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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

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Manuscripts

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3 1 **The association of industry sponsorship with outcomes of studies examining the effect of**
4 **wholegrain foods on cardiovascular disease and mortality: Systematic review and Meta-**
5 **2 analysis**
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1
2
3 30 **Abstract**

4
5 31 **Objective:** To determine if the presence of food industry sponsorship or author conflicts of
6
7 32 interest with the food industry (COI) (industry ties) in primary nutrition studies examining the
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9 33 association of wholegrain foods with cardiovascular disease outcomes is associated with
10
11 34 statistical significance of results, effect size or conclusions that favour the study sponsor. To
12
13 35 determine whether studies with industry ties differ in their risk of bias compared with studies
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15 36 with no industry ties.

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19 37 **Design:** Systematic review and meta-analysis of observational studies.

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21
22 38 **Data sources:** We searched 8 databases from 1997-2017 and hand searched the reference lists
23
24 39 of included studies.

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26
27 40 **Eligibility Criteria for selecting studies:** Primary observational studies that quantitatively
28
29 41 examined the association of wholegrains or wholegrain foods with cardiovascular disease
30
31 42 outcomes in healthy adults or children.

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33
34 43 **Results:** 21 of the 22 studies had a serious or critical risk of bias. Studies with industry ties were
35
36 44 more likely to have favourable results than those with no industry ties, RR= 1.44 (95% CI 0.88-
37
38 45 2.35), although the difference was not statistically significant. The same association was found
39
40 46 for study conclusions. We did not find an important difference in effect size (magnitude of RRs)
41
42 47 between studies with industry ties, RR = 0.77 (95% CI 0.58-1.01) and studies with no industry
43
44 48 ties, RR = 0.85 (95% CI 0.73-1.00) (P=0.50) I² 0%. These results were comparable for studies that
45
46 49 measured the magnitude using hazard ratios; industry ties HR=0.82 (95% CI 0.76-0.88) vs. no
47
48 50 industry ties HR=0.86 (95% CI 0.81-0.91) (P=0.34) I² 0%.

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3 51 **Conclusions:** These findings suggest, but do not establish, that the presence of food industry
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6 52 sponsorship or authors with a COI with the food industry, may be associated with both results
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8 53 and conclusions that favour industry sponsors. Our findings support international reforms to
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10 54 improve the disclosure and management of the conflicts of interest in nutrition research.

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13 55 **Systematic review registration:** PROSPERO ID CRD42017055841
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3 67 **Strengths and limitations of this study**
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- 5 68 - This is the first systematic review and meta-analysis to evaluate the association of
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7
8 69 industry sponsorship and author conflicts of interest (COI) with the results, conclusions
9
10 70 and risk of bias of primary nutrition studies examining the effect of wholegrain foods on
11
12
13 71 cardiovascular disease outcomes.
14
15 72 - We conducted a comprehensive search and followed explicit and well-defined inclusion
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17
18 73 and exclusion criteria for the included studies.
19
20 74 - Although our sample was small, we searched several databases and reference lists of
21
22
23 75 included studies.
24
25 76 - We did not attempt to contact the authors of studies lacking a COI disclosure statement,
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27
28 77 thus, we may be underestimating the number of articles that had authors with conflicts
29
30 78 of interest.
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32 79 - Our assessment of risk of bias in the included studies was based on a tool that is under
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34
35 80 development, but changes to the tool are unlikely to affect the risk of bias ratings.
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37 81

82 **Background**

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

92
93 Dietary guidelines use a variety of methods to assess bias in primary research studies, but these
94 do not assess one potential source of bias – financial conflicts of interest.¹⁰ Across a variety of
95 research areas, industry sponsorship and author conflicts of interest (COI) have been found to
96 be associated with outcomes that favour the study sponsor.¹¹⁻¹³ Even when controlling for
97 methodological biases, industry sponsored studies are more likely to have results that favour
98 the sponsor's product than those studies with no or other sources of sponsorship.¹¹ Industry
99 sponsors may bias research via the questions they ask (research agenda), how they design and
100 conduct a study, the selection of results they report and through 'spin' on conclusions.¹⁴⁻¹⁷

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3 102 A systematic review of methodological studies that compared food industry sponsored studies
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5 103 with those that had no or other sources of sponsorship found that food industry sponsored
6
7
8 104 studies were more likely to have favourable conclusions than non-industry sponsored studies.¹⁸
9

10 105 However, there were insufficient data to quantitatively assesses the association of sponsorship
11
12 106 with study results. Only one methodological study examined the association of author COI and
13
14
15 107 conclusions, and found a statistically significant association between them.¹⁹
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20 109 Funding sources and author COI may be a risk of bias in studies of wholegrain consumption as
21
22 110 these studies could test formulated or processed wholegrain products, such as breakfast
23
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25 111 cereals. Industry sponsors may gain financially from finding that these types of products have
26
27 112 health benefits that can be used to market their products. There has been no assessment of the
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29
30 113 association of food industry sponsorship and author COI with the food industry and the
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32 114 statistical significance of results, effect sizes, conclusions and risk of bias of observational
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35 115 studies examining the cardiovascular health benefits of wholegrain consumption. The primary
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37 116 objective of this review is to determine whether:

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40 117 • Primary studies examining the association of wholegrain foods with cardiovascular
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42 118 disease with food industry sponsorship and / or authors with COI with the food industry
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44
45 119 are more likely to have results and/ or conclusions that are favourable to industry than
46
47 120 those with no industry ties.
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50 121 • This review also examines whether any differences between industry and non-industry
51
52 122 sponsored studies could be related to their methods or interpretation of results.
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3 123 The secondary objectives of this review are to determine whether:
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6 124 • Studies with food industry sponsorship and / or authors with COI with the food industry
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9 125 differ in their risk of bias compared with studies with no industry ties.
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12 126 • Studies with food industry sponsorship and / or authors with COI with the food industry
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14 127 have a higher level of discordance between study results and conclusions, with the
15
16 128 conclusions more likely to be favourable compared to the results.
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20 129 **METHODS**

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22
23 130 We conducted a systematic review of observational studies examining the association of
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25 131 wholegrain consumption with cardiovascular disease.
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28 132 29 30 133 **Literature search strategy**

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32 134 The search was based on the Process Manual used in the development of the 2013 Australian
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34 135 Dietary Guidelines²⁰ and the advice of an information specialist. We searched the following
35
36 136 databases from January 1997-October 2017: MEDLINE; CINAHL; PubMed; PreMEDLINE;
37
38 137 Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy we used for Ovid
39
40 138 MEDLINE is shown in Supplementary file 1. We adapted this strategy for the other databases.
41
42 139 We also hand searched the references lists of identified studies and reviews. The search also
43
44 140 included terms for randomized control trials to identify relevant trials for a future systematic
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46 141 review.
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52 142 53 54 143 **Eligibility Criteria**

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3 144 This review included primary nutrition studies of cohort or case control designs that
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6 145 quantitatively examined the benefits or harms of wholegrain consumption related to
7
8 146 cardiovascular disease outcomes in healthy children and/or adults.
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13 148 We included studies that defined wholegrains in any way, as defined by the author. If total
14
15 149 wholegrain consumption had been assessed in the study, we included this as our only exposure.
16
17
18 150 If total wholegrain consumption as an exposure was not available, we included any type of
19
20 151 wholegrain consumption (i.e. wholegrain cereal, breakfast cereal, bread, rice etc) as our
21
22 152 exposure. We included studies that compared wholegrain food to other foods or compared
23
24
25 153 various levels of wholegrain consumption. We included the result representing the effect of the
26
27 154 highest level of wholegrain consumption compared to the lowest level of wholegrain
28
29
30 155 consumption (e.g., 'yes' to wholegrain consumption vs. 'no' to wholegrain consumption, tertile
31
32 156 3 vs. tertile 1, quartile 4 vs. quartile 1, quintile 5 vs. quintile 1). If our pre-specified rules for
33
34
35 157 selection did not uniquely identify one exposure for inclusion in the meta-analysis, we randomly
36
37 158 selected one result.
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42 160 We included studies that had a clinical outcome measure related to cardiovascular disease,
43
44 161 defined as mortality related to specific cardiovascular events, and/or cardiovascular events,
45
46 162 (e.g., first myocardial infarction, total stroke etc.). If 'cardiovascular disease mortality/death/s'
47
48
49 163 (verbatim) had been assessed, we included this as our only outcome. If not, we included any
50
51 164 type of cardiovascular disease mortality (e.g., coronary heart disease mortality, stroke mortality
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53
54 165 etc.) as our outcome. If there were no mortality outcomes assessed in the study, we included

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3 166 any cardiovascular disease event as our outcome. If a study assessed subgroups of
4
5 167 cardiovascular disease deaths and events (e.g., intracerebral haemorrhages, ischaemic stroke)
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8 168 and also assessed them collectively (e.g., cerebrovascular diseases), we took the result that had
9
10 169 assessed them collectively. If our pre-specified rules for selection did not uniquely identify one
11
12
13 170 outcome for inclusion in the meta-analysis, we randomly selected one result.
14

15 171
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18 172 We excluded conferences presentations, opinion pieces and letters to the editor. We had no
19
20 173 language restrictions.
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23 174

25 175 **Types of Outcome Measures**

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27 176

30 177 **Primary Outcomes**

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32 178 We hypothesized that studies with food industry sponsorship and/or authors with a COI with
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34
35 179 the food industry would be more likely to have favourable findings than those with no industry
36
37 180 ties. We assessed three primary outcomes:

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40 181 1. Statistical significance of results favourable to the sponsor

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42 182 Favourable results were defined as results that were favourable to the sponsor's product(s),
43
44
45 183 either indicating greater health benefits or less harm than the comparator. Specifically, for
46
47 184 studies of health benefits of wholegrains, favourable results were defined as those that were
48
49 185 statistically significant at the 0.05 level. For studies of harms of wholegrains, favourable results
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52 186 were defined as those where harms were not statistically significant at the 0.05 level or there
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3 187 were a statistically significant higher number of harms in the comparator group. Otherwise,
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5 188 results were classified as unfavourable.
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10 190 2. Effect size of results
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15 192 Effect size was defined as the risk ratio of the association between whole grains and a clinical
16
17 193 outcome of cardiovascular disease. We compared the magnitude of the pooled effect estimates
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19 194 in studies with food industry sponsorship and/or authors with a COI compared with studies with
20
21 195 no industry ties.
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26
27 197 3. Conclusions
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32 199 Conclusions that suggested that the wholegrain intervention being studied was beneficial to
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34 200 health and / or safe were considered favourable to the study sponsor. Otherwise, the
35
36 201 conclusions were considered unfavourable.
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3 204 **Secondary Outcomes**
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6 205 We assessed two secondary outcomes:
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9 206 1. The risk of bias of the included studies
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14 208 We hypothesized that studies with industry sponsorship and/or authors with a COI with the
15

16 209 food industry would have the same overall risk of bias as those with no industry ties.
17
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21
22 211 2. Concordance between study results and conclusions
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27 213 We hypothesized that studies with industry sponsorship and/or authors with a COI would be
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29 214 more likely to have discordant results and conclusions, with results not favouring the sponsor
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31 215 and conclusions favouring the sponsor, than those with no industry ties.
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36 217 **Selection of studies**
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39 218 Three investigators (NC, SMc & JT, working in pairs) independently screened the titles and
40

41 219 abstracts of all retrieved records for obvious exclusions. Full text of potentially eligible studies
42

43
44 220 was then retrieved, and three investigators (NC, SMc & JT) assessed these against our inclusion
45

46 221 criteria. Agreement was reached by consensus.
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3 224 **Data Collection and analysis**
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5 225 Three assessors (NC, SMc & JT) independently extracted the following data from each included
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7 226 study. Discrepancies in data extraction were resolved by consensus. If agreement could not be
8
9
10 227 reached, a fourth assessor (LB) adjudicated the outcome.

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12
13 228 From each study we extracted:

- 14
15 229 • Year of publication
16
17 230 • Study design (cohort or case control)
18
19
20 231 • Sample size of study
21
22
23 232 • Age of participants
24
25 233 • Intervention or observation period
26
27
28 234 • How the study defined wholegrain (verbatim)
29
30 235 • Level of wholegrain content in wholegrain foods
31
32
33 236 • Disclosure of funding source (no disclosure, yes and there is a sponsor, the authors state
34
35 237 they received no funding for their work)
36
37
38 238 • Name of the funders of the study (verbatim)
39
40 239 • Role of the funders (role of the sponsor not mentioned, sponsor not involved in study
41
42 240 design and analyses, sponsor involved, N/A)
43
44
45 241 • Disclosure of author COI (no disclosure, yes, the authors state they had no conflicts of
46
47 242 interest to declare)
48
49
50 243 • Authors COI statement (verbatim)
51
52
53 244 • Outcomes assessed in the study (any cardiovascular disease death and/or event)
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3 245 • The numerical results of the study (eg., OR, HR)
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8 247 We stored all extracted data from the included studies in REDcap, a secure web-based
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10 248 application for the collection and management of data.²¹
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15 250 ***Classification of industry sponsorship and author conflicts of interest***
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18 251 Sponsorship was categorized as 1) industry or 2) non-industry. We defined industry sponsored
19
20 252 studies as those declaring any sponsorship from the food industry, including if the study
21
22 253 received 'mixed funding' from the food industry, non-profit organizations or other industries
23
24 254 (i.e. pharmaceutical). Any study with an author with any disclosed financial tie to the food
25
26 255 industry was classified as having a conflict of interest (COI). Author COI were categorized as 1)
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28 256 presence of a COI with the food industry or 2) no COI. Any studies that did not contain an
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30 257 author COI disclosure statement were classified as no COI. We contacted the authors of one
31
32 258 paper²² for clarification on their disclosure of funding source.
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40 260 **Assessment of risk of bias in included studies**
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42 261 We used an adapted version of the Cochrane Collaboration's 'Risk of Bias in Non-Randomized
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44 262 Studies-of Interventions' (ROBINS-I)²³ tool to measure the risk of bias of included observational
45
46 263 studies. The tool assesses bias across seven domains. Each domain is assessed at a low,
47
48 264 moderate, serious or critical risk of bias, or no information. The domain rating with the highest
49
50 265 risk of bias determines the overall risk of bias rating for the study. For example, if a study is
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52 266 rated as being at a serious risk of bias in one domain, the overall risk of bias rating is 'serious.'
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267 **Analysis**

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

271
272 We calculated risk ratios (and 95% confidence intervals) to quantify the association between
273 food industry sponsorship and / or authors with COI with the food industry and favourable
274 results, favourable conclusions and the overall study risk of bias rating. For the risk of bias rating
275 analysis we dichotomised the overall risk of bias ratings as low (low or moderate) or high
276 (serious or critical). We had planned to calculate a RR for level of concordance, however since in
277 all studies there was concordance between the results and conclusions, we did not undertake
278 this analysis.

279
280 We used meta-analysis to examine whether food industry sponsorship and / or authors with COI
281 with the food industry modified the magnitude of association between whole grains and
282 cardiovascular disease outcomes. Specifically, we undertook a subgroup analysis within a
283 random effects meta-analysis model that compared the pooled associations across subgroups
284 defined by industry sponsorship. The associations were pooled using inverse variance weighting
285 and DerSimonian and Laird's method of moments estimator was used to estimate between
286 study heterogeneity. Separate meta-analyses were fitted for studies that had measured the
287 association using hazard ratios and those that had used either risk ratios or odds ratios. Given
288 cardiovascular events were rare, the odds ratios approximated risk ratios. We quantified

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3 289 heterogeneity for subgroup differences using the I^2 statistic²⁴ and tested for heterogeneity
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5 290 using the Chi2 test. Review Manager 5.3 was used to analyse the data.²⁵
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11 292 **Protocol Registration**

14 293 The protocol is published in PROSPERO²⁶ ID CRD42017055841. (Supplementary file 2)

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20 295 **Patient Involvement**

23 296 No patients were involved in the completion of this review.

25 297

28 298 **RESULTS**

30 299 **Search results**

32 300 We identified 6818 references for screening, from which, 22 studies met the inclusion criteria
33
34 301 (Figure 1). See Supplementary file 3 for 'List of excluded Studies' and reasons for exclusion.
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36

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42 304 **Characteristics of included Studies**

44 305 All studies were published between 1998 and 2015. Three of the studies were case control and
45
46 306 19 were cohort design. All studies contained a sponsorship disclosure. Five studies disclosed
47
48
49 307 food industry sponsorship, but only one of these had a statement describing the role of the
50
51 308 sponsor. Five studies contained an author with a COI with the food industry. Ten studies did not
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309 contain a disclosure statement. Nine studies contained either food industry sponsorship or had
 310 an author with a COI.

311
 312 A greater proportion of industry sponsored studies (67%) than non-industry sponsored studies
 313 (31%) used a definition of wholegrain as greater than 25%, and most of these examined
 314 breakfast cereals (Table 1). Industry sponsored studies were also more likely than non-industry
 315 studies to focus on a specific food (44%) than total wholegrain intake (23%) (Table 1). Non-
 316 industry sponsored studies (85%) had a greater proportion of studies with a serious or critical
 317 risk of bias in classification of exposures than industry sponsored studies (56%). Other
 318 characteristics were similarly distributed across industry vs. non-industry sponsored studies.
 319 Details of each individual study are in Supplementary file 4.

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

Characteristic	Category	Funding Source, n (% ¹)		
		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

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329 **Risk of bias in included studies**

330 One study²⁷ was assessed as having an overall moderate risk of bias, four as having a serious
331 risk of bias and 17 as having critical risk of bias (Figure 2). The majority of studies had a critical
332 risk of bias in the confounding domain. All but one study was assessed at a low risk of bias on
333 the outcome measurement domain. For all domains, except classification of exposure, the risk
334 of bias ratings were similarly distributed across industry vs. non-industry sponsored studies
335 (Table 1).

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

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

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

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

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3 351 $I^2 = 0\%$) (Figure 3). For studies that had measured the association using hazard ratios there was
4
5
6 352 also no important difference found in the magnitude of HRs between studies with industry
7
8 353 sponsorship and/or authors with a COI with the food industry HR=0.82 (95% CI 0.76-0.88) and
9
10 354 studies with no industry sponsorship or author COI HR=0.86 (95% CI 0.81-0.91) (subgroup test
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12
13 355 $P=0.34$, $I^2 = 0\%$) (Figure 4).

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18 357 Our analysis comparing studies with industry sponsorship RR 0.63 (95% CI 0.28-1.39) and those
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20 358 with no industry sponsorship RR 0.85 (95% CI 0.74-0.97) (subgroup test $P=0.46$, $I^2 = 0\%$), showed
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22
23 359 no important difference in the magnitude of RRs. This was again comparable between industry
24
25 360 sponsored HR 0.82 (95% CI 0.77-0.87) and non-industry sponsored studies HR 0.85 (95% CI 0.81-
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27 361 0.90) (subgroup test $P=0.29$), $I^2=12.2\%$) that measured the association using hazard ratios.

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34 364 **Favourable conclusions: Industry sponsored versus non-industry sponsored**

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37 365 As there was concordance between the results and conclusions of every included study, the
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40 366 same associations were found for conclusions as for the statistical significance of results. Studies
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42 367 with industry sponsorship and/or authors with a COI with the food industry were more likely to
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45 368 have favourable conclusions compared to those with no industry sponsorship or author COI RR=
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47 369 1.44 (95% CI 0.88-2.35), however the confidence interval was wide. When studies were
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50 370 compared only by industry sponsorship, the risk was again smaller RR = 1.13 (95% CI 0.66-1.94).

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53 54 372 **Risk of Bias Assessment**

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3 373 Studies with industry sponsorship and/or authors with a COI with the food industry were less
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5 374 likely (0/9) to have an overall low risk of bias rating compared to those studies with no industry
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8 375 sponsorship or author COI (1/13), RR = 0.47 (95% CI 0.02 -10.32), however there was large
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10 376 uncertainty in the association.

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15 378 **DISCUSSION**

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17 379 Although observational studies examining the effect of wholegrain consumption on
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20 380 cardiovascular disease outcomes that were sponsored by the food industry and / or had authors
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23 381 with a COI with the food industry more often had favourable results than research not tied to
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25 382 the food industry, the difference was not statistically significant. We found no evidence of a
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28 383 difference in the magnitude of effect between industry sponsored and non-industry sponsored
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30 384 studies. It is difficult to detect differences in effect size by sponsorship as many study design
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33 385 features, such as dose and duration of exposures, and specific cardiovascular disease outcomes,
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35 386 vary across studies and may influence the effect size. In previous assessments of drug studies
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38 387 that have demonstrated that industry funded studies are more likely to have results that favour
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40 388 the study sponsors, there was no statistically significant difference found in effect sizes between
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42 389 industry and non-industry sponsored studies.¹¹

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47 391 Although all the included studies had a sponsorship disclosure, almost half were missing
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49 392 disclosures about author COI. Nondisclosed COIs in nutrition research are a concern.⁴⁸ Larger
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52 393 samples of industry funded studies and studies with disclosed author COI could make it possible
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54 394 to establish the association of sponsorship with research outcomes.

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6 396 Studies that were sponsored by the food industry and / or had authors with a COI with the food
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8 397 industry more often had favourable conclusions than studies with no industry ties, although
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10 398 there was uncertainty in this relationship. There was absence of spin in the included studies as
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13 399 all the results agreed with the conclusions.
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17 401 The overall risk of bias in every study, other than one non-industry sponsored study²⁷, was
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19 402 classified as high (either serious or critical). The overall risk of bias rating was based on the
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21 403 domain with the highest/worst risk of bias rating within each study, and most of the studies had
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23 404 a risk of bias related to confounding. Across each domain, we found little difference in the risk
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25 405 of bias between industry sponsored and non-industry sponsored studies.
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31 32 407 **Strengths and limitations of this review**

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35 408 Our review was registered in PROSPERO²⁶. We conducted a comprehensive search and followed
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37 409 explicit and well-defined inclusion and exclusion criteria for the included studies. Although our
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39 410 sample was small, we searched several databases and reference lists of included studies.
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42 411 Authors of the studies for which we required clarification on funding source were also
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44 412 contacted, but we did not attempt to contact the authors of studies lacking a COI disclosure
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46 413 statement. Thus, we may be underestimating the number of articles that had authors with
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48 414 conflicts of interest. Our assessment of risk of bias in the included studies was based on a tool
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50 415 that is under development, but changes to the tool are unlikely to affect the risk of bias
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53 416 ratings.²³
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6 418 **Agreements and disagreements with other studies or reviews**
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8 419 The relationship that we identified between food industry sponsorship and authors with a COI
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10 420 and favourable study outcomes towards the study sponsor has been previously demonstrated in
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12 421 an assessment of a broad range of nutrition research.¹⁸ Only one study has reported an
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14 422 association of food industry funding with effect sizes.⁴⁹ Of studies examining the association
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16 423 between soft drink consumption and adverse health outcomes, food industry sponsored studies
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18 424 reported significantly smaller effects than non-food industry sponsored studies. Compared to
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20 425 our study, this study examined studies with a homogeneous population of industry funders,
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22 426 sugar sweetened beverage companies, which may have a more consistent influence on study
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24 427 outcomes than the diverse pool of food industry sponsors in our study.

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31 428 There was also no difference in the level of risk of bias between industry sponsored and non-
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33 429 industry sponsored studies. This is consistent with previous assessments of pharmaceutical,
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35 430 tobacco and nutrition research that has shown industry-sponsored studies are of equal or better
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37 431 quality than non-industry-sponsored studies.^{11 18 50-52}

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43 433 **Implications for clinicians, policy makers and future research**
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45 434 The recent critiques to reform the methods used in the development of dietary guidelines have
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47 435 proposed steps to improve the transparency of how evidence is evaluated and synthesized into
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49 436 recommendations.¹² However, until the influence of industry sponsorship in primary nutrition
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51 437 studies has been further explored and measured with larger samples of industry sponsored
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3 438 studies, this bias may still be unaccounted for in dietary guidelines. Although there was
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6 439 uncertainty around the differences in the results and conclusions that we observed between
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8 440 industry and non-industry studies, the differences are unlikely to be explained by
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10 441 methodological risks of bias in these studies.
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15 443 There are ways that study sponsorship can influence outcomes other than through the design of
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17 444 research. Bias may also be introduced in the way industry sponsored studies code events and
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19 445 analyse data,^{53 54} through the selective reporting of study outcomes and through publication
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21 446 bias.⁵⁵ It has been demonstrated in other areas of medical research that there is a greater
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23 447 propensity to publish studies with statistically significant results.⁵⁶ Therefore, selective
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25 448 publication of study results or studies in their entirety, may limit the availability of all relevant
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27 449 nutrition data and can skew results that are used in dietary guideline development.⁵⁷
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29 450 Publication bias could be minimized with the introduction of study registries for nutrition
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31 451 research, as has been established in pharmaceutical research.⁵⁸ The association of food
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33 452 industry sponsorship with the reporting of nutrition research still needs to be assessed.
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42 454 Almost half of the studies included in this review had authors that did not disclose if they had a
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44 455 COI with the food industry or not. Compliance with COI disclosure policies is now well
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46 456 documented across many domains of research.⁵⁹⁻⁶⁴ Recent examinations of the levels of
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48 457 disclosure in research assessing the effects of artificially sweetened beverages on weight
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50 458 outcomes found similarly poor disclosure rates.⁵⁰ Several solutions have been proposed to
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52 459 increase transparency and disclosure rates, including the use of different databases and
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3 460 additional resources to identify conflicted authors, and the introduction of mandatory
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5 461 disclosure requirements in all journals, with the use of penalties for those who do not adhere to
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8 462 the stated policies.^{18 50}
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13 464 This research further strengthens calls for stricter policies relating to the disclosure and
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15 465 management of conflicts of interest in nutrition research. These findings suggest, but do not
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18 466 establish, that the presence of food industry sponsorship or authors with a conflict of interest
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20 467 with the food industry, may be associated with both the results and conclusions that favour
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23 468 industry sponsors.
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3 470 **Figure 1. Study Flow Diagram**
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6 471 **Figure 2. Risk of Bias of Included Studies**
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8 472 **Figure 3: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored &**
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10 473 **no author COI studies, Risk Ratio**
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13 474 **Figure 4: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored &**
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15 475 **no author COI studies, Hazard Ratio**
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3 630 **Contributors:** NC, AF, SMc, MA-F and LB designed and wrote the review protocol. NC wrote the
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5
6 631 search strategy and undertook the literature search. NC, SMc and JT conducted the title and
7
8 632 abstract screening and full article screening for final study inclusion. NC, SMc and JT conducted
9
10 633 data collection and cleaning, LB supervised. NC and JMc undertook all data analysis. LB advised
11
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30
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34
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36
37 644 might have an interest in the submitted work in the previous three years. The authors report no
38
39 645 other relationships or activities that could appear to have influenced the submitted work.
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44 646 **Ethical Approval:** Not required

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48 647 **Transparency declaration:** The authors affirm that this manuscript is a honest, accurate, and
49
50 648 transparent account of the study being reported, that no important aspects of the study have
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52 649 been omitted and that any discrepancies from the study as planned have been explained.
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8 652 forms, formats and media (whether known now or created in the future), to i) publish,
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10 653 reproduce, distribute, display and store the Contribution, ii) translate the Contribution into
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12 654 other languages, create adaptations, reprints, include within collections and create summaries,
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14 655 extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on
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16 656 the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of
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18 657 electronic links from the Contribution to third party material where-ever it may be located; and,
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22 658 vi) licence any third party to do any or all of the above.

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26 659 **Data Sharing:** Available from The University of Sydney data repository. DOI to be determined.
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Figure 1. Study Flow Diagram

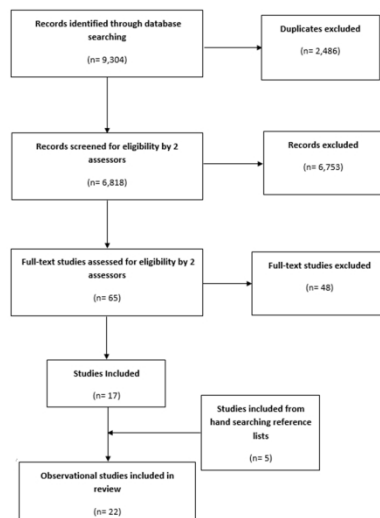


Figure 1. Study Flow Diagram

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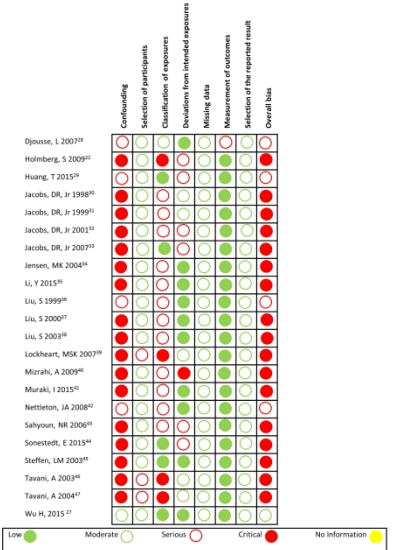


Figure 2. Risk of Bias Table
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Figure 3: Effect Size - Industry Sponsored &/OR Author COI versus Non-Industry Sponsored & No Author COI, RR

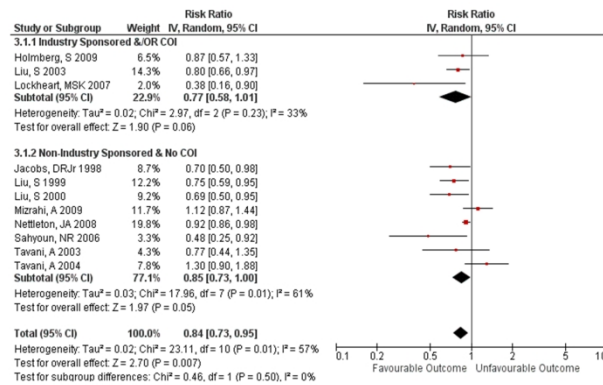


Figure 3. Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Risk Ratio

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

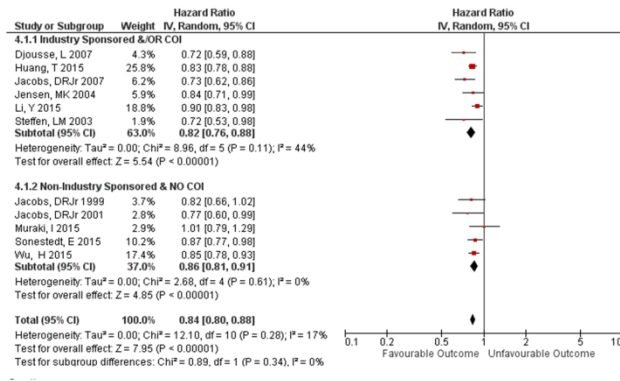


Figure 4: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Hazard Ratio

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3 **1 Supplementary File 1: Search Strategy**
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6 2 OVID Medline: wholegrain & CVD
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8
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11 4 1. Randomized controlled trial*.sh.
12

13
14 5 2. experimental design.tw.
15

16
17 6 3. intervention*.tw.
18

19
20 7 4. (RCT* or rct*).tw.
21

22
23 8 5. random* control* trial*.tw.
24

25
26 9 6. clinical trial*.sh.
27

28
29 10 7. field trial*.tw.
30

31
32 11 8. community trial*.tw.
33

34
35 12 9. controlled clinical trial*.tw.
36

37
38 13 10. pragmatic trial*.tw.
39

40
41 14 11. observational study.sh.
42

43
44 15 12. cohort study.tw.
45

46
47 16 13. prospective cohort*.tw.
48

49
50 17 14. retrospective cohort*.tw.
51

52
53 18 15. case control*.sh.
54

55
56 19 16. ecological study.tw.
57

58
59 20 17. time series analys?s.tw.
60

21 18. before-after study.tw.

22 19. pre-post study.tw.

- 1
2
3 23 20. follow up stud*.sh.
4
5
6 24 21. comparative stud*.sh.
7
8 25 22. evaluation stud*.sh.
9
10
11 26 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
12 27 or 21 or 22
13
14
15 28 24. Edible Grain/ae, me [Adverse Effects, Metabolism]
16
17 29 25. grain*.tw.
18
19
20 30 26. Dietary Carbohydrates/ or Edible Grain/ or Bread/ or Dietary Fiber/
21
22 31 27. whole grain*.tw.
23
24
25 32 28. partially processed grains.tw.
26
27 33 29. whole wheat.tw.
28
29
30 34 30. wholemeal.tw.
31
32 35 31. rice*.tw.
33
34
35 36 32. oat*.tw.
36
37 37 33. barley*.tw.
38
39
40 38 34. wheat*.tw.
41
42 39 35. Amaranthus/ae, me [Adverse Effects, Metabolism]
43
44
45 40 36. amaranth.tw.
46
47 41 37. Millets/me [Metabolism]
48
49
50 42 38. millet*.tw.
51
52 43 39. Sorghum/me [Metabolism]
53
54
55 44 40. sorghum*.tw.
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2
3 45 41. maize*.tw.
4
5
6 46 42. spelt*.tw.
7
8 47 43. buckwheat*.tw.
9
10
11 48 44. Triticale/me [Metabolism]
12
13 49 45. triticale*.tw.
14
15
16 50 46. fonio*.tw.
17
18 51 47. emmer.tw.
19
20
21 52 48. einkorn*.tw.
22
23 53 49. kamut*.tw.
24
25
26 54 50. canary seed*.tw.
27
28 55 51. Bread/ae, an, me [Adverse Effects, Analysis, Metabolism]
29
30
31 56 52. bread*.tw.
32
33 57 53. breakfast cereal*.tw.
34
35
36 58 54. pasta*.tw.
37
38 59 55. noodle*.tw.
39
40
41 60 56. Flour/ae, an, st [Adverse Effects, Analysis, Standards]
42
43 61 57. flour*.tw.
44
45
46 62 58. polenta*.tw.
47
48 63 59. semolina*.tw.
49
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51 64 60. bran.tw.
52
53 65 61. corn.tw.
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56 66 62. wheat germ*.tw.
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2
3 67 63. corn cake*.tw.
4
5 68 64. scone*.tw.
6
7
8 69 65. couscous.tw.
9
10
11 70 66. crumpet*.tw.
12
13 71 67. dietary fiber.tw.
14
15 72 68. dietary carbohydrate*.tw.
16
17
18 73 69. glycemic index.tw.
19
20
21 74 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
22 75 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
23 76 or 60 or 61 or 62 or 64 or 65 or 66 or 67 or 68 or 69
24
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26 77 71. Coronary Disease/ or Cardiovascular Diseases/ or Hypertension/ or Atherosclerosis/
27
28
29 78 72. cardiovascular disease*.tw.
30
31 79 73. coronary*.tw.
32
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34 80 74. heart*.tw.
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36 81 75. cardia*.tw.
37
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39 82 76. myocard*.tw.
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41 83 77. isch?em*.tw.
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44 84 78. angina*.tw.
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46 85 79. ventric*.tw.
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49 86 80. tachycardi*.tw.
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51 87 81. pericard*.tw.
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54 88 82. endocardi*.tw.
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2
3 89 83. atrial fibrillat*.tw.
4
5 90 84. arrhythmi*.tw.
6
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8 91 85. athero*.tw.
9
10 92 86. arterio*.tw.
11
12
13 93 87. HDL.tw.
14
15 94 88. LDL.tw.
16
17
18 95 89. VLDL.tw.
19
20 96 90. lipid*.tw.
21
22
23 97 91. lipoprotein*.tw.
24
25
26 98 92. triacylglycerol*.tw.
27
28 99 93. hyperlipid*.tw.
29
30 100 94. hypercholesterol*.tw.
31
32
33 101 95. hypercholester?emia*.tw.
34
35
36 102 96. hypertriglycerid?emia*.tw.
37
38 103 97. Cholesterol/
39
40
41 104 98. Stroke/
42
43 105 99. Cerebrovascular Disorders/
44
45
46 106 100. vascular accident*.tw.
47
48
49 107 101. TIA.tw.
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51 108 102. Thrombosis/
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53 109 103. thrombosis.tw.
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56 110 104. Embolism/ or Pulmonary Embolism/
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3 111 105. apoplexy.tw.
4
5
6 112 106. (brain adj2 accident*).tw.
7
8 113 107. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
9
10
11 114 108. Blood Pressure/ or Hypertension/
12
13 115 109. systolic blood pressure.tw.
14
15
16 116 110. diastolic blood pressure.tw.
17
18 117 111. Peripheral Vascular Diseases/ or Peripheral Arterial Disease/
19
20
21 118 112. (coronar\$ adj5 (bypas\$ or graft\$ or disease\$ or event\$)).tw.
22
23 119 113. (cerebrovasc\$ or cardiovasc\$ or mortal\$ or angina\$ or stroke or strokes).tw.
24
25
26 120 114. (myocardi\$ adj5 (infarct\$ or revascular\$ or ischaemi\$ or ischemi\$)).tw.
27
28 121 115. (morbid\$ adj5 (heart\$ or coronar\$ or ischaem\$ or ischem\$ or myocard\$)).tw.
29
30
31 122 116. (vascular\$ adj5 (peripheral\$ or disease\$ or complication\$)).tw.
32
33 123 117. (heart\$ adj5 (disease\$ or attack\$ or bypass\$)).tw.
34
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36 124 118. Mortality/
37
38 125 119. mortality.tw.
39
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41 126 120. Diabetes Mellitus, Type 2/
42
43 127 121. Hyperglycemia/
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46 128 122. hyperglycemi*.tw.
47
48 129 123. (glucose adj2 intoleran*).tw.
49
50
51 130 124. Insulin Resistance/
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53 131 125. (metabolic adj3 syndrome adj3 x).tw.
54
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56 132 126. metabolic cardiovascular syndrome.tw.
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3 133 127. dysmetabolic syndrome x.tw.
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5
6 134 128. HbA1c.tw.
7

8 135 129. (glyc?emic adj3 control).tw.
9

10 136 130. 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

11 137 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

12 138 105 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

13 139 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129
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18 140 131. 23 and 70 and 130
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20 141 132. limit 131 to (humans and yr="1997 -Current")
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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.
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- 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

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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

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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 62.25 ± 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

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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-Industry ¹⁷	No ⁱ
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 ¹

*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

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For peer review only

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- 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
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- 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

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3 l) None reported
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For peer review only

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

review only

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:	<i>BMJ Open</i>
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Primary Subject Heading:	Research methods
Secondary Subject Heading:	Nutrition and metabolism, Public health
Keywords:	NUTRITION & DIETETICS, STATISTICS & RESEARCH METHODS, PUBLIC HEALTH

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Manuscripts

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3 1 **The association of industry ties with outcomes of studies examining the effect of wholegrain**
4 **foods on cardiovascular disease and mortality: Systematic review and Meta-analysis**
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48 1881
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51 27 **Keywords:** Nutrition, Industry Sponsorship, Conflict of Interest, Bias, Food Industry
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54 28 **Word Count:** 4264
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1
2
3 **29 Abstract**

4 **30 Objective:** To determine if observational studies examining the association of wholegrain foods
5
6
7 **31** with cardiovascular disease with food industry sponsorship and / or authors with conflicts of
8
9
10 **32** interest with the food industry are more likely to have results and/ or conclusions that are
11
12 **33** favourable to industry than those with no industry ties. To determine whether studies with
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15 **34** industry ties differ in their risk of bias compared with studies with no industry ties.

16
17 **35 Design:** Systematic review and meta-analysis of observational studies.

18
19
20 **36 Data sources:** We searched 8 databases from 1997-2017 and hand searched the reference lists
21
22 **37** of included studies.

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24 **38 Eligibility Criteria for selecting studies:** Cohort and case control studies that quantitatively
25
26
27 **39** examined the association of wholegrains or wholegrain foods with cardiovascular disease
28
29
30 **40** outcomes in healthy adults or children.

31
32 **41 Results:** 21 of the 22 studies had a serious or critical risk of bias. Studies with industry ties more
33
34
35 **42** often had favourable results compared to those with no industry ties, but the confidence
36
37 **43** interval was wide, RR= 1.44 (95% CI 0.88-2.35). The same association was found for study
38
39
40 **44** conclusions. We did not find a difference in effect size (magnitude of RRs) between studies with
41
42 **45** industry ties, RR = 0.77 (95% CI 0.58-1.01) and studies with no industry ties, RR = 0.85 (95% CI
43
44 **46** 0.73-1.00) (P=0.50) I² 0%. These results were comparable for studies that measured the
45
46
47 **47** magnitude using hazard ratios; industry ties HR=0.82 (95% CI 0.76-0.88) vs. no industry ties
48
49 **48** HR=0.86 (95% CI 0.81-0.91) (P=0.34) I² 0%.

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51 **49 Conclusions:** We did not establish that the presence of food industry sponsorship or authors
52
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54 **50** with a COI with the food industry was associated with results or conclusions that favour industry

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3 51 sponsors. The association of food industry sponsorship or authors with a COI with the food
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6 52 industry and favourable results or conclusions is uncertain. However, our analysis was hindered
7
8 53 by the low level of COI disclosure in the included studies. Our findings support international
9
10 54 reforms to improve the disclosure and management of conflicts of interest in nutrition research.
11
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13 55 Without such disclosures, it will not be possible to determine if the results of nutrition research
14
15 56 are free of food industry influences and potential biases.

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18 57 **Systematic review registration:** PROSPERO ID CRD42017055841
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3 69 **Strengths and limitations of this study**
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6 70 - This is the first systematic review and meta-analysis to evaluate the association of
7
8 71 industry sponsorship and author conflicts of interest (COI) with the results, conclusions
9
10 72 and risk of bias of primary nutrition studies examining the effect of wholegrain foods on
11
12 73 cardiovascular disease outcomes.
13
14
15 74 - We conducted a comprehensive search and followed explicit and well-defined inclusion
16
17 and exclusion criteria for the included studies.
18 75
19
20 76 - Although our sample was small, we searched several databases and reference lists of
21
22 included studies.
23 77
24
25 78 - We did not attempt to contact the authors of studies lacking a COI disclosure statement,
26
27 thus, we may be underestimating the number of articles that had authors with conflicts
28 79
29 of interest.
30 80
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32 81 - Our assessment of risk of bias in the included studies was based on a tool that is under
33
34 development, but changes to the tool are unlikely to affect the risk of bias ratings.
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84 **Background**

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

97
98 Wholegrain products can be defined in various ways, including by the species (e.g., wheat, oats),
99 components (e.g., endosperm, bran, germ), and percentages (e.g., 25%-100%). While some food
100 regulators use a definition of 100% retention of wholegrain content, the epidemiological
101 literature typically uses 25% or more retained content. In the development of the Australian
102 Dietary Guidelines, the most common definition for whole grain foods was those containing
103 25% or more of wholegrains.¹¹

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3 105 Dietary guidelines use a variety of methods to assess bias in primary research studies, but these
4
5 106 do not assess one potential source of bias – financial conflicts of interest.¹² Across a variety of
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7
8 107 research areas, industry sponsorship and author conflicts of interest (COI) have been found to
9
10 108 be associated with outcomes that favour the study sponsor.¹³⁻¹⁵ Even when controlling for
11
12 109 methodological biases, industry sponsored studies are more likely to have results that favour
13
14 110 the sponsor's product than those studies with no or other sources of sponsorship.¹³ Industry
15
16 111 sponsors may bias research via the questions they ask (research agenda), how they design and
17
18 112 conduct a study, the selection of results they report and through 'spin' on conclusions.¹⁶⁻¹⁹
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25 114 A systematic review of methodological studies that compared food industry sponsored studies
26
27 115 with those that had no or other sources of sponsorship found that food industry sponsored
28
29 116 studies were more likely to have favourable conclusions than non-industry sponsored studies.²⁰
30
31 117 However, there were insufficient data to quantitatively assesses the association of sponsorship
32
33 118 with study results. Only one methodological study examined the association of author COI and
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35 119 conclusions, and found a statistically significant association between them.²¹
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42 121 Funding sources and author COI may be a risk of bias in studies of wholegrain consumption as
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44 122 these studies could test formulated or processed wholegrain products, such as breakfast
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46 123 cereals. Industry sponsors may gain financially from finding that these types of products have
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48 124 health benefits that can be used to market their products. There has been no assessment of the
49
50 125 association of food industry sponsorship and author COI with the food industry and the
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52 126 statistical significance of results, effect sizes, conclusions and risk of bias of observational
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3 127 studies examining the cardiovascular health benefits of wholegrain consumption. The primary
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6 128 objective of this review is to determine whether:

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8 129 • Primary studies examining the association of wholegrain foods with cardiovascular
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10 130 disease with food industry sponsorship and / or authors with COI with the food industry
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12
13 131 are more likely to have results and/ or conclusions that are favourable to industry than
14
15 132 those with no industry ties.
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18 133 • This review also examines whether any differences between industry and non-industry
19
20 134 sponsored studies could be related to their methods or interpretation of results.
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24 135 The secondary objectives of this review are to determine whether:

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28 136 • Studies with food industry sponsorship and / or authors with COI with the food industry
29
30 137 differ in their risk of bias compared with studies with no industry ties.
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33 138 • Studies with food industry sponsorship and / or authors with COI with the food industry
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36 139 have a higher level of discordance between study results and conclusions, with the
37
38 140 conclusions more likely to be favourable compared to the results.
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41 141 **METHODS**

42 142 We conducted a systematic review of observational studies examining the association of
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46 143 wholegrain consumption with cardiovascular disease.
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146 **Literature search strategy**

147 The search was based on the Process Manual used in the development of the 2013 Australian
148 Dietary Guidelines²² and the advice of an information specialist. We searched the following
149 databases from January 1997-October 2017: MEDLINE; CINAHL; PubMed; PreMEDLINE;
150 Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy we used for Ovid
151 MEDLINE is shown in Supplementary file 1. We adapted this strategy for the other databases.
152 We also hand searched the references lists of identified studies and reviews. The search also
153 included terms for randomized control trials to identify relevant trials for a future systematic
154 review.

156 **Eligibility Criteria**

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

162
163 We included studies that defined wholegrains in any way, as defined by the author of the
164 included study. If total wholegrain consumption had been assessed in the study, we included
165 this as our only exposure. If total wholegrain consumption as an exposure was not available, we
166 included any type of wholegrain consumption (i.e. wholegrain cereal, breakfast cereal, bread,
167 rice etc) as our exposure. We included studies that compared wholegrain food to other foods

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3 168 or compared various levels of wholegrain consumption. We included the result representing the
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6 169 effect of the highest level of wholegrain consumption compared to the lowest level of
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8 170 wholegrain consumption (e.g., 'yes' to wholegrain consumption vs. 'no' to wholegrain
9
10 171 consumption, tertile 3 vs. tertile 1, quartile 4 vs. quartile 1, quintile 5 vs. quintile 1). If our pre-
11
12 172 specified rules for selection did not uniquely identify one exposure for inclusion in the meta-
13
14 173 analysis, we randomly selected one result.
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19
20 175 We included studies that had a clinical outcome measure related to cardiovascular disease,
21
22 176 defined as mortality related to specific cardiovascular events, and/or cardiovascular events,
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24 177 (e.g., first myocardial infarction, total stroke etc.). If 'cardiovascular disease mortality/death/s'
25
26 178 (verbatim) had been assessed, we included this as our only outcome. If not, we included any
27
28 179 type of cardiovascular disease mortality (e.g., coronary heart disease mortality, stroke mortality
29
30 180 etc.) as our outcome. If there were no mortality outcomes assessed in the study, we included
31
32 181 any cardiovascular disease event as our outcome. If a study assessed subgroups of
33
34 182 cardiovascular disease deaths and events (e.g., intracerebral haemorrhages, ischaemic stroke)
35
36 183 and also assessed them collectively (e.g., cerebrovascular diseases), we took the result that had
37
38 184 assessed them collectively. If our pre-specified rules for selection did not uniquely identify one
39
40 185 outcome for inclusion in the meta-analysis, we randomly selected one result.
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49 187 We excluded conferences presentations, opinion pieces and letters to the editor. We had no
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51 188 language restrictions.
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190 **Types of Outcome Measures**

191 **Primary Outcomes**

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

195 1. Statistical significance of results favourable to the sponsor

196 Favourable results were defined as results that were favourable to the sponsor's product(s),
197 either indicating greater health benefits or less harm than the comparator. Specifically, for
198 studies of health benefits of wholegrains, favourable results were defined as those that were
199 statistically significant at the 0.05 level (two tailed). For studies of harms of wholegrains,
200 favourable results were defined as those where harms were not statistically significant at the
201 0.05 level or there were a statistically significant higher number of harms in the comparator
202 group. Otherwise, results were classified as unfavourable.

204 2. Effect size of results

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

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3 211 3. Conclusions
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5 212 Conclusions that suggested that the wholegrain intervention being studied was beneficial to
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8 213 health and / or safe were considered favourable to the study sponsor. Otherwise, the
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10 214 conclusions were considered unfavourable.

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15 216 **Secondary Outcomes**

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18 217 We assessed two secondary outcomes:

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21 218 1. The risk of bias of the included studies
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26 220 We hypothesized that studies with industry sponsorship and/or authors with a COI with the
27
28 221 food industry would have the same overall risk of bias as those with no industry ties.
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34 223 2. Concordance between study results and conclusions
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39 225 We hypothesized that studies with industry sponsorship and/or authors with a COI would be
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41 226 more likely to have discordant results and conclusions, with results not favouring the sponsor
42
43 227 and conclusions favouring the sponsor, than those with no industry ties.
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49 229 **Selection of studies**

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51 230 Three investigators (NC, SMc & JT, working in pairs) independently screened the titles and

52
53 231 abstracts of all retrieved records for obvious exclusions. Full text of potentially eligible studies
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3 232 was then retrieved, and three investigators (NC, SMc & JT) assessed these against our inclusion
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5 233 criteria. Agreement was reached by consensus.
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10 235 **Data Collection and analysis**

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12 236 Three assessors (NC, SMc & JT) independently extracted the following data from each included
13
14 237 study. Discrepancies in data extraction were resolved by consensus. If agreement could not be
15
16 238 reached, a fourth assessor (LB) adjudicated the outcome.
17
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20 239 From each study we extracted:
21

- 22
23 240 • Year of publication
24
25 241 • Study design (cohort or case control)
26
27 242 • Sample size of study
28
29 243 • Age of participants
30
31 244 • Exposure duration or observation period
32
33 245 • How the study defined wholegrain (verbatim)
34
35 246 • Level of wholegrain content in wholegrain foods
36
37 247 • Disclosure of funding source (no disclosure, yes and there is a sponsor, the authors state
38
39 248 they received no funding for their work)
40
41 249 • Name of the funders of the study (verbatim)
42
43 250 • Role of the funders (role of the sponsor not mentioned, sponsor not involved in study
44
45 251 design and analyses, sponsor involved, N/A)
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3 252 • Disclosure of author COI (no disclosure, yes, the authors state they had no conflicts of
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6 253 interest to declare)
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8 254 • Authors COI statement (verbatim)
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11 255 • Outcomes assessed in the study (any cardiovascular disease death and/or event)
12
13 256 • The numerical results of the study (eg., OR, HR)
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18 258 We stored all extracted data from the included studies in REDcap, a secure web-based
19
20 259 application for the collection and management of data.²³
21
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24 25 261 ***Classification of industry sponsorship and author conflicts of interest***

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28 262 Sponsorship was categorized as 1) industry or 2) non-industry. We defined industry sponsored
29
30 263 studies as those declaring any sponsorship from the food industry, including if the study
31
32 264 received 'mixed funding' from the food industry, non-profit organizations or other industries
33
34
35 265 (i.e. pharmaceutical). Any study with an author with any disclosed financial tie to the food
36
37 266 industry was classified as having a conflict of interest (COI). Author COI were categorized as 1)
38
39 267 presence of a COI with the food industry or 2) no COI. Any studies that did not contain an
40
41
42 268 author COI disclosure statement were classified as no COI. We contacted the authors of one
43
44
45 269 paper²⁴ for clarification on their disclosure of funding source.
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48 270

49 50 271 **Assessment of risk of bias in included studies**

51
52 272 We used an adapted version of the Cochrane Collaboration's 'Risk of Bias in Non-Randomized
53
54 273 Studies-of Interventions' (ROBINS-I)²⁵ tool to measure the risk of bias of included observational
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3 274 studies. The tool assesses bias across seven domains. Each domain is assessed at a low,
4
5 275 moderate, serious or critical risk of bias, or no information. The domain rating with the highest
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7 276 risk of bias determines the overall risk of bias rating for the study. For example, if a study is
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9 277 rated as being at a serious risk of bias in one domain, the overall risk of bias rating is 'serious.'

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14 15 279 **Analysis**

16
17 280 We report frequencies and percentages of study characteristics across all studies, and
18
19 281 separately, by funding source. We visually depict the overall risk of bias rating and the ratings
20
21 282 for each domain by study.
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26
27 284 We calculated risk ratios or hazard ratios (and 95% confidence intervals) to quantify the
28
29 285 association between food industry sponsorship and / or authors with COI with the food industry
30
31 286 and favourable results, favourable conclusions and the overall study risk of bias rating. For the
32
33 287 risk of bias rating analysis we dichotomised the overall risk of bias ratings as low (low or
34
35 288 moderate) or high (serious or critical). We had planned to calculate a RR for level of
36
37 289 concordance, however since in all studies there was concordance between the results and
38
39 290 conclusions, we did not undertake this analysis.
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46
47 292 We used meta-analysis to examine whether food industry sponsorship and / or authors with COI
48
49 293 with the food industry modified the magnitude of association between whole grains and
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51 294 cardiovascular disease outcomes. Specifically, we undertook a subgroup analysis within a
52
53 295 random effects meta-analysis model that compared the pooled associations across subgroups

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3 296 defined by industry sponsorship. The associations were pooled using inverse variance weighting
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6 297 and DerSimonian and Laird's method of moments estimator was used to estimate between
7
8 298 study heterogeneity. Separate meta-analyses were fitted for studies that had measured the
9
10 299 association using hazard ratios and those that had used either risk ratios or odds ratios. Given
11
12
13 300 cardiovascular events were rare, the odds ratios approximated risk ratios. We quantified
14
15 301 heterogeneity for subgroup differences using the I^2 statistic ²⁶ and tested for heterogeneity
16
17 302 using the Chi2 test. Review Manager 5.3 was used to analyse the data. ²⁷
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23 304 **Protocol Registration**

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27 305 The protocol is published in PROSPERO ²⁸ ID CRD42017055841. (Supplementary file 2)
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31 307 **Patient Involvement**

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33 308 No patients were involved in the completion of this review.
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40 310 **RESULTS**

41 311 **Search results**

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44 312 We identified 6818 references for screening, from which, 22 studies met the inclusion criteria
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46
47 313 (Figure 1). See Supplementary file 3 for 'List of excluded Studies' and reasons for exclusion.
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316 **Characteristics of included Studies**

317 All studies were published between 1998 and 2015. Three of the studies were case control and
 318 19 were cohort design. All studies contained a sponsorship disclosure. Five studies disclosed
 319 food industry sponsorship, but only one of these had a statement describing the role of the
 320 sponsor. Five studies contained an author with a COI with the food industry. Ten studies did not
 321 contain an author conflict of interest disclosure statement. Nine studies contained either food
 322 industry sponsorship or had an author with a COI.

323
 324 A greater proportion of industry sponsored studies (67%) than non-industry sponsored studies
 325 (31%) used a definition of wholegrain as greater than 25%, and most of these examined
 326 breakfast cereals (Table 1). Industry sponsored studies were also more likely than non-industry
 327 studies to focus on a specific food (44%) than total wholegrain intake (23%) (Table 1). Industry
 328 sponsored studies were less likely (56%) to have a serious or critical risk of bias in classification
 329 of exposures than non-industry sponsored studies (85%). Other characteristics were similarly
 330 distributed across industry vs. non-industry sponsored studies. Details of each individual study
 331 are in Supplementary file 4.

332

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

334

Characteristic	Category	Funding Source, n (% ¹)		
		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)

335 ¹ Percentages may not add to 100 due to rounding

336 * Case control studies were not followed up

337 **Any wholegrain foods defined as >25%

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

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340 **Risk of bias in included studies**

341 One study²⁹ was assessed as having an overall moderate risk of bias, four as having a serious
 342 risk of bias and 17 as having a critical risk of bias (Figure 2). The majority of studies had a critical
 343 risk of bias in the confounding domain. For example, a confounder was fruit and vegetable
 344 intake. If this was not appropriately controlled for when assessing the effect of wholegrain
 345 intake on a cardiovascular disease outcome, the study was rated as having a risk of bias for
 346 confounding. All but one study was assessed at a low risk of bias on the outcome measurement
 347 domain. For all domains, except classification of exposure, the risk of bias ratings were similarly
 348 distributed across industry vs. non-industry sponsored studies (Table 1).

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

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

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3 355 sponsored (n=5) and non-industry sponsored studies (n=17), the risk was smaller RR = 1.13 (95%
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6 356 CI 0.66-1.94).

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10 358 **Favourable results - Effect size: Industry sponsored versus non-industry sponsored studies**

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13 359 There was no difference in the magnitude of RRs (measuring the association between
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15 360 wholegrains and cardiovascular disease outcomes) between studies with industry sponsorship
16
17 361 and/or authors with a COI with the food industry RR = 0.77 (95% CI 0.58-1.01) and those studies
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19 362 with no industry sponsorship or author COI RR = 0.85 (95% CI 0.73-1.00) (subgroup test P=0.50,
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21 363 I² = 0%) (Figure 3). For studies that had measured the association using hazard ratios there was
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23 364 also no difference found in the magnitude of HRs between studies with industry sponsorship
24
25 365 and/or authors with a COI with the food industry HR=0.82 (95% CI 0.76-0.88) and studies with
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27 366 no industry sponsorship or author COI HR=0.86 (95% CI 0.81-0.91) (subgroup test P=0.34, I² =
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29 367 0%) (Figure 4).

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35 369 Our analysis comparing studies with industry sponsorship RR 0.63 (95% CI 0.28-1.39) and those
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37 370 with no industry sponsorship RR 0.85 (95% CI 0.74-0.97) (subgroup test P=0.46, I² = 0%), showed
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39 371 no important difference in the magnitude of RRs. This was again comparable between industry
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41 372 sponsored HR 0.82 (95% CI 0.77-0.87) and non-industry sponsored studies HR 0.85 (95% CI 0.81-
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43 373 0.90) (subgroup test P=0.29), I²=12.2%) that measured the association using hazard ratios.
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3 376 **Favourable conclusions: Industry sponsored versus non-industry sponsored**
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6 377 As there was concordance between the results and conclusions of every included study, the
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8 378 same associations were found for conclusions as for the statistical significance of results. Studies
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10 379 with industry sponsorship and/or authors with a COI with the food industry were more likely to
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12 380 have favourable conclusions compared to those with no industry sponsorship or author COI RR=
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14 381 1.44 (95% CI 0.88-2.35), however the confidence interval was wide. When studies were
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16 382 compared only by industry sponsorship, the risk was again smaller RR = 1.13 (95% CI 0.66-1.94).
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23 384 **Risk of Bias Assessment by Industry Ties**
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25 385 Studies with industry sponsorship and/or authors with a COI with the food industry were less
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27 386 likely (0/9) to have an overall low risk of bias rating compared to those studies with no industry
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29 387 sponsorship or author COI (1/13), RR = 0.47 (95% CI 0.02 -10.32), however there was large
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31 388 uncertainty in the association.
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37 390 **DISCUSSION**
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40 391 Observational studies examining the effect of wholegrain consumption on cardiovascular
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42 392 disease outcomes that were sponsored by the food industry and / or had authors with a COI
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44 393 with the food industry more often had favourable results than research not tied to the food
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46 394 industry. However, this finding was inconclusive with respect to the association between
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48 395 industry ties and favorable results, as the relative risk could be as high as 2.35 or as low as 0.88.
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50 396 We found no evidence of a difference in the magnitude of effect between industry sponsored
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52 397 and non-industry sponsored studies. It is difficult to detect differences in effect size by
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3 398 sponsorship as many study design features, such as dose and duration of exposures, and specific
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5 399 cardiovascular disease outcomes, vary across studies and may influence the effect size. In
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8 400 previous assessments of drug studies that have demonstrated that industry funded studies are
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10 401 more likely to have results that favour the study sponsors, there was no statistically significant
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13 402 difference found in effect sizes between industry and non-industry sponsored studies.¹³
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17 404 Although all the included studies had a sponsorship disclosure, almost half were missing
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19 405 disclosures about author COI. Nondisclosed COIs in nutrition research are a concern.³⁰ Larger
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21 406 samples of industry funded studies and studies with disclosed author COI could make it possible
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23 407 to establish the association of sponsorship with research outcomes.
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29 409 Studies that were sponsored by the food industry and / or had authors with a COI with the food
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31 410 industry more often had favourable conclusions than studies with no industry ties, although
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33 411 there was uncertainty in this relationship. There was absence of spin in the included studies as
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35 412 all the results agreed with the conclusions.
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41 414 The overall risk of bias in every study, other than one non-industry sponsored study,²⁹ was
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43 415 classified as high (meaning either serious or critical). The overall risk of bias rating was based on
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45 416 the domain with the highest risk of bias rating within each study, and most of the studies had a
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47 417 risk of bias related to confounding. Across each domain, we found little difference in the risk of
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49 418 bias between industry sponsored and non-industry sponsored studies.
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420 **Strengths and limitations of this review**

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

431 **Agreements and disagreements with other studies or reviews**

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

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3 441 There was also no difference in the level of risk of bias between industry sponsored and non-
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5 442 industry sponsored studies. This is consistent with previous assessments of pharmaceutical,
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8 443 tobacco and nutrition research that has shown industry-sponsored studies are of equal or better
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10 444 quality than non-industry-sponsored studies.^{13 20 32-34}

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14 15 446 **Implications for clinicians, policy makers and future research**

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17 447 The recent critiques to reform the methods used in the development of dietary guidelines have
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20 448 proposed steps to improve the transparency of how evidence is evaluated and synthesized into
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23 449 recommendations.^{1 2} However, until the influence of industry sponsorship in primary nutrition
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25 450 studies has been further explored and measured with larger samples of industry sponsored
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28 451 studies, or studies that have author disclosure statements, this bias may still be unaccounted for
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30 452 in dietary guidelines. Although there was uncertainty around the differences in the results and
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33 453 conclusions that we observed between industry and non-industry studies, the differences are
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35 454 unlikely to be explained by methodological risks of bias in these studies.

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40 456 There are ways that study sponsorship can influence outcomes other than through the design of
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42 457 research. Bias may also be introduced in the way industry sponsored studies code events and
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45 458 analyse data,^{35 36} through the selective reporting of study outcomes and through publication
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47 459 bias.³⁷ It has been demonstrated in other areas of medical research that there is a greater
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50 460 propensity to publish studies with statistically significant results.³⁸ Therefore, selective
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52 461 publication of study results or studies in their entirety, may limit the availability of all relevant
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55 462 nutrition data and can skew results that are used in dietary guideline development.³⁹

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3 463 Publication bias could be minimized with the introduction of study registries for nutrition
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6 464 research, as has been established in pharmaceutical research.⁴⁰ The association of food
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8 465 industry sponsorship with the reporting of nutrition research still needs to be assessed.
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13 467 Almost half of the studies included in this review had authors that did not disclose if they had a
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15 468 COI with the food industry or not. Compliance with COI disclosure policies is now well
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18 469 documented across many domains of research.⁴¹⁻⁴⁶ Recent examinations of the levels of
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20 470 disclosure in research assessing the effects of artificially sweetened beverages on weight
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22 471 outcomes found similarly poor disclosure rates.³² Several solutions have been proposed to
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24 472 increase transparency and disclosure rates, including the use of different databases and
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26 473 additional resources to identify conflicted authors, and the introduction of mandatory
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28 474 disclosure requirements in all journals, with the use of penalties for those who do not adhere to
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32 475 the stated policies.^{20 32}
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37 477 **Conclusion**
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40 478 We did not establish that the presence of food industry sponsorship or authors with a COI with
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42 479 the food industry was associated with results or conclusions that favour industry sponsors. The
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44 480 association of food industry sponsorship or authors with a COI with the food industry and
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46 481 favourable results or conclusions is uncertain. However, our analysis was hindered by the low
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48 482 level of COI disclosure in the included studies. This research further strengthens calls for stricter
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50 483 policies relating to the disclosure and management of conflicts of interest in nutrition research.
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484 Without such disclosures, it will not be possible to determine if the results of nutrition research
485 are free of food industry influences and potential biases.

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For peer review only

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3 488 **Figure 1. Study Flow Diagram**
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5 489 **Figure 2. Risk of Bias of Included Studies**
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8 490 **Figure 3: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored &**
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10 491 **no author COI studies, Risk Ratio**
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12 492 **Figure 4: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored &**
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14 493 **no author COI studies, Hazard Ratio**
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3 622 **Contributors:** NC, AF, SMc, MA-F and LB designed and wrote the review protocol. NC wrote the
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5
6 623 search strategy and undertook the literature search. NC, SMc and JT conducted the title and
7
8 624 abstract screening and full article screening for final study inclusion. NC, SMc and JT conducted
9
10 625 data collection and cleaning, LB supervised. NC and JMc undertook all data analysis. LB advised
11
12 626 on methods, statistical analyses, and interpretation of findings. All authors contributed to the
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14
15 627 final manuscript. NC and LB are guarantors.

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28
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32
33
34 634 (Charles Perkins Centre summer scholarship) from the University of Sydney.

35
36
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39
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41
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44
45 638 might have an interest in the submitted work in the previous three years. The authors report no
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47 639 other relationships or activities that could appear to have influenced the submitted work.

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50 640 **Ethical Approval:** Not required
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3 641 **Transparency declaration:** The authors affirm that this manuscript is a honest, accurate, and
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5 642 transparent account of the study being reported, that no important aspects of the study have
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8 643 been omitted and that any discrepancies from the study as planned have been explained.
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34 653 **Data Sharing:** Available from The University of Sydney data repository. DOI to be determined.
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Figure 1. Study Flow Diagram

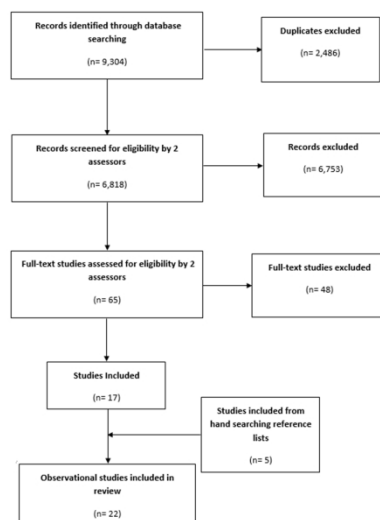


Figure 1. Study Flow Diagram

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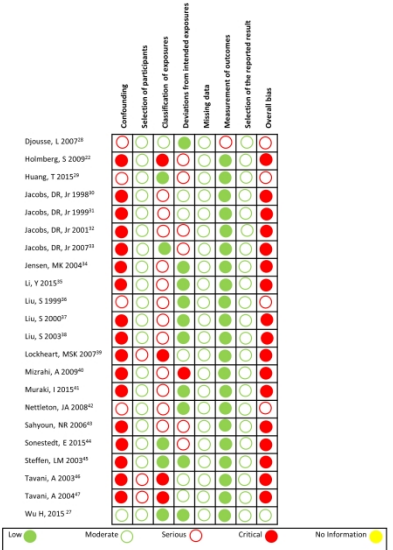


Figure 2. Risk of Bias Table
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Figure 3: Effect Size - Industry Sponsored &/OR Author COI versus Non-Industry Sponsored & No Author COI, RR

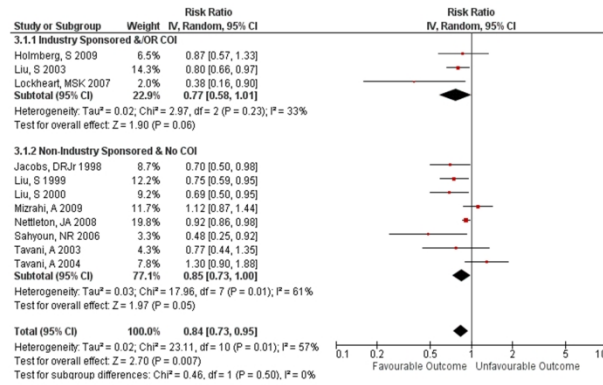


Figure 3. Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Risk Ratio

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

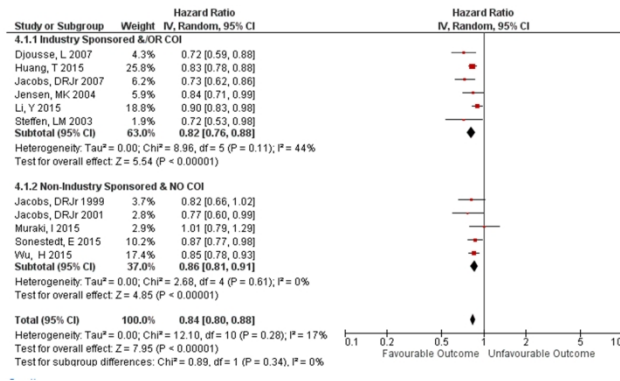


Figure 4: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Hazard Ratio

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3 **1 Supplementary File 1: Search Strategy**
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5
6 2 OVID Medline: wholegrain & CVD
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8
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10
11 4 1. Randomized controlled trial*.sh.
12

13
14 5 2. experimental design.tw.
15

16
17 6 3. intervention*.tw.
18

19
20 7 4. (RCT* or rct*).tw.
21

22
23 8 5. random* control* trial*.tw.
24

25
26 9 6. clinical trial*.sh.
27

28
29 10 7. field trial*.tw.
30

31
32 11 8. community trial*.tw.
33

34
35 12 9. controlled clinical trial*.tw.
36

37
38 13 10. pragmatic trial*.tw.
39

40
41 14 11. observational study.sh.
42

43
44 15 12. cohort study.tw.
45

46
47 16 13. prospective cohort*.tw.
48

49
50 17 14. retrospective cohort*.tw.
51

52
53 18 15. case control*.sh.
54

55
56 19 16. ecological study.tw.
57

58
59 20 17. time series analys?s.tw.
60

21 18. before-after study.tw.

22 19. pre-post study.tw.

- 1
2
3 23 20. follow up stud*.sh.
4
5
6 24 21. comparative stud*.sh.
7
8 25 22. evaluation stud*.sh.
9
10
11 26 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
12 27 or 21 or 22
13
14
15 28 24. Edible Grain/ae, me [Adverse Effects, Metabolism]
16
17 29 25. grain*.tw.
18
19
20 30 26. Dietary Carbohydrates/ or Edible Grain/ or Bread/ or Dietary Fiber/
21
22 31 27. whole grain*.tw.
23
24
25 32 28. partially processed grains.tw.
26
27 33 29. whole wheat.tw.
28
29
30 34 30. wholemeal.tw.
31
32 35 31. rice*.tw.
33
34
35 36 32. oat*.tw.
36
37 37 33. barley*.tw.
38
39
40 38 34. wheat*.tw.
41
42 39 35. Amaranthus/ae, me [Adverse Effects, Metabolism]
43
44
45 40 36. amaranth.tw.
46
47 41 37. Millets/me [Metabolism]
48
49
50 42 38. millet*.tw.
51
52 43 39. Sorghum/me [Metabolism]
53
54
55 44 40. sorghum*.tw.
56
57
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- 1
2
3 45 41. maize*.tw.
4
5 46 42. spelt*.tw.
6
7
8 47 43. buckwheat*.tw.
9
10 48 44. Triticale/me [Metabolism]
11
12
13 49 45. triticale*.tw.
14
15 50 46. fonio*.tw.
16
17
18 51 47. emmer.tw.
19
20 52 48. einkorn*.tw.
21
22
23 53 49. kamut*.tw.
24
25 54 50. canary seed*.tw.
26
27
28 55 51. Bread/ae, an, me [Adverse Effects, Analysis, Metabolism]
29
30 56 52. bread*.tw.
31
32
33 57 53. breakfast cereal*.tw.
34
35 58 54. pasta*.tw.
36
37
38 59 55. noodle*.tw.
39
40 60 56. Flour/ae, an, st [Adverse Effects, Analysis, Standards]
41
42
43 61 57. flour*.tw.
44
45 62 58. polenta*.tw.
46
47
48 63 59. semolina*.tw.
49
50 64 60. bran.tw.
51
52
53 65 61. corn.tw.
54
55 66 62. wheat germ*.tw.
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2
3 67 63. corn cake*.tw.
4
5 68 64. scone*.tw.
6
7
8 69 65. couscous.tw.
9
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11 70 66. crumpet*.tw.
12
13 71 67. dietary fiber.tw.
14
15 72 68. dietary carbohydrate*.tw.
16
17
18 73 69. glycemic index.tw.
19
20
21 74 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
22 75 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
23 76 or 60 or 61 or 62 or 64 or 65 or 66 or 67 or 68 or 69
24
25
26 77 71. Coronary Disease/ or Cardiovascular Diseases/ or Hypertension/ or Atherosclerosis/
27
28
29 78 72. cardiovascular disease*.tw.
30
31 79 73. coronary*.tw.
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34 80 74. heart*.tw.
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36 81 75. cardia*.tw.
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39 82 76. myocard*.tw.
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41 83 77. isch?em*.tw.
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44 84 78. angina*.tw.
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46 85 79. ventric*.tw.
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49 86 80. tachycardi*.tw.
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51 87 81. pericard*.tw.
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54 88 82. endocardi*.tw.
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2
3 89 83. atrial fibrillat*.tw.
4
5 90 84. arrhythmi*.tw.
6
7
8 91 85. athero*.tw.
9
10 92 86. arterio*.tw.
11
12
13 93 87. HDL.tw.
14
15 94 88. LDL.tw.
16
17
18 95 89. VLDL.tw.
19
20 96 90. lipid*.tw.
21
22
23 97 91. lipoprotein*.tw.
24
25
26 98 92. triacylglycerol*.tw.
27
28 99 93. hyperlipid*.tw.
29
30 100 94. hypercholesterol*.tw.
31
32
33 101 95. hypercholester?emia*.tw.
34
35
36 102 96. hypertriglycerid?emia*.tw.
37
38 103 97. Cholesterol/
39
40
41 104 98. Stroke/
42
43 105 99. Cerebrovascular Disorders/
44
45
46 106 100. vascular accident*.tw.
47
48
49 107 101. TIA.tw.
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51 108 102. Thrombosis/
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53 109 103. thrombosis.tw.
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56 110 104. Embolism/ or Pulmonary Embolism/
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2
3 111 105. apoplexy.tw.
4
5
6 112 106. (brain adj2 accident*).tw.
7
8 113 107. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
9
10
11 114 108. Blood Pressure/ or Hypertension/
12
13 115 109. systolic blood pressure.tw.
14
15
16 116 110. diastolic blood pressure.tw.
17
18 117 111. Peripheral Vascular Diseases/ or Peripheral Arterial Disease/
19
20
21 118 112. (coronar\$ adj5 (bypas\$ or graft\$ or disease\$ or event\$)).tw.
22
23 119 113. (cerebrovasc\$ or cardiovasc\$ or mortal\$ or angina\$ or stroke or strokes).tw.
24
25
26 120 114. (myocardi\$ adj5 (infarct\$ or revascular\$ or ischaemi\$ or ischemi\$)).tw.
27
28 121 115. (morbid\$ adj5 (heart\$ or coronar\$ or ischaem\$ or ischem\$ or myocard\$)).tw.
29
30
31 122 116. (vascular\$ adj5 (peripheral\$ or disease\$ or complication\$)).tw.
32
33 123 117. (heart\$ adj5 (disease\$ or attack\$ or bypass\$)).tw.
34
35
36 124 118. Mortality/
37
38 125 119. mortality.tw.
39
40
41 126 120. Diabetes Mellitus, Type 2/
42
43 127 121. Hyperglycemia/
44
45
46 128 122. hyperglycemi*.tw.
47
48 129 123. (glucose adj2 intoleran*).tw.
49
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51 130 124. Insulin Resistance/
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53 131 125. (metabolic adj3 syndrome adj3 x).tw.
54
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56 132 126. metabolic cardiovascular syndrome.tw.
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3 133 127. dysmetabolic syndrome x.tw.
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5
6 134 128. HbA1c.tw.
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8 135 129. (glyc?emic adj3 control).tw.
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10 136 130. 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

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12 137 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

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14 138 105 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

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16 139 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129
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18 140 131. 23 and 70 and 130
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20 141 132. limit 131 to (humans and yr="1997 -Current")
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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
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- 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.
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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

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Supplementary File 4: Characteristics of Included Studies

Study ID	Study Design	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 62.25 ± 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

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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-Industry ¹⁷	No ⁱ
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 ¹

*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

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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
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- 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

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3 l) None reported
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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

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