

Figure 4: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Hazard Ratio

References

1. National Academies of Sciences, Engineering, and Medicine. Redesigning the process for establishing the dietary guidelines for Americans 2017 [Available from: https://www.nap.edu/catalog/24883/redesigning-the-process-for-establishing-the-dietary-guidelines-for-americans (accessed Nov 2017)].
2. National Academies of Sciences, Engineering, and Medicine. Optimizing the process for establishing the Dietary Guidelines for Americans: the selection process 2017 [Available from: https://www.nap.edu/catalog/24637/optimizing-the-process-for-establishing-the-dietary-guidelines-for-americans (accessed Nov 2017)].
3. Bero L. Developing reliable dietary guidelines. *BMJ* 2017;359 doi: 10.1136/bmj.j4845
4. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition December 2015 [Available from: https://health.gov/dietaryguidelines/2015/guidelines/(accessed Dec 2017)].
5. National Health and Medical Research Council: Department of Health and Ageing. Australian Dietary Guidelines. Canberra, Commonwealth of Australia: NHMRC, 2013.
6. Public Health England. The Eatwell Guide 2017 [December 4, 2017]. Available from: https://www.gov.uk/government/publications/the-eatwell-guide.
7. Aune D, Keum N, Giovannucci E, et al. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: systematic review and dose-response meta-analysis of prospective studies. *BMJ* 2016;353 doi: 10.1136/bmj.i2716
8. Benisi-Kohansal S, Saneei P, Salehi-Marzijarani M, et al. Whole-Grain Intake and Mortality from All Causes, Cardiovascular Disease, and Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. *Advances in Nutrition: An International Review Journal* 2016;7(6):1052-65. doi: 10.3945/an.115.011635
9. Zhang B, Zhao Q, Guo W, et al. Association of whole grain intake with all-cause, cardiovascular, and cancer mortality: a systematic review and dose-response meta-analysis from prospective cohort studies. *Eur J Clin Nutr* 2017 doi: 10.1038/ejcn.2017.149
10. Kelly SAM, Hartley L, Loveman E, et al. Whole grain cereals for the primary or secondary prevention of cardiovascular disease. *Cochrane Database of Systematic Reviews* 2017(8) doi: 10.1002/14651858.CD005051.pub3
11. Jacobs Jr DR, Meyer KA, Kushi LH, et al. Whole-grain intake may reduce the risk of ischemic heart disease death in postmenopausal women: The Iowa women's health study. *American Journal of Clinical Nutrition* 1998;68(2):248-57.
12. Blake P, Durao S, Naude CE, et al. An analysis of methods used to synthesize evidence and grade recommendations in food-based dietary guidelines. *Nutr Rev* 2018 doi: 10.1093/nutrit/nux074 [published Online First: 2018/02/10]
13. Lundh A, Lexchin J, Mintzes B, et al. Industry sponsorship and research outcome. *The Cochrane database of systematic reviews* 2017;2:Mr000033. doi: 10.1002/14651858.MR000033.pub3 [published Online First: 2017/02/17]
14. Huss A, Egger M, Hug K, et al. Source of funding and results of studies of health effects of mobile phone use: systematic review of experimental studies. *Ciencia & saude coletiva* 2008;13(3):1005-12. [published Online First: 2008/09/25]
15. Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. *Jama* 1998;279(19):1566-70.
16. Lexchin J. Those who have the gold make the evidence: how the pharmaceutical industry biases the outcomes of clinical trials of medications. *Science & Engineering Ethics*;18(2):247-61.

17. Sismondo S. How pharmaceutical industry funding affects trial outcomes: causal structures and responses. *Social science & medicine (1982)* 2008;66(9):1909-14. doi: 10.1016/j.socscimed.2008.01.010 [published Online First: 2008/02/27]
18. Boutron I, Dutton S, Ravaud P, et al. Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. *Jama* 2010;303(20):2058-64. doi: 10.1001/jama.2010.651 [published Online First: 2010/05/27]
19. Odierna DH, Forsyth SR, White J, et al. The cycle of bias in health research: a framework and toolbox for critical appraisal training. *Accountability in research* 2013;20(2):127-41. doi: 10.1080/08989621.2013.768931 [published Online First: 2013/02/26]
20. Chartres N, Fabbri A, Bero LA. Association of industry sponsorship with outcomes of nutrition studies: A systematic review and meta-analysis. *JAMA Internal Medicine* 2016;176(12):1769-77. doi: 10.1001/jamainternmed.2016.6721
21. Diels J, Cunha M, Manaia C, et al. Association of financial or professional conflict of interest to research outcomes on health risks or nutritional assessment studies of genetically modified products. *Food Policy* 2011;36(2):197-203. doi: 10.1016/j.foodpol.2010.11.016
22. Dietitians Association of Australia. A review of the evidence to address targeted questions to inform the revision of the Australian dietary guidelines 2009: Process Manual, 2011.
23. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of biomedical informatics* 2009;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010
24. Holmberg S, Thelin A, Stiernstrom EL. Food choices and coronary heart disease: a population based cohort study of rural Swedish men with 12 years of follow-up. *International Journal of Environmental Research & Public Health [Electronic Resource]* 2009;6(10):2626-38.
25. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355 doi: 10.1136/bmj.i4919
26. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60. doi: 10.1136/bmj.327.7414.557
27. Version 5.3 [program]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
28. National Institute for Health Research. International Prospective Register for Sytematic Reviews [Internet]. 2015 [Available from: http://www.crd.york.ac.uk/PROSPERO/ accessed 11/03 2015.
29. Wu H, Flint AJ, Qi Q, et al. Association between dietary whole grain intake and risk of mortality: two large prospective studies in US men and women. *JAMA Internal Medicine* 2015;175(3):373-84. doi: 10.1001/jamainternmed.2014.6283
30. Nestle M. Corporate Funding of Food and Nutrition Research: Science or Marketing? *JAMA Intern Med* 2016;176(1):13-4. doi: 10.1001/jamainternmed.2015.6667 [published Online First: 2015/11/26]
31. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *American journal of public health* 2007;97(4):667-75. doi: 10.2105/ajph.2005.083782 [published Online First: 2007/03/03]
32. Mandrioli D, Kearns CE, Bero LA. Relationship between Research Outcomes and Risk of Bias, Study Sponsorship, and Author Financial Conflicts of Interest in Reviews of the Effects of Artificially Sweetened Beverages on Weight Outcomes: A Systematic Review of Reviews. *PloS one* 2016;11(9):e0162198. doi: 10.1371/journal.pone.0162198
33. Barnes DE, Bero LA. Industry-funded research and conflict of interest: an analysis of research sponsored by the tobacco industry through the Center for Indoor Air Research. *Journal of Health Politics, Policy & Law* 1996;21(3):515-42.

34. Cho MK, Bero LA. The quality of drug studies published in symposium proceedings. *Ann Intern Med* 1996;124(5):485-9. [published Online First: 1996/03/01]
35. Psaty BM, Prentice RL. Minimizing bias in randomized trials: the importance of blinding. *Jama* 2010;304(7):793-4. doi: 10.1001/jama.2010.1161 [published Online First: 2010/08/19]
36. Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. *Jama* 2008;299(15):1813-7. doi: 10.1001/jama.299.15.1813 [published Online First: 2008/04/17]
37. Hart B, Lundh A, Bero L. Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses. *British Medical Journal* 2012;344 doi: 10.1136/bmj.d7202
38. Hopewell S, Loudon K, Clarke MJ, et al. Publication bias in clinical trials due to statistical significance or direction of trial results. *The Cochrane database of systematic reviews* 2009(1):Mr000006. doi: 10.1002/14651858.MR000006.pub3 [published Online First: 2009/01/23]
39. Misakian AL, Bero LA. Publication bias and research on passive smoking: comparison of published and unpublished studies. *JAMA* 1998;280(3):250-3.
40. Dickersin K, Rennie D. The evolution of trial registries and their use to assess the clinical trial enterprise. *Jama* 2012;307(17):1861-4. doi: 10.1001/jama.2012.4230 [published Online First: 2012/05/03]
41. Forsyth SR, Odierna DH, Krauth D, et al. Conflicts of interest and critiques of the use of systematic reviews in policymaking: an analysis of opinion articles. *Systematic reviews* 2014;3:122. doi: 10.1186/2046-4053-3-122 [published Online First: 2014/11/25]
42. Ruff K. Scientific journals and conflict of interest disclosure: what progress has been made? *Environmental health : a global access science source* 2015;14:45. doi: 10.1186/s12940-015-0035-6 [published Online First: 2015/05/31]
43. Resnik DB. Science and money: problems and solutions. *Journal of microbiology & biology education* 2014;15(2):159-61. doi: 10.1128/jmbe.v15i2.792 [published Online First: 2015/01/13]
44. Roseman M, Milette K, Bero LA, et al. Reporting of conflicts of interest in meta-analyses of trials of pharmacological treatments. *Jama* 2011;305(10):1008-17. doi: 10.1001/jama.2011.257 [published Online First: 2011/03/10]
45. Bero L. Addressing bias and conflict of interest among biomedical researchers. *JAMA* 2017;317(17):1723-24. doi: 10.1001/jama.2017.3854
46. Grundy Q, Dunn AG, Bourgeois FT, et al. Prevalence of disclosed conflicts of interest in biomedical research and associations with journal impact factors and altmetric scores. *JAMA* 2018;319(4):408-09. doi: 10.1001/jama.2017.20738

Contributors: NC, AF, SMc, MA-F and LB designed and wrote the review protocol. NC wrote the search strategy and undertook the literature search. NC, SMc and JT conducted the title and abstract screening and full article screening for final study inclusion. NC, SMc and JT conducted data collection and cleaning, LB supervised. NC and JMc undertook all data analysis. LB advised on methods, statistical analyses, and interpretation of findings. All authors contributed to the final manuscript. NC and LB are guarantors.

Acknowledgement: We thank Matthew Page, Monash University for answering specific statistical questions.

Funding: This work was funded by National Health and Medical Research Council Grant #APP1139997. Nicholas Chartres is a recipient of the James Millner PhD Scholarship in Pharmacy from the University of Sydney. Sally McDonald is a scholarship recipient (Charles Perkins Centre summer scholarship) from the University of Sydney. Jessica Turton is a scholarship recipient (Charles Perkins Centre summer scholarship) from the University of Sydney.

Competing interests: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf. No support was received from any organisation for the submitted work. The authors have no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. The authors report no other relationships or activities that could appear to have influenced the submitted work.

Ethical Approval: Not required

Transparency declaration: The authors affirm that this manuscript is a honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Data Sharing: Available from The University of Sydney data repository. DOI to be determined.

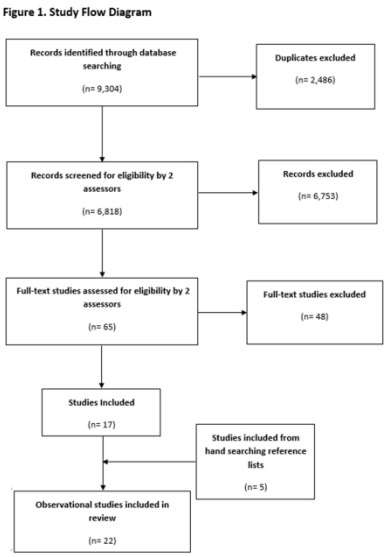

Figure 1. Study Flow Diagram

338x190mm (300 x 300 DPI)

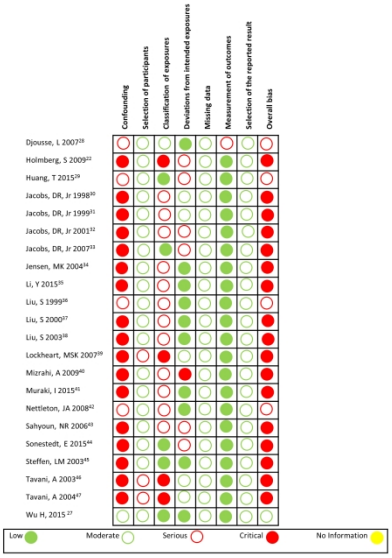

Figure 2. Risk of Bias Table

338x190mm (300 x 300 DPI)

Figure 3: Effect Size - Industry Sponsored &/OR Author COI versus Non-Industry Sponsored & No Author COI, RR

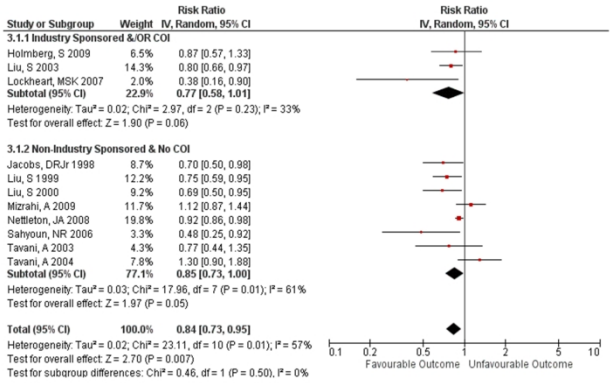

Figure 3. Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Risk Ratio

338x190mm (300 x 300 DPI)

Figure 4: Effect Size - Industry Sponsored &/OR Author COI versus Non-Industry Sponsored & No Author COI, HR

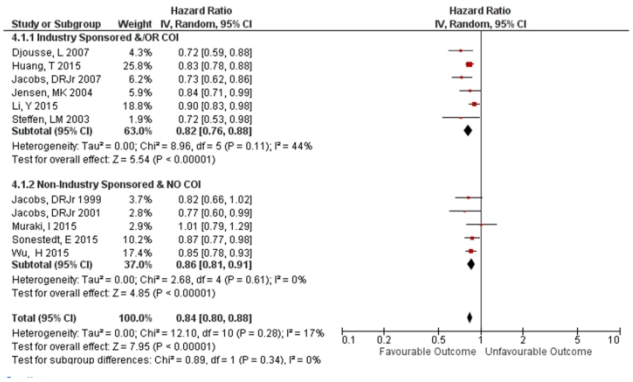

Figure 4: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Hazard Ratio

338x190mm (300 x 300 DPI)

Supplementary File 1: Search Strategy

OVID Medline: wholegrain & CVD

1. Randomized controlled trial*.sh.
2. experimental design.tw.
3. intervention*.tw.
4. (RCT* or rct*).tw.
5. random* control* trial*.tw.
6. clinical trial*.sh.
7. field trial*.tw.
8. community trial*.tw.
9. controlled clinical trial*.tw.
10. pragmatic trial*.tw.
11. observational study.sh.
12. cohort study.tw.
13. prospective cohort*.tw.
14. retrospective cohort*.tw.
15. case control*.sh.
16. ecological study.tw.
17. time series analys?s.tw.
18. before-after study.tw.
19. pre-post study.tw.

20. follow up stud*.sh.

21. comparative stud*.sh.

22. evaluation stud*.sh.

23. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22

24. Edible Grain/ae, me [Adverse Effects, Metabolism]

25. grain*.tw.

26. Dietary Carbohydrates/ or Edible Grain/ or Bread/ or Dietary Fiber/

27. whole grain*.tw.

28. partially processed grains.tw.

29. whole wheat.tw.

30. wholemeal.tw.

31. rice*.tw.

32. oat*.tw.

33. barley*.tw.

34. wheat*.tw.

35. Amaranthus/ae, me [Adverse Effects, Metabolism]

36. amaranth.tw.

37. Millets/me [Metabolism]

38. millet*.tw.

39. Sorghum/me [Metabolism]

40. sorghum*.tw.

41. maize*.tw.

42. spelt*.tw.

43. buckwheat*.tw.

44. Triticale/me [Metabolism]

45. triticale*.tw.

46. fonio*.tw.

47. emmer.tw.

48. einkorn*.tw.

49. kamut*.tw.

50. canary seed*.tw.

51. Bread/ae, an, me [Adverse Effects, Analysis, Metabolism]

52. bread*.tw.

53. breakfast cereal*.tw.

54. pasta*.tw.

55. noodle*.tw.

56. Flour/ae, an, st [Adverse Effects, Analysis, Standards]

57. flour*.tw.

58. polenta*.tw.

59. semolina*.tw.

60. bran.tw.

61. corn.tw.

62. wheat germ*.tw.

63. corn cake*.tw.

64. scone*.tw.

65. couscous.tw.

66. crumpet*.tw.

67. dietary fiber.tw.

68. dietary carbohydrate*.tw.

69. glycemic index.tw.

70. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 64 or 65 or 66 or 67 or 68 or 69

71. Coronary Disease/ or Cardiovascular Diseases/ or Hypertension/ or Atherosclerosis/

72. cardiovascular disease*.tw.

73. coronary*.tw.

74. heart*.tw.

75. cardia*.tw.

76. myocard*.tw.

77. isch?em*.tw.

78. angina*.tw.

79. ventric*.tw.

80. tachycardi*.tw.

81. pericard*.tw.

82. endocardi*.tw.

83. atrial fibrillat*.tw.

84. arrhythmi*.tw.

85. athero*.tw.

86. arterio*.tw.

87. HDL.tw.

88. LDL.tw.

89. VLDL.tw.

90. lipid*.tw.

91. lipoprotein*.tw.

92. triacylglycerol*.tw.

93. hyperlipid*.tw.

94. hypercholesterol*.tw.

95. hypercholester?emia*.tw.

96. hypertriglycerid?emia*.tw.

97. Cholesterol/

98. Stroke/

99. Cerebrovascular Disorders/

100. vascular accident*.tw.

101. TIA.tw.

102. Thrombosis/

103. thrombosis.tw.

104. Embolism/ or Pulmonary Embolism/

111 105. apoplexy.tw.

112 106. (brain adj2 accident*).tw.

113 107. ((brain* or cerebral or lacunar) adj2 infarct*).tw.

114 108. Blood Pressure/ or Hypertension/

115 109. systolic blood pressure.tw.

116 110. diastolic blood pressure.tw.

117 111. Peripheral Vascular Diseases/ or Peripheral Arterial Disease/

118 112. (coronar$ adj5 (bypas$ or graft$ or disease$ or event$)).tw.

119 113. (cerebrovasc$ or cardiovasc$ or mortal$ or angina$ or stroke or strokes).tw.

120 114. (myocardi$ adj5 (infarct$ or revascular$ or ischaemi$ or ischemi$)).tw.

121 115. (morbid$ adj5 (heart$ or coronar$ or ischaem$ or ischem$ or myocard$)).tw.

122 116. (vascular$ adj5 (peripheral$ or disease$ or complication$)).tw.

123 117. (heart$ adj5 (disease$ or attack$ or bypass$)).tw.

124 118. Mortality/

125 119. mortality.tw.

126 120. Diabetes Mellitus, Type 2/

127 121. Hyperglycemia/

128 122. hyperglycemi*.tw.

129 123. (glucose adj2 intoleran*).tw.

130 124. Insulin Resistance/

131 125. (metabolic adj3 syndrome adj3 x).tw.

132 126. metabolic cardiovascular syndrome.tw.

127. dysmetabolic syndrome x.tw.

128. HbA1c.tw.

129. (glyc?emic adj3 control).tw.

130. 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129

131. 23 and 70 and 130

132. limit 131 to (humans and yr="1997 -Current")

UNIVERSITY of York
Centre for Reviews and Dissemination

NHS
National Institute for
Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
The association of industry sponsorship with outcomes of studies examining the effect of intake of wholegrain foods with cardiovascular disease and mortality: protocol

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
28/11/2016

4 Anticipated completion date
Give the date by which the review is expected to be completed.
31/05/2017

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Mr Chartres

7 Named contact email
Enter the electronic mail address of the named contact.
ngar0960@uni.sydney.edu.au

8 Named contact address
Enter the full postal address for the named contact.
THE UNIVERSITY OF SYDNEY D17, The Hub, 6th floor, Charles Perkins Centre| The University of Sydney | NSW | 2006

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
02 8627 4328

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed

as 'None' if the review is not affiliated to any organisation.
THE UNIVERSITY OF SYDNEY

Website address:
sydney.edu.au

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Mr	Nicholas	Chartres	The Hub, 6th floor, Charles Perkins Centre, The University of Sydney
Dr	Alice	Fabbri	The Hub, 6th floor, Charles Perkins Centre, The University of Sydney
Miss	Sally	McDonald	The Hub, 6th floor, Charles Perkins Centre, The University of Sydney
Miss	Jessica	Turton	The Hub, 6th floor, Charles Perkins Centre, The University of Sydney
Professor	Margaret	Allman-Farinelli	Charles Perkins Centre, The University of Sydney
Professor	Lisa	Bero	D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
Nicholas Chartres is a scholarship recipient (James Milner PhD scholarship in Pharmacy) from the University of Sydney. Alice Fabbri is a PhD student. She is recipient of a scholarship from the Italian Ministry of Education, Universities and Research. Sally McDonald is a scholarship recipient (Charles Perkins Centre summer scholarship) from the University of Sydney. Jessica Turton is a scholarship recipient (Charles Perkins Centre summer scholarship) from the University of Sydney.

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
The objective of this study is to determine if the presence of food industry sponsorship in primary nutrition studies examining the association of wholegrain foods with cardiovascular outcomes is associated with effect sizes, statistical significance of results and/ or conclusions that are favorable to the sponsor.

We will also determine whether industry sponsored primary nutrition studies assessing the association of wholegrain foods with cardiovascular outcomes differ in their risk of bias compared with studies with no or other sources of sponsorship.

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
We will search the following databases from 1997-2016: Ovid MEDLINE; CINAHL; PubMed; PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC.

17 URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
No

18 Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
public health - nutrition

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
studies of adults and / or children were eligible for inclusion Inclusion Criteria • The study quantitatively measure the effects of wholegrain consumption in humans • The study involves or considers research with healthy children and/or adults with BMI 25% wholegrain, which may be whole, partially processed, ground or milled grain products in which every part of the grain is present in proportions that represent those present in the whole grain • The study has an outcome measure related to cardiovascular disease. • The study evaluates clinical outcomes (e.g. risk ratio/hazard ratio/odds ratio (RR/HR/OR) of cardiovascular mortality, nonfatal heart attack, stroke, etc.) and/or the surrogate outcomes of Blood Pressure (mmHg), LDL cholesterol, or HbA1c. • If the study examines mixed interventions (e.g. nutritional and educational) we will include them only if data related to wholegrain consumption are reported separately or can be obtained from the authors • In case of multiple reports from the same study, we will use the most complete and/or recently reported data Exclusion Criteria • Cross sectional studies, reviews and meta-analysis, commentaries. • The study examines dietary patterns only (e.g. the “Mediterranean diet”) • The study examines nutrients in an altered state (i.e. cereal fibre supplements or bran fortification) • The study examines total grain intake without differentiating between wholegrains and refined grains, or includes significant refined grain products in the wholegrain category. • The study examines only refined grain products, including cereal products containing high added fat or sugar (e.g. cakes, biscuits, pastries). • The study examines intake of supplemented or enriched foods (e.g. with the addition of bran) and not intake of wholegrain foods.

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Wholegrain vs Wholegrain (different doses) Wholegrain vs Wholegrain (different grains) Wholegrain vs no Wholegrain Wholegrain vs Refined grain Wholegrain vs Other food Other (mixed intervention)

22 Types of study to be included
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Inclusion: RCT/ cluster RCT Controlled Trial/ pseudo-randomized Cohort Case-control Pre/Post Exclusion: Cross sectional studies reviews and meta-analysis commentaries.

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 Primary outcome(s)
Give the most important outcomes.
a. Primary Outcome 1 and 2 (Results and effect size) - Statistical significance of results - Effect size of outcomes b. Primary Outcome 3 (Conclusions) For this study, we will use clinical outcomes only for observational studies and both clinical and surrogate outcomes for interventional studies. We define as clinically relevant cardiovascular outcomes as mortality related to specific cardiovascular events, and/or number of cardiovascular events (including myocardial infarction, stroke). We define relevant surrogate outcomes as blood pressure (mmHg), lipid marker (LDL cholesterol),

or HbA1c. Our rationale for including only these outcomes is that these were used to measure cardiovascular disease risk factors in the development of the Australian Dietary Guidelines We will define favorable results and conclusions as those showing a statistically significant association of wholegrain consumption and decreased cardiovascular disease risk. For each study we will record the stated hypothesis for the study, including the stated outcomes to be measured. If primary outcomes are not stated we will take mortality (related to specific cardiovascular events) as the primary outcome to be measured. In the absence of mortality outcomes, we will take number of cardiovascular events (including non-fatal myocardial infarction and stroke) as the primary outcome. In the absence of these, blood pressure, LDL cholesterol, or HbA1C as risk factors will be used as the primary outcome.

Give information on timing and effect measures, as appropriate.
variable

25 Secondary outcomes

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
Secondary Outcome 1 (Methodological risk of bias) Secondary Outcome 2 (Concordance between results and conclusions) Risk of Bias Assessment We will use the Cochrane Risk of Bias tool for randomised studies to measure the methodological quality of randomized controlled trials. The tool assesses bias across 7 domains and each of these will be reported separately. To measure methodological quality in observational studies we will use the ROBINS-E tool for non-randomized studies (ROBINS-E), which also measures bias across 7 domains. We will classify concordance between study results and conclusions as 'yes' if the authors' conclusions are supported by all outcomes. This will include the reporting of all significant and non-significant results. Otherwise, concordance will be classified as 'no'.

Give information on timing and effect measures, as appropriate.
variable

26

Supplementary File 3: List of Excluded Studies

Author: Year	Title	Reason For Exclusion
Ahn, Y 2013[1]	Rice-eating pattern and the risk of metabolic syndrome especially waist circumference in Korean Genome and Epidemiology Study (KoGES)	No wholegrain rice group on its own. Only mixed meals
Alonso, A 2006[2]	Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort	Fiber from cereals was not exclusively from wholegrain products
Altorf-van der Kuil, W 2012[3]	Sources of dietary protein and risk of hypertension in a general Dutch population	The study does not specify grain source of protein is from wholegrains
Appleby, PN 1999[4]	The Oxford Vegetarian Study: an overview	No analysis of wholegrains, only dietary fiber
Assmann, KE 2015[5]	A Healthy Dietary Pattern at Midlife, Combined with a Regulated Energy Intake, Is Related to Increased Odds for Healthy Aging	Dietary pattern assessment only. No separate analysis of wholegrains
Bae, JM 2002[6]	A nested case-control study on the high-normal blood pressure as a risk factor of hypertension in Korean middle-aged men	No measurement of wholegrain intake, only total dietary fiber
Bazzano, LA 2003[7]	Dietary fiber intake and reduced risk of coronary heart disease in US men and women: the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study	No separate analysis of dietary fiber from wholegrains
Bernstein, AM 2011[8]	Cereal fiber and coronary heart disease: a comparison of modeling approaches for repeated dietary measurements, intermediate outcomes, and long follow-up	No separate analysis of cereal fiber from wholegrains
Bertoia, ML 2014[9]	Mediterranean and Dietary Approaches to Stop Hypertension dietary patterns and risk of sudden cardiac death in postmenopausal women	Dietary pattern assessment only. No separate analysis of wholegrains

Bingham, CM 2012[10]	Food choices and health during military service: increases in sugar- and fibre-containing foods and changes in anthropometric and clinical risk factors	Cross sectional analysis only of diet. No measurement of whole grain foods
Buil-Cosiales, P 2014[11]	Fiber intake and all-cause mortality in the Prevención con Dieta Mediterránea (PREDIMED) study	Participants did not meet the inclusion criteria
Burger, KN 2011[12]	Dietary glycemic load and glycemic index and risk of coronary heart disease and stroke in Dutch men and women: the EPIC-MORGEN study	No measurement of wholegrain intake
Burke, V 2005[13]	Predictors of body mass index and associations with cardiovascular risk factors in Australian children: a prospective cohort study	No measurement of wholegrain intake
Chuang, S-C 2012[14]	Fiber intake and total and cause-specific mortality in the European Prospective Investigation into Cancer and Nutrition cohort	No separate analysis of cereal fiber from wholegrains
Crowe, FL 2012[15]	Dietary fibre intake and ischaemic heart disease mortality: the European Prospective Investigation into Cancer and Nutrition-Heart study	No separate analysis of cereal fiber from wholegrains
Djoussé, L 2009[16]	Relation between modifiable lifestyle factors and lifetime risk of heart failure	No separate analysis of cereal from wholegrains
Eshak, ES 2014[17]	Rice consumption is not associated with risk of cardiovascular disease morbidity or mortality in Japanese men and women: a large population-based, prospective cohort study	No separate analysis of brown/unrefined rice
Flint, AJ 2009[18]	Whole grains and incident hypertension in men	No clinical CVD outcome measured

Guo, J 2013[19]	Influence of dietary patterns on the risk of acute myocardial infarction in China population: the INTERHEART China study	Only 'Grains' measured for association with risk of MI. No separate analysis for wholegrains
Hansen-Krone, IJ 2012[20]	Heart healthy diet and risk of myocardial infarction and venous thromboembolism. The Tromso Study	Dietary pattern assessment only. No separate analysis of wholegrains
Iso, H 2007[21]	Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC)	No separate analysis of brown/unrefined rice
Jacobs, DR Jr 2000[22]	Fiber from whole grains, but not refined grains, is inversely associated with all-cause mortality in older women: the Iowa women's health study	Fiber from cereals was not exclusively from whole grain products for the high wholegrain fiber group (29% from refined grain)
Jansen, MC 1999[23]	Dietary fiber and plant foods in relation to colorectal cancer mortality: the seven countries study	No clinical CVD outcome measured
Johnsen, NF 2015[24]	Whole-grain products and whole-grain types are associated with lower all-cause and cause-specific mortality in the Scandinavian HELGA cohort	No combined data for men and woman
Kanda, A 1999[25]	Association of lifestyle parameters with the prevention of hypertension in elderly Japanese men and women: a four-year follow-up of normotensive subjects	No separate analysis of brown/unrefined rice No clinical CVD outcome measured
Kochar, J 2012[26]	Breakfast cereals and risk of hypertension in the Physicians' Health Study I	No clinical CVD outcome measured
Kokubo, Y 2011[27]	Dietary fiber intake and risk of cardiovascular disease in the Japanese population: the Japan Public Health Center-based study cohort	No separate analysis of fiber from wholegrains
Larsson, SC 2016[28]	Dietary Approaches to Stop Hypertension Diet and Incidence of Stroke: Results From 2 Prospective Cohorts	Dietary pattern assessment only. No separate analysis of wholegrains
Li, S 2014[29]	Dietary fiber intake and mortality among survivors of myocardial infarction: prospective cohort study	Participants did not meet the inclusion criteria

Liang, W 2010[30]	White rice-based food consumption and ischemic stroke risk: a case-control study in southern china	No separate analysis of brown rice/wholegrains
Liu, S 2000[31]	A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women	No clinical CVD outcome measured
Mozaffarian, D 2003[32]	Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals	No separate analysis of cereal fiber from wholegrains
Negri, E 2003[33]	Fiber intake and risk of nonfatal acute myocardial infarction	No separate analysis of cereal fiber from wholegrains
Oh, K 2005[34]	Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women	No separate analysis of cereal fiber from wholegrains
Pan, A 2012[35]	Red meat consumption and mortality: results from 2 prospective cohort studies	No analysis of whole grain intake and CVD outcomes
Park, Y 2011[36]	Dietary fiber intake and mortality in the NIH-AARP diet and health study	No separate analysis of cereal fiber from wholegrains. No combined data for men and woman
Pierucci, P 2012[37]	Diet and myocardial infarction: a nested case-control study in a cohort of elderly subjects in a Mediterranean area of southern Italy	No analysis of wholegrains
Rebello, SA 2014[38]	Amount, type, and sources of carbohydrates in relation to ischemic heart disease mortality in a Chinese population: a prospective cohort study	No combined data for men and woman
Rodriguez-Campello, A 2014[39]	Dietary habits in patients with ischemic stroke: a case-control study	No separate analysis of breaded foods from wholegrains
Shi, Z 2012[40]	Rice intake, weight change and risk of the metabolic syndrome development among Chinese adults: the Jiangsu Nutrition Study (JIN)	No analysis of wholegrain intake and CVD outcomes
Steffen, LM 2005[41]	Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white adults: the Coronary Artery Risk	No clinical CVD outcome measured

	Development in Young Adults (CARDIA) Study	
Streppel, MT 2008[42]	Dietary fiber intake in relation to coronary heart disease and all-cause mortality over 40 y: the Zutphen Study	No separate analysis of bread and cereal fiber from wholegrains
Threapleton, DE 2013[43]	Dietary fibre and cardiovascular disease mortality in the UK Women's Cohort Study	No separate analysis of total and breakfast cereal fiber from wholegrains
Threapleton, DE 2015[44]	Dietary fibre intake and risk of ischaemic and haemorrhagic stroke in the UK Women's Cohort Study	No separate analysis of total and breakfast cereal fiber from wholegrains
Wang, L 2007[45]	Whole- and refined-grain intakes and the risk of hypertension in women	No clinical CVD outcome measured
Wolk, A 1999[46]	Long-term intake of dietary fiber and decreased risk of coronary heart disease among women	No separate analysis of fiber from wholegrains
Yu, D 2014[47]	Adherence to dietary guidelines and mortality: a report from prospective cohort studies of 134,000 Chinese adults in urban Shanghai	Dietary pattern assessment only. No separate analysis of wholegrains
Yu, D 2016[48]	Dietary glycemic index, glycemic load, and refined carbohydrates are associated with risk of stroke: a prospective cohort study in urban Chinese women	No analysis of wholegrains

1. Ahn Y, Park SJ, Kwack HK, et al. Rice-eating pattern and the risk of metabolic syndrome especially waist circumference in Korean Genome and Epidemiology Study (KoGES). *BMC Public Health* 2013;**13**:61.

2. Alonso A, Beunza JJ, Bes-Rastrollo M, et al. Vegetable protein and fiber from cereal are inversely associated with the risk of hypertension in a Spanish cohort. *Arch Med Res* 2006;**37**(6):778-86.

3. Altorf-van der Kuil W, Engberink MF, Geleijnse JM, et al. Sources of dietary protein and risk of hypertension in a general Dutch population. *Br J Nutr 2012*;**108**(10):1897-903.

4. Appleby PN, Thorogood M, Mann JI, et al. The Oxford Vegetarian Study: an overview. *Am J Clin Nutr* 1999;**70**(3 Suppl):525S-31S.

5. Assmann KE, Lassale C, Andreeva VA, et al. A Healthy Dietary Pattern at Midlife, Combined with a Regulated Energy Intake, Is Related to Increased Odds for Healthy Aging. *J Nutr* 2015;**145**(9):2139-45.

6. Bae JM, Ahn YO. A nested case-control study on the high-normal blood pressure as a risk factor of hypertension in Korean middle-aged men. *J Korean Med Sci* 2002;**17**(3):328-36.

7. Bazzano LA, He J, Ogden LG, et al. Dietary fiber intake and reduced risk of coronary heart disease in US men and women: the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. *Arch Intern Med* 2003;**163**(16):1897-904.

8. Bernstein AM, Rosner BA, Willett WC. Cereal fiber and coronary heart disease: a comparison of modeling approaches for repeated dietary measurements, intermediate outcomes, and long follow-up. *Eur J Epidemiol* 2011;**26**(11):877-86.

9. Bertoia ML, Triche EW, Michaud DS, et al. Mediterranean and Dietary Approaches to Stop Hypertension dietary patterns and risk of sudden cardiac death in postmenopausal women. *Am J Clin Nutr* 2014;**99**(2):344-51.

10. Bingham CM, Lahti-Koski M, Absetz P, et al. Food choices and health during military service: increases in sugar- and fibre-containing foods and changes in anthropometric and clinical risk factors. *Public Health Nutr* 2012;**15**(7):1248-55.

11. Buil-Cosiales P, Zazpe I, Toledo E, et al. Fiber intake and all-cause mortality in the Prevención con Dieta Mediterránea (PREDIMED) study. *Am J Clin Nutr* 2014;**100**(6):1498-507.

12. Burger KN, Beulens JW, Boer JM, et al. Dietary glycemic load and glycemic index and risk of coronary heart disease and stroke in Dutch men and women: the EPIC-MORGEN study. *PLoS One* 2011;**6**(10):e25955.

13. Burke V, Beilin LJ, Simmer K, et al. Predictors of body mass index and associations with cardiovascular risk factors in Australian children: a prospective cohort study. *Int J Obes* 2005;**29**(1):15-23.

14. Chuang S-C, Norat T, Murphy N, et al. Fiber intake and total and cause-specific mortality in the European Prospective Investigation into Cancer and Nutrition cohort. *Am J Clin Nutr* 2012;**96**(1):164-74.

15. Crowe FL, Key TJ, Appleby PN, et al. Dietary fibre intake and ischaemic heart disease mortality: the European Prospective Investigation into Cancer and Nutrition-Heart study. *Eur J Clin Nutr* 2012;**66**(8):950-6.

16. Djoussé L, Driver JA, Gaziano JM, et al. Relation between modifiable lifestyle factors and lifetime risk of heart failure. *JAMA* 2009;**302**(4):394-400.

17. Eshak ES, Hiroyasu I, Kazumasa Y, et al. Rice consumption is not associated with risk of cardiovascular disease morbidity or mortality in Japanese men and women: a large population-based, prospective cohort study. *Am J Clin Nutr* 2014;**100**(1):199-207.

18. Flint AJ, Hu FB, Glynn RJ, et al. Whole grains and incident hypertension in men. *Am J Clin Nutr* 2009;**90**(3):493-98.

19. Guo J, Li W, Wang Y, et al. Influence of dietary patterns on the risk of acute myocardial infarction in China population: the INTERHEART China study. *Chin Med J* 2013;**126**(3):464-70.

20. Hansen-Krone IJ, Enga KF, Njolstad I, et al. Heart healthy diet and risk of myocardial infarction and venous thromboembolism. The Tromso Study. *Thromb Haemost* 2012;**108**(3):554-60.

21. Iso H, Kubota Y. Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pacific journal of cancer prevention: *APJCP* 2007;**8 Suppl**:35-80.

22. Jacobs DR, Pereira MA, Meyer KA, et al. Fiber from whole grains, but not refined grains, is inversely associated with all-cause mortality in older women: the Iowa women's health study. *J Am Coll Nutr* 2000;**19**(3 Suppl):326S-30S.

23. Jansen MC, Bueno-de-Mesquita HB, Buzina R, et al. Dietary fiber and plant foods in relation to colorectal cancer mortality: the Seven Countries Study. *Int J Cancer* 1999;**81**(2):174-9.

24. Johnsen NF, Frederiksen K, Christensen J, et al. Whole-grain products and whole-grain types are associated with lower all-cause and cause-specific mortality in the Scandinavian HELGA cohort. *Br J Nutr* 2015;**114**(4):608-23.

25. Kanda A, Hoshiyama Y, Kawaguchi T. Association of lifestyle parameters with the prevention of hypertension in elderly Japanese men and women: a four-year follow-up of normotensive subjects. *Asia Pac J Public Health* 1999;**11**(2):77-81.

26. Kochar J, Gaziano JM, Djousse L. Breakfast cereals and risk of hypertension in the Physicians' Health Study I. *Clin Nutr* 2012;**31**(1):89-92.

27. Kokubo Y, Iso H, Saito I, et al. Dietary fiber intake and risk of cardiovascular disease in the Japanese population: the Japan Public Health Center-based study cohort. *Eur J Clin Nutr* 2011;**65**(11):1233-41.

28. Larsson SC, Wallin A, Wolk A. Dietary Approaches to Stop Hypertension Diet and Incidence of Stroke: Results From 2 Prospective Cohorts. *Stroke* 2016;**47**(4):986-90.

29. Li S, Flint A, Pai JK, et al. Dietary fiber intake and mortality among survivors of myocardial infarction: prospective cohort study. *BMJ* 2014;**348**:g2659.

30. Liang W, Lee AH, Binns CW. White rice-based food consumption and ischemic stroke risk: a case-control study in southern china. *J Stroke Cerebrovasc Dis* 2010;**19**(6):480-84.

31. Liu S, Manson JE, Stampfer MJ, et al. A prospective study of whole-grain intake and risk of type 2 diabetes mellitus in US women. *Am J Public Health* 2000;**90**(9):1409-15.

32. Mozaffarian D, Kumanyika SK, Lemaitre RN, et al. Cereal, fruit, and vegetable fiber intake and the risk of cardiovascular disease in elderly individuals. *JAMA* 2003;**289**(13):1659-66.

33. Negri E, La Vecchia C, Pelucchi C, et al. Fiber intake and risk of nonfatal acute myocardial infarction. *Eur J Clin Nutr* 2003;**57**(3):464-70.

34. Oh K, Hu FB, Cho E, et al. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. *Am J Epidemiol* 2005;**161**(2):161-9.

35. Pan A, Sun Q, Bernstein AM, et al. Red meat consumption and mortality: results from 2 prospective cohort studies. *Arch Intern Med* 2012;**172**(7):555-63.

36. Park Y, Subar AF, Hollenbeck A, et al. Dietary fiber intake and mortality in the NIH-AARP diet and health study. *Arch Intern Med* 2011;**171**(12):1061-8.

37. Pierucci P, Misciagna G, Ventura MT, et al. Diet and myocardial infarction: a nested case-control study in a cohort of elderly subjects in a Mediterranean area of southern Italy. *Nutr Metab Cardiovasc Dis* 2012;**22**(9):727-33.

38. Rebello SA, Hiromi K, Chen C, et al. Amount, type, and sources of carbohydrates in relation to ischemic heart disease mortality in a Chinese population: a prospective cohort study. *Am J Clin Nutr* 2014;**100**(1):53-64.

39. Rodriguez-Campello A, Jimenez-Conde J, Ois A, et al. Dietary habits in patients with ischemic stroke: a case-control study. *PLoS One* 2014;**9**(12):e114716.

40. Shi Z, Taylor AW, Hu G, et al. Rice intake, weight change and risk of the metabolic syndrome development among Chinese adults: the Jiangsu Nutrition Study (JIN). *Asia Pac J Clin Nutr* 2012;**21**(1):35-43.

41. Steffen LM, Kroenke CH, Yu X, et al. Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Clin Nutr* 2005;**82**(6):1169-77; quiz 363-4.

42. Streppel MT, Ocké MC, Boshuizen HC, et al. Dietary fiber intake in relation to coronary heart disease and all-cause mortality over 40 y: the Zutphen Study. *Am J Clin Nutr* 2008;**88**(4):1119-25.

43. Threapleton DE, Greenwood DC, Burley VJ, et al. Dietary fibre and cardiovascular disease mortality in the UK Women's Cohort Study. *Eur J Epidemiol* 2013;**28**(4):335-46.

44. Threapleton DE, Burley VJ, Greenwood DC, et al. Dietary fibre intake and risk of ischaemic and haemorrhagic stroke in the UK Women's Cohort Study. *Eur J Clin Nutr* 2015;**69**(4):467-74.

45. Wang L, Gaziano JM, Liu S, et al. Whole- and refined-grain intakes and the risk of hypertension in women. *Am J Clin Nutr* 2007;**86**(2):472-79.

46. Wolk A, Manson KE, Stampfer MJ, et al. Long-term intake of dietary fiber and decreased risk of coronary heart disease among women. *JAMA* 1999;**281**(21):1998-2004.

47. Yu D, Zhang X, Xiang Y-B, et al. Adherence to dietary guidelines and mortality: a report from prospective cohort studies of 134,000 Chinese adults in urban Shanghai. *Am J Clin Nutr* 2014.

48. Yu D, Zhang X, Shu XO, et al. Dietary glycemic index, glycemic load, and refined carbohydrates are associated with risk of stroke: a prospective cohort study in urban Chinese women. *Am J Clin Nutr* 2016;**104**(5):1345-51.

Supplementary File 4: Characteristics of Included Studies

Study ID	Study Deign	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to wholegrain foods)	Comparison (lowest tertile/quartile/quintile or 'no' to wholegrain foods)	Outcomes Measured	Funding Source	Disclosed author conflicts of interest
Djousse, L 2007	Cohort	19.6 years (average)	21,376	53.7 ±9.5 years	Wholegrain Breakfast Cereal ≥ 7 (1 serving=1 cup [250 mL]) servings/week	Wholegrain Breakfast Cereal 0 servings/week	Heart Failure	Non-Industry[1]	Yes[a]
Holmberg, S 2009	Cohort	12 years	1,752	50.2 years	Whole meal bread (wholegrain rye bread and crisp/hard bread)	White or Rye bread	Coronary Heart Disease Death or Event (death or hospitalization)	Industry[2]	No disclosure
Huang, T 2015	Cohort	14 years (average)	367,442	61.7 years	Wholegrain 1.20 oz eq/day	Wholegrain 0.13 oz eq/day	Cardiovascular Disease Death	Industry[3]	Yes[b]
Jacobs, DRJr 1998	Cohort	10 years	34,492	55–69 years	Wholegrain 22.5 servings/week (median)	Wholegrain 1.5 servings/week (median)	Ischemic Heart Disease Death	Non-Industry[4]	No disclosure
Jacobs, DRJr 1999	Cohort	10 years	38,740	61.5 years	Wholegrain 22.5 servings/week (median)	Wholegrain 1.5 servings/week (median)	Cardiovascular Disease Death (all cardiovascular disease)	Non-Industry[5]	No disclosure
Jacobs, DRJr 2001	Cohort	Baseline 1977-83, followed through to 1994	33,848	35-56 years	Wholegrain Bread Score (2.25-5.40) *	Wholegrain Bread Score (0.05-0.60) *	Cardiovascular Disease Death (total cardiovascular disease)	Non-Industry[6]	No disclosure
Jacobs, DRJr 2007	Cohort	17 years	27, 312	55–69 years	Wholegrain ≥ 19 servings/week	Wholegrain 0–3.5 servings/week	Cardiovascular Disease Death	Industry[7]	No[c]
Jensen, MK 2004	Cohort	14 years	42,850	40-75 years	Wholegrain 42.4 g/day (median)	Wholegrain 3.5 g/day (median)	Coronary Heart Disease Death or Event (non-fatal MI infarction & fatal CHD)	Industry[8]	No[d]
Li, Y 2015	2 Cohorts	30 years & 24 years	127,536	NHS 30-55 years	Wholegrain 4.6 % of total Energy Intake	Wholegrain 0.4 % of total Energy Intake	Coronary Heart Disease Death or	Non-Industry[9]	Yes[e]

				HPFS 40-75 years			Event (non-fatal MI & CHD deaths)		
Liu, S 1999	Cohort	10 years	75,521	38-63 years	Wholegrain 2.70 servings/day (median)	Wholegrain 0.13 servings/day (median)	Coronary Heart Disease Death or Event (non-fatal MI & fatal CHD)	Non-Industry[10]	No disclosure
Liu, S 2000	Cohort	12 years	75,521	38-63 years	Wholegrain 2.70 servings/day (median)	Wholegrain 0.13 servings/day (median)	Ischemic Stroke Death or Event	Non-Industry[11]	No disclosure
Liu, S 2003	Cohort	5.5 years (average)	86,190	40–84 years	Wholegrain Breakfast Cereal 1 servings/day	Rarely	Cardiovascular Disease Deaths	Non-Industry[12]	Yes[f]
Lockheart, MSK 2007	Case Control		211	Case 62·5 ± 7·7 Control 62·2 5 ± 7·7	Wholegrain Breakfast Cereal 36 g/day (median) & Wholegrain breads 240 g/day (median)	0 94 g/day	Myocardial Infarction (first MI)	Industry[13]	No Disclosure
Mizrahi, A 2009	Cohort	24 years	3,932	40–74 years	Wholegrain Men 280–1321 g/day (range) Women 195–963 g/day (range)	Wholegrain Men 0–139 g/day (range) Women 0–89 g/day (range)	Cerebrovascular Disease Death or Event (total strokes, including all acute strokes, subarachnoidal haemorrhages and other, undefined strokes; ischaemic stroke and intracerebral haemorrhage)	Non-Industry[14]	No[g]
Muraki I, 2015	3 Cohorts	26 years, 20 years & 24 years	207,556	Not available	Brown Rice ≥ 5 servings/week	Brown Rice < 1 servings/week	Cardiovascular Disease Death or Event (nonfatal MI, fatal CAD, and stroke (nonfatal or fatal))	Non-Industry[15]	No[h]

Nettleton, JA 2008	Cohort	13.3 years (average)	14,153	45-64 years	Wholegrain 1.3 ± 0.01 servings/day	Wholegrain 1.1 ± 0.04 servings/day	Heart Failure Death or Event	Non-Industry[16]	No[i]
Sahyoun, NR 2006	Cohort	Baseline 1981-84, followed through to 1995	535	60–98 years	Wholegrain >1.94 servings/day	Wholegrain ≤0.56 servings/day	Cardiovascular Disease Death	Non-Indusry[17]	No[j]
Sonestedt, E 2015	Cohort	14 year (average)	26,445	44–74 years	Wholegrain 2.5 portions/day	Wholegrain 0 portions/day	Cardiovascular Disease Death or Event (Incident CVD events, Stroke events, CHD (fatal or non-fatal myocardial infarction or death due to ischemic heart disease), Ischemic stroke).	Non-Industry[18]	No Disclosure
Steffen, L M 2003	Cohort	11 years	11,940	45–64 years	Wholegrain 3.0 servings/day	Wholegrain 0.1 servings/day	Coronary Artery Disease Death or Event (the first definite or probable MI, silent MI by electrocardiography, definite CAD death, or coronary revascularization) & Ischemic Stroke Death or Event (first definite or probable cardioembolic or thrombotic brain infarction)	Non-Industry[19]	Yes[k]
Tavani, A 2003	Case Control		881	25–79 years	Wholegrain Bread Consumers	Wholegrain Bread Non-Consumers	Myocardial Infarction (first acute)	Non-Industry[20]	No Disclosure

Tavani, A 2004	3 Case Controls		1,602	17–79 years	Wholegrain >2 portions/per week	Wholegrain <2 portions/per week	Myocardial Infarction (first acute)	Non-Industry[21]	No Disclosure
Wu, H 2015	2 Cohort	26 years & 24 years	118,085	NHS 30-55 years HPFS 32-87 years	Wholegrain NHS 33 g/day (median) HPFS 47.8 g/day (median)	Wholegrain NHS 4.2 g/day (median) HPFS 5.9 g/day (median)	Cardiovascular Disease Death	Non-Industry[22]	No[l]

*Wholegrain bread score: slices eaten per day (question 1) times the percentage wholegrain flour used in bread. Q5 = 9 slices of bread usually eaten per day x 60% wholegrain flour. Q1 = 1 slice of bread per day x 5% wholegrain flour

Description of Funding Source (Verbatim)

1. The PHS is supported by grants CA-34944 and CA-40360 from the National Cancer Institute and grants HL-26490 and HL-34595 from the National Heart Lung and Blood Institute (NHLBI), Bethesda, Maryland. Dr Djousse´ is supported by grant K01 HL70444 from the NHLBI
2. This study was supported by grants from AFA Insurance, LRF Research Foundation, The Swedish Council for Working Life and Social Research and Kronoberg County Council
3. This study is funded by an unrestricted research fund from NutraSource.Dr. Qi was supported by grants from the National Heart, Lung, and Blood Institute (HL071981), the National Institute of Diabetes and Digestive and Kidney Diseases (DK091718), the Boston Obesity Nutrition Research Center (DK46200), and United States–Israel Binational Science Foundation Grant 2011036. Dr. Qi was a recipient of the American Heart Association Scientist Development Award (0730094 N). Funding from NutraSource. There were no other relationships or activities that could appear to have influenced the submitted work
4. Supported by the National Institutes of Health (research grant CA-39742)
5. This research was supported by grant CA-39742 from the National Institutes of Health
6. Institute for Nutrition Research, University of Oslo and National Health Screening Service, Oslo, Norway

7. RB was supported by grants from the Norwegian Research Council, The Johan Throne Holst Nutrition Research Foundation, and The Norwegian Cancer Society. DRJ was supported by the Norwegian Research Council and by a grant (RO1 CA39742) from the National Cancer Institute.
8. Supported by research grants HL35464 and CA55075 from the National Institutes of Health and a scholarship from the Danish Research Foundation (to MKJ). The Kellogg Company provided unrestricted funding of the development of the whole-grain database
9. The cohorts were supported by grants UM1 CA186107, R01 HL034594, R01 HL35464, R01 HL60712, and UM1 CA167552 from the National Institutes of Health.
10. Supported by research grants HL24074, HL34594, and CA40356 and by nutrition training grant T32DK07703 from the National Institutes of Health
11. The work reported in this article was supported by grants CA40356, HL24074, HL34594, and DK02767 from the National Institutes of Health
12. Supported by grants HL-42441 and DK02767 from the National Institutes of Health
13. The present study was supported by NIH NRSA T32HL007779. CVD Epidemiology and Prevention, American Heart Association, Greater Midwest Affiliate. Throne Holst's Foundation for Nutrition Research. The Norwegian Association of Margarine Producers. DeNoFa Fabriker A/S and Tine Norwegian Dairies

14. The present study received funds from the Social Insurance Institution, Finland.

15. Supported by NIH grants CA50385, CA87969, CA176726, CA167552, HL60712, HL034594, HL088521, and HL35464. QS was supported by a career development grant R00HL098459 sponsored by the National Heart, Lung, and Blood Institute. FI was supported by Medical Research Council Epidemiology Unit Core Support (MC_UU_12015/5)

16. This research was supported by the National Institutes of Health grant HL73366, training grant T32 HL07779, and contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01- HC-55022 from the National Heart, Lung, and Blood Institute.

17. Supported by the US Department of Agriculture, under agreement no. 58-1950-4-401

18. This study was supported by the Swedish Medical Research Council, the Swedish Heart and Lung Foundation, the Skåne University Hospital, the Albert Påhlsson Research Foundation, and the Crafoord Foundation

19. Supported by the National Heart, Lung, and Blood Institute (contract nos. N01-HC-55015, N01-HC-55016, HC-55018, N01-HC-55019, HC-55020,N01-HC-55021, and N01-HC-55022)

20. This study was partly supported by "Ministero della Salute" (contract No 177, RF 2001).

21. Partly supported by ''Ministero della Salute'' (Contract n.177, RF 2001) and by the Commission of the EuropeanCommunities (Contract No. QLK1-CT-2000-00069)

22. This work was supported by research grants R01 DK58845 (Dr Hu), P01 CA87969, R01 HL034594, UM1 CA167552 (DrWillett), R01 HL35464 (Dr Rimm), HL60712 (DrHu), U54CA155626 (Dr Hu), and CA055075 from the National Institutes of Health and Career Development Award R00HL098459 from the National Heart, Lung, and Blood Institute (Dr Sun)

Description of Author Disclosure Statement (Verbatim)

a) Dr Gaziano has received investigator-initiated research grants from BASF, DSM Pharmaceuticals, Wyeth Pharmaceuticals, McNeil Consumer Products, and Pliva as well as honoraria from Bayer and Pfizer for speaking engagements. He is a consultant for Bayer, McNeil Consumer Products, Wyeth Pharmaceuticals, Merck, Nutraquest, and GlaxoSmithKline

b) A Lee NutraSource (AWL), Royal Oak, MI 48073, USA. S Cho NutraSource (SSC), Clarksville, MD 21029, USA

c) None of the authors had a conflict of interest

d) None of the authors had any conflicts of interest

e) Dr. Hu has received honoraria from the Hass Avocado Board for participating in an academic symposium; and grant support from Metagenics and the California Walnut Commission

f) In 2001 SL received honoraria from General Mills Co for a presentation unrelated to this article

g) None of the authors had any personal or financial conflict of interest.

h) All authors reported no conflicts of interest related to the study.

i) The authors have no conflicts of interest to report

j) None of the authors had a conflict of interest

k) None of the authors had any conflicts of interest except for DRJ, who holds a research award from General Mills, Inc, Minneapolis

l) None reported

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	7
2	Hypothesis statement	10
3	Description of study outcome(s)	10-11
4	Type of exposure or intervention used	9-10
5	Type of study designs used	9
6	Study population	9
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	8
8	Search strategy, including time period included in the synthesis and key words	& Supp File 1
9	Effort to include all available studies, including contact with authors	8
10	Databases and registries searched	8
11	Search software used, name and version, including special features used (eg, explosion)	8
12	Use of hand searching (eg, reference lists of obtained articles)	8
13	List of citations located and those excluded, including justification	16 & Supplementary File 3
14	Method of addressing articles published in languages other than English	10
15	Method of handling abstracts and unpublished studies	10
16	Description of any contact with authors	14
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	9-10
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	7 (according to published protocol Supp File 2)
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	13-14
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	14, (included in RoB assessment)
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	14 & 19
22	Assessment of heterogeneity	15-16
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	15-16
24	Provision of appropriate tables and graphics	17-18
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	21
26	Table giving descriptive information for each study included	17 & Supplementary

		File 4
27	Results of sensitivity testing (eg, subgroup analysis)	N/A
28	Indication of statistical uncertainty of findings	19-21

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	21
30	Justification for exclusion (eg, exclusion of non-English language citations)	N/A
31	Assessment of quality of included studies	21-23
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	21-22
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	21-22
34	Guidelines for future research	24-25
35	Disclosure of funding source	33