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## The association of food industry ties with findings of studies examining the effect of dairy foods intake on cardiovascular disease and mortality: Systematic review and Meta-analysis

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3 1 **The association of food industry ties with findings of studies examining the effect of**  
4 **dairy foods intake on cardiovascular disease and mortality: Systematic review and**  
5 **Meta-analysis**  
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## 20 Abstract

21 **Objective:** To determine if the effects of dairy foods on cardiovascular disease outcomes  
22 differ between studies with food industry ties versus those without industry ties. To determine  
23 whether studies with or without industry ties differ in their risk of bias.

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

25 **Setting:** We searched 8 databases from 2000-2019 and hand searched the reference lists of  
26 included studies.

27 **Participants:** We included cohort and case control studies that estimated the effects of dairy  
28 foods on cardiovascular disease (CVD) outcomes in healthy adults.

29 **Primary and secondary outcome measures:** Primary, 1) statistical significance of results  
30 favourable to dairy, 2) effect size of results, and 3) conclusions; and Secondary, 1) the risk of  
31 bias of the included studies, and 2) concordance between study results and conclusions.

32 **Results:** There was no clear evidence of an association between studies with industry ties  
33 (1/14) vs. no industry ties (8/29) and the reporting of favourable results, RR= 0.26 (95% CI  
34 0.04, 1.87; n=43 studies) and studies with industry ties (4/14) vs. no industry ties (11/29) and  
35 favourable conclusions, RR= 0.75 (95% CI 0.29, 1.95; n=43). For most outcomes, we did not  
36 find a difference in effect sizes between studies with or without industry ties. Studies with  
37 industry sponsorship, (HR =0.78; n= 3 studies) showed a decreased magnitude of risk of  
38 CVD outcomes compared to studies with no industry sponsorship (HR=0.97; n=18) (ratio of  
39 HRs 0.80 (95% CI 0.66, 0.97)) P=0.03.

40 **Conclusions:** There was no clear evidence of an association between studies with food  
41 industry ties and the reporting of favourable results and conclusions compared with studies  
42 without industry ties. The statistically significant difference in the magnitude of effects  
43 identified in industry sponsored studies compared to non-industry sponsored studies,  
44 however, is important in quantifying industry influence on studies included in dietary  
45 guidelines.

46  
47 **Keywords:** Industry Sponsorship, Conflicts of Interest, Bias, Dietary Guidelines

## 49 Strengths and limitations of this study

- 50 • This is the first systematic review and meta-analysis to evaluate the association of  
51 food industry ties (industry sponsorship and / or author conflicts of interest (COI))

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2  
3 52 with the results, conclusions and risk of bias of primary nutrition studies examining  
4 the effect of dairy foods on cardiovascular disease outcomes and mortality.  
5 53  
6  
7 54 • We conducted a comprehensive search and followed explicit and well-defined  
8 inclusion and exclusion criteria for the included studies.  
9 55  
10 56 • For studies missing a funding or author COI disclosure, we did not contact the  
11 authors; thus we may be underestimating the number of studies with industry ties.  
12 57  
13 58 • The tool that we used to assess the risk of bias is still under modification, however it  
14 is unlikely any future changes to the tool will affect the risk of bias ratings.  
15 59  
16 60 • We did not analyse studies of low and full fat dairy separately. Industry ties may have  
17 different effects on studies of low or full fat dairy foods.  
18  
19 61  
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21 62

## 63 INTRODUCTION

64 The effect of dairy foods on cardiovascular disease (CVD) is unclear. Recent systematic  
65 reviews and meta-analyses of observational studies have reported conflicting results between  
66 the association of total dairy consumption and risk of CVD, with some showing decreased  
67 risk and some showing no clear evidence.<sup>1-4</sup> The beneficial effects of decreasing blood  
68 pressure, however, appear more consistent.<sup>4,5</sup> Further, dairy intake recommendations made in  
69 dietary guidelines around the world vary. Although the Australian Dietary Guidelines  
70 concluded that there is a probable association between dairy food consumption and a reduced  
71 risk of cardiovascular events,<sup>6</sup> recent amendments to the Eatwell guidelines by Public Health  
72 England recommend a significant reduction in the daily intake of dairy foods.<sup>7</sup>

73

74 Food industry sponsors and authors with a conflict of interest (COI) with the food industry  
75 may gain financially from finding that dairy foods have health benefits, since such a finding  
76 can be used to market dairy products. Such a driver may lead industry sponsors to magnify  
77 (or bias) the health benefits of dairy foods by influencing the research agenda, design and  
78 conduct of the study, or reporting of the results.<sup>8-11</sup> Prior examinations of pharmaceutical and  
79 tobacco research have identified that even when controlling for methodological biases,  
80 studies sponsored by industry were more likely to have results that favoured the sponsor than  
81 studies with other sources of sponsorship.<sup>12-14</sup>

82

83 The effects of food industry sponsorship or author COI with the food industry on study  
84 results needs further examination.<sup>15</sup> A systematic review assessing the effects of wholegrain  
85 foods on CVD and mortality found that studies with food industry ties more often have  
86 favourable results and conclusions compared to those with no industry ties, but the  
87 association was uncertain.<sup>16</sup> One study has demonstrated an association of food industry  
88 sponsorship with the magnitude of effect estimates.<sup>17</sup> In this examination, studies of soft  
89 drink consumption sponsored by the food industry reported significantly smaller harm effect  
90 estimates than those with no food industry sponsorship. A recent dairy industry funded meta-  
91 analysis of observational studies found that studies without food industry sponsorship showed  
92 that dairy consumption was associated with a statistically significant decreased risk of  
93 developing CVD and Type 2 diabetes, while studies with food industry sponsorship did not.<sup>18</sup>

1  
2  
3 94 The primary objective of this systematic review and meta-analysis is to determine whether:  
4

- 5 95 • Studies of observational design examining the effects of dairy foods on CVD with  
6  
7 96 food industry ties (industry sponsorship and / or authors with a COI) with the food  
8  
9 97 industry are more likely to have results and / or conclusions that are favourable to  
10  
11 98 industry than those with no industry ties.  
12  
13 99

14  
15 100 The secondary objectives of this review are to determine whether observational studies with  
16  
17 101 food industry ties compared with no industry ties:

- 18 102 I. differ in their risk of bias;  
19  
20 103 II. have a higher level of discordance between study results and conclusions, with the  
21  
22 104 conclusions more likely to be favourable compared to the results.  
23  
24  
25 105

## 26 27 106 **METHODS**

28  
29 107 We conducted a systematic review of observational studies examining the effect of dairy  
30  
31 108 consumption on CVD. Our study is registered with Prospero ID CRD42019129659 (see  
32  
33 109 Supplementary file 1).<sup>19</sup>  
34  
35 110

### 36 111 **Search Strategy**

37  
38 112 The search included terms to locate observational studies and randomised control trials, the  
39  
40 113 latter of which are for a separate systematic review. The search used was based on the  
41  
42 114 Process Manual used to develop the 2013 Australian Dietary Guidelines and the guidance of  
43  
44 115 an information specialist.<sup>20</sup> The search dates used were to ensure that we identified the  
45  
46 116 studies used to inform the recommendations in these guidelines. We therefore searched the  
47  
48 117 following databases from January 2000-February 2019: MEDLINE; CINAHL; PubMed;  
49  
50 118 PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy  
51  
52 119 used for Ovid MEDLINE on February 1, 2019 is shown in Supplementary file 2. We adapted  
53  
54 120 this strategy for the other databases. We hand searched references lists of the identified  
55  
56 121 studies and reviews.  
57  
58 122  
59 123  
60 124



## 125 **Eligibility Criteria**

126 We included studies of cohort or case control designs that estimated the effects of dairy  
127 consumption on CVD outcomes in healthy adults. We focused on these study designs as they  
128 are often used to assess the association of diet with long term health outcomes.

129  
130 We included studies with no restriction on the authors' definition of dairy. For example, some  
131 authors' defined dairy as milk, yogurt and cheese, while others defined dairy as 'whole fat'  
132 milk, yogurt and cheese. We included studies that compared dairy foods to other foods or  
133 compared various levels of dairy consumption.

134  
135 We included studies that measured any clinical outcome of CVD, defined as either mortality  
136 related to specific CVD events, and / or CVD events, (e.g., first myocardial infarction, total  
137 stroke etc.) or incidence of elevated blood pressure / hypertension.

138  
139 We excluded conferences presentations, opinion pieces and letters to the editor. We had no  
140 language restrictions.

## 142 **Types of Outcome Measures**

### 143 **Primary Outcomes**

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

#### 147 1. Statistical significance of results favourable to dairy

148 Favourable results were defined as those that were in the direction of showing a health  
149 benefit of dairy product(s), and were statistically significant at the 0.05 level (two tailed),  
150 such as a statistically significant decreased risk of CVD compared to the comparator (i.e.  
151 another food or lower dairy consumption). Otherwise, results were classified as unfavourable.  
152 In the circumstance where a study reported multiple results (e.g. first myocardial infarction  
153 and total stroke), only one result needed to be 'favourable' for the study as a whole to be  
154 classified as 'favourable'.

#### 156 2. Effect size of results

157 Effect size was defined as the risk ratio (RR), hazard ratio (HR) or odds ratio (OR) between  
158 dairy foods tested versus comparator on the CVD outcome.

159

### 3. Conclusions

Conclusions that suggested that the dairy consumption was beneficial to health by decreasing CVD were considered favourable. Otherwise, the conclusions were considered unfavourable. In the circumstance where a study reported multiple results (e.g. first myocardial infarction and total stroke), only one conclusion needed to be 'favourable' for the study as a whole to be classified as 'favourable'.

166

#### **Secondary Outcomes**

We assessed two secondary outcomes:

##### 1. The risk of bias of the included studies

To evaluate the risk of bias of included observational studies, we used an adapted version of the Cochrane Collaboration's 'Risk of Bias in Non-Randomized Studies-of Interventions' (ROBINS-I) tool,<sup>21</sup> the ROBINS-E<sup>22</sup>. Bias is assessed across seven domains ('Bias due to confounding', 'Bias in selection of participants', 'Bias in classification of exposures', 'Bias due to deviations from exposures', 'Bias due to missing data', 'Bias in measurement of outcomes', 'Bias in selection of reported results'), with each domain classified low, moderate, serious, critical risk of bias, or no information. An overall risk of bias rating for the study is given based on the domain with the highest risk of bias rating. For example, if a study is rated as being at a 'critical' risk of bias in one domain, the overall risk of bias rating is 'critical.' In the circumstance where a study reported multiple results (e.g. stroke and myocardial infarction), the risk of bias was only assessed for one randomly selected outcome.

181

##### 2. Concordance between study results and conclusions

Results unfavourable to the sponsor with conclusions favourable to the sponsor, were considered discordant. Otherwise, the results and conclusions were considered concordant.

185

#### **Selection of studies**

Three investigators (NC, SMc & AF), working independently in pairs, screened the titles and abstracts of all records for obvious exclusions. If both investigators agreed on excluding the study, the full text was not retrieved. Three investigators (NC, SMc & AF) working independently in pairs, assessed the full text of potentially eligible studies against the

191 inclusion criteria. If agreement could not be reached, a fourth investigator (LB) resolved the  
192 conflict.

193

### 194 **Selection of results for meta-analysis**

195 If total dairy consumption had been assessed in the study, we included this as our only  
196 exposure. If total dairy consumption had not been assessed, we included any type of dairy  
197 consumption (e.g. milk, yogurt, and cheese; or low fat, high fat) other than fermented milk as  
198 our exposure. We included the results comparing the highest level of dairy consumption to  
199 the lowest level of dairy consumption (e.g., 'yes' to dairy consumption vs. 'no' to dairy  
200 consumption, tertile 3 vs. tertile 1, quartile 4 vs. quartile 1, quintile 5 vs. quintile 1). For the  
201 meta-analyses if our pre-specified rules for selecting results did not allow us to uniquely  
202 identify one exposure for inclusion, we randomly selected one result.

203

204 If 'cardiovascular disease mortality/death/s' (verbatim) had been assessed, we included this  
205 as our only outcome. If not, we included any type of CVD mortality (e.g., coronary heart  
206 disease mortality, stroke mortality etc.) as our outcome. If there were no mortality outcomes  
207 assessed in the study, we included any CVD event or incidence of elevated blood pressure /  
208 hypertension as our outcome. If a study used a composite outcome, which was a combination  
209 of multiple outcomes, the result pertaining to the composite outcome was selected. For the  
210 meta-analyses if our pre-specified rules for selecting results did not allow us to uniquely  
211 identify one outcome for inclusion, we randomly selected one result.

212

### 213 **Data Collection**

214 From each study we extracted:

- 215 • Year of publication
- 216 • Study design (cohort or case control)
- 217 • Sample size of study
- 218 • Age of participants (combined or if reported, separately)
- 219 • Exposure duration or observation period
- 220 • How the study defined dairy (verbatim)
- 221 • Disclosure of funding source (no disclosure, yes and there is a sponsor, the authors  
222 state they received no funding for their work)
- 223 • Name of the funders of the study (verbatim)

- 1  
2  
3 224 • Role of the funders (role of the sponsor not mentioned, sponsor not involved in study  
4 design and analyses, sponsor involved, N/A)  
5 225  
6  
7 226 • Disclosure of author COI (no disclosure, yes (if at least 1 author had a COI), the authors  
8 state they had no conflicts of interest to declare)  
9 227  
10 228 • Authors COI statement (verbatim)  
11  
12 229 • Outcomes assessed in the study (any CVD death and/or event or blood  
13 pressure/hypertension)  
14 230  
15 231 • The numerical results of the study (e.g., OR, HR, RR)  
16  
17 232

19 233 All extracted data from the included studies was stored in REDcap, a secure web-based  
20 application for the collection and management of data.<sup>23</sup> Five investigators (NC, SMc, AF,  
21 234 AL & JD) working independently in pairs extracted data from the included studies.  
22  
23 235 Discrepancies in data extraction were resolved by consensus. If agreement could not be  
24 236 reached, a sixth investigator (LB) resolved the discrepancy.  
25 237  
26 238

### 29 239 **Classification of industry sponsorship and author conflicts of interest**

31 240 Sponsorship was categorized as 1) industry or 2) non-industry. Industry sponsored studies  
32 were defined as those that declared any sponsorship from the food industry, including ‘Big  
33 241 Food’ (i.e. Danone, Kraft, Unilever etc), trade associations (i.e. dairy associations and  
34 242 organisations) and dairy industry (i.e. primary producers). Studies with food industry  
35 243 sponsorship plus any other sponsorship were classified as industry. Any study that did not  
36 244 contain a funding disclosure statement was classified as ‘non-industry’.  
37 245  
38 246

43 247 Studies with at least one author with any disclosed financial tie with the food industry were  
44 248 classified as having a conflict of interest (COI). Author COI were categorised as 1) COI or 2)  
45 249 no COI. Studies with no authors with disclosed financial ties with the food industry were  
46 250 classified as ‘no conflict of interest’.  
47 251  
48 252

52 252 Since the number of studies with industry sponsorship or author COI was small, we also  
53 253 categorized studies as having “industry ties” for analysis. Studies classified as having an  
54 254 industry tie were industry sponsored and / or had an author COI. Otherwise, they were  
55 255 classified as having no industry ties.  
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## 257 **Analysis**

258 We report the frequencies and percentages of the study characteristics across all studies, and  
259 separately, by sponsorship, COI and industry ties. We visually present the risk of bias rating  
260 for each domain and overall across each study.

261  
262 To quantify the association between industry ties, food industry sponsorship, or authors with  
263 a conflict of interest with the food industry and (i) favourable results, (ii) favourable  
264 conclusions, (iii) overall risk of bias across each study, and (iv) level of concordance, we  
265 calculated RR (and 95% confidence intervals). To analyse the risk of bias rating for each  
266 study, we dichotomised the overall risk of bias ratings as low (low or moderate) or high  
267 (serious or critical).

268  
269 To examine whether studies with food industry ties, food industry sponsorship, or authors  
270 with a conflict of interest with the food industry modified the magnitude of effect of dairy on  
271 CVD outcomes we used meta-analysis. For each outcome, we combined effect estimates  
272 using a random effects meta-analysis model using the inverse variance method. DerSimonian  
273 and Laird's method of moments estimator was used to estimate between study heterogeneity.  
274 We fitted separate meta-analyses for studies that had measured the association using HRs and  
275 those that had used either RRs or ORs. It is not recommended to combine HRs with RRs and  
276 ORs in a meta-analysis, as HRs represent instantaneous risk over the study time period,  
277 whereas RRs and ORs estimate risk/odds at a fixed time point.<sup>24</sup> We considered that the ORs  
278 approximated RRs given CVD events were rare.

279  
280 We undertook a fixed-effects test for subgroup differences (defined by industry sponsorship /  
281 authors conflict of interest) using the Chi<sup>2</sup> test and calculated the ratio of RRs (ORs) or HRs  
282 along with 95% confidence intervals. Analyses were undertaken in Review Manager 5.3.<sup>25</sup>

283  
284 We planned to use sensitivity analysis to assess the influence of risk of bias by restricting the  
285 analysis to studies at 'low risk of bias' overall (i.e. an overall risk of bias rating of low or  
286 moderate). However, as the overall risk of bias was high across all studies, this was not  
287 undertaken.

288

289

## 290 **RESULTS**

291 As shown in Figure 1, there were 1, 858 studies screened for inclusion and 43 studies were  
292 included (3 case controls, 40 cohorts). See Supplementary file 3 for ‘List of excluded studies  
293 and reasons for exclusion’.

### 295 **Characteristics of included Studies**

296 All studies were published between 2001 and 2019. All but one contained a funding  
297 disclosure. Eight studies disclosed food industry sponsorship, but only two of these studies  
298 described the role of the sponsor. Six studies did not contain an author COI disclosure  
299 statement. Ten studies contained an author with a COI with the food industry. Fourteen  
300 studies were classified as having industry ties, disclosing food industry sponsorship and / or  
301 an author with a COI.

302  
303 As shown in Table 1, most characteristics were similarly distributed across studies with  
304 industry ties or no industry ties. Studies with industry ties (64%) were more likely to have  
305 sample sizes <5000 than non-industry sponsored studies (34%). A greater proportion of  
306 industry sponsored studies (100%) than non-industry sponsored studies (83%) focused on  
307 total dairy intake rather than a specific food. Details of the individual studies are in  
308 Supplementary file 4.

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319 **Table 1. Characteristics of the included studies by sponsorship, author conflict of**  
 320 **interest and industry ties**

321 Funding Source, n (%<sup>a</sup>)

Characteristic	Category	Total N = 43	Sponsorship		COI		Industry Ties	
			Industr y N= 8	Non- Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non- Industry/ No COI N = 29
<b>Sex</b>	Male	5 (12)	0 (0)	5 (14)	0 (0)	5 (15)	0 (0)	5 (17)
	Female	2 (5)	0 (0)	2 (6)	0 (0)	2 (6)	0 (0)	2 (7)
	Both	36 (84)	8 (100)	28 (80)	10 (100)	26 (79)	14 (100)	22 (76)
<b>Sample Size</b>	<5000	19 (44)	6 (75)	13 (37)	7 (70)	12 (36)	9 (64)	10 (34)
	5000-50,000	18 (42)	0 (0)	18 (51)	2 (20)	16 (48)	2 (14)	16 (55)
	>50,000	6 (14)	2 (25)	4 (11)	1 (10)	5 (15)	3 (21)	3 (10)
<b>Length of Follow up</b>	N/A*	3 (7)	2 (25)	1 (3)	1 (10)	2 (6)	2 (14)	1 (3)
	<10 years	11 (26)	3 (38)	8 (23)	2 (20)	9 (27)	3 (21)	8 (28)
	10-15 years	21 (49)	2 (25)	19 (54)**	6 (60)	15 (45)**	7 (50)	14 (48)
	>15 years	8 (19)	1 (13)	7 (20)	1 (10)	7 (21)	2 (14)	6 (21)
<b>Type of Dairy</b>	Total Dairy Intake***	37 (86)	8 (100)	29 (83)	9 (90)	28 (85)	13 (93)	24 (83)
	Individual Dairy Foods****	6 (14)	0 (0)	6 (17)	1 (10)	5 (15)	1 (7)	5 (17)

322 <sup>a</sup> Percentages may not add to 100 due to rounding

323 \* Follow up is not applicable for case control studies

324 \*\* Follow up for Johansson, I 2018 described the follow up as '8-12 years', we took the median of 10 years

325 \*\*\* This includes studies that looked at nutrients e.g calcium, fat & protein by measuring total dairy intake

326 \*\*\*\*Individual foods included milk, cheese & yogurt

### 327 **Risk of bias in included studies**

328 Every study was classified as having an overall high risk of bias, with 10 assessed as having a  
329 serious risk of bias and 33 as having a critical risk of bias (Figure 2). Most studies were  
330 assessed as having a critical risk of bias rating for the domain 'Bias due to confounding'. For  
331 example, a confounder was fruit and vegetable intake. If these confounders were not  
332 controlled for appropriately when measuring the effect of dairy intake on a CVD outcome,  
333 the study was classified as having a risk of bias for the confounding domain.

334  
335 Studies without industry ties or without an author with a COI were more likely to have a  
336 serious or critical risk of bias rating for 'Bias in classification of exposures'. For example, if a  
337 study did not use a validated food frequency questionnaire to measure the dietary intake of  
338 dairy, the study was classified as having a risk of bias for the domain of classification of  
339 exposures. For all other domains, the risk of bias classifications were similarly distributed  
340 across studies with industry ties, industry sponsorship or COI vs no industry ties, industry  
341 sponsorship or COI, respectively (see Supplementary file 5).

### 343 **Favourable results - Statistical significance: Industry ties vs no industry ties; industry 344 sponsorship vs no sponsorship; COI v no COI**

345 There was no clear evidence of an association between the reporting of favourable results and  
346 studies with industry ties (1/14) compared to those with no industry ties (8/29), RR= 0.26  
347 (95% CI 0.04, 1.87; n=43 studies) (Supplementary file 6). When comparing studies with  
348 industry sponsorship (1/8) with those with no industry sponsorship (8/35), there was no clear  
349 evidence of an association, RR = 0.55 (95% CI 0.08, 3.77; n=43 studies). There was again no  
350 clear evidence of an association between the reporting of favourable results and studies with  
351 an author with a COI (0/10) than those with no COI (9/33), RR= 0.16 (95% CI 0.01, 2.57;  
352 n=43 studies).

### 354 **Effect Size, Cardiovascular Disease: Industry ties v no industry ties; industry 355 sponsorship vs no industry sponsorship; COI v no COI**

356 For studies that quantified the association between dairy consumption and CVD outcomes  
357 using a RR, we found no important difference in the magnitude of the effect in studies with  
358 industry ties (RR = 0.89; n=3 studies) compared with those studies with no industry ties, (RR  
359 = 0.99; n=7 studies) (ratio of RRs 0.90 (95% CI 0.74, 1.09)); P=0.27 (Supplementary file 7).



1  
2  
3 360 For studies that had quantified the association using HRs, we similarly did not find an  
4  
5 361 important difference in the magnitude of HRs between studies with industry ties, (HR=0.96;  
6  
7 362 n=7 studies) and those studies with no industry ties, (HR=0.95; n=14 studies) (ratio of HRs  
8  
9 363 1.01 (95% CI 0.90, 1.13)); P=0.86.

10 364  
11  
12 365 In our analysis comparing studies with industry sponsorship, (RR 0.83; n=2 studies) and  
13  
14 366 those with no industry sponsorship, (RR 0.97; n=8 studies) we again did not find an  
15  
16 367 important difference in the magnitude of RRs (ratio of RRs 0.86 (95% CI 0.44, 1.66));  
17  
18 368 P=0.65 (Supplementary file 7). However, when we compared industry sponsored studies,  
19  
20 369 (HR =0.78; n=3 studies) and non-industry sponsored studies, (HR=0.97; n=18 studies) that  
21  
22 370 measured the association using HRs, we found a statistically significant difference in the  
23  
24 371 magnitude of the HRs (ratio of HRs 0.80 (95%CI 0.66, 0.97)); P=0.03 (Figure 3).

25 372  
26 373 In our analysis comparing studies with an author with a COI (RR 0.89; n=2 studies) and those  
27  
28 374 with no COI, (RR 0.99; n= 8 studies) we found no important difference in the magnitude of  
29  
30 375 RRs (ratio of RRs 0.90 (95% CI 0.76-1.07)); P=0.22 (Supplementary file 7). When we  
31  
32 376 compared studies with a COI, (HR =1.00; n= 5 studies) and studies with no COI, (HR=0.93;  
33  
34 377 n=16 studies) that measured the association using HRs, we again found no difference in the  
35  
36 378 magnitude of the HRs (ratio of HRs 1.08 (95% CI 0.99, 1.17)); P=0.12.

37 379  
38 380 **Effect Size, Elevated Blood Pressure / Hypertension: Industry ties v no industry ties,**  
39  
40 381 **and industry sponsorship vs no sponsorship**

41 382 We found no important difference in the magnitude of the HRs for elevated blood pressure /  
42  
43 383 hypertension in studies with industry ties, (HR = 0.89; n =2) and those studies with no  
44  
45 384 industry ties, (HR = 0.78; n= 5) (ratio of HRs 1.14 (95% CI 0.88, 1.49); P=0.32  
46  
47 385 (Supplementary file 7).

48 386  
49  
50 387 All of these studies with industry ties also had industry sponsorship, so the ratio of HRs was  
51  
52 388 the same.

53 389  
54  
55 390 **Favourable conclusions: Industry ties vs no industry ties; industry sponsorship vs no**  
56  
57 391 **sponsorship; COI v no COI**

58 392 There was no clear evidence of an association between the reporting of favourable  
59  
60 393 conclusions and studies with industry ties (4/14) compared to those with no industry ties

1  
2  
3 394 (11/29), RR= 0.75 (95% CI 0.29, 1.95; n=43) (Supplementary file 6). When we compared  
4  
5 395 studies only by industry sponsorship, there was no clear evidence of an association between  
6  
7 396 industry sponsored studies (3/8), compared to studies with no sponsorship (12/35), RR = 1.09  
8  
9 397 (95% CI 0.40, 2.99; n=43). There was again no clear evidence of an association between the  
10  
11 398 reporting of favourable conclusions and studies with an author with a COI (2/10) than those  
12  
13 399 without a COI (13/33), RR= 0.51 (95% CI 0.14, 1.88; n=43 studies).

400

#### 401 **Risk of Bias Assessment by Industry Ties**

402 As every study had an overall high (serious or critical) risk of bias rating, there was no  
403  
404 difference in the proportion of studies at a high risk of bias between those with industry ties,  
405  
406 industry sponsorship or COI and those without industry ties, sponsorship or COI.

405

#### 406 **Concordance between study results and conclusions**

407 Six (of 43) studies, all with unfavorable results, overemphasized the benefits of the dairy  
408  
409 exposure in their conclusions and thus were coded as 'favourable' conclusions.

409 There was no clear evidence of an association between discordant results and conclusions and  
410  
411 studies with industry ties (3/14) than those with no industry ties (3/29), RR = 2.07 (95% CI  
412  
413 0.48, 8.99; n=43) (Supplementary file 6). There was no clear evidence of an association when  
414  
415 comparing studies with industry sponsorship (2/8) to those with no industry sponsorship  
416  
417 (4/35), RR = 2.19 (95% CI 0.48-9.94). There was again no clear evidence of an association  
418  
419 between studies with an author with a COI (2/10) than those with no COI (4/33), RR = 1.65  
420  
421 (95% CI 0.35, 7.72; n=43).

416

#### 417 **DISCUSSION**

418 There was no clear evidence of an association between studies with food industry ties and the  
419  
420 reporting of favourable results and conclusions of observational studies measuring the effects  
421  
422 of dairy foods on cardiovascular disease outcomes. The 'mixed' group of funders we  
423  
424 identified in the industry sponsored studies may influence these results, as the funding effect  
425  
426 may be diluted by this heterogeneous group of sponsors. Unlike in drug studies,<sup>12</sup> the funders  
427  
428 in the studies included in this review were extremely diverse, with Big Food and trade  
429  
430 association jointly sponsoring several studies. Thus, dairy foods are not their sole interest.

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3 425 The meta-analysis of hazard ratios of CVD outcomes found that studies with industry  
4 sponsorship showed a greater benefit from dairy than studies without industry sponsorship,  
5 426 and this difference was statistically significant. The meta-analysis of risk ratios of CVD  
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7 427 outcomes found a similar estimate; however, this was not statistically significant. The likely  
8  
9 428 reason for this was that the meta-analysis of RRs had fewer studies, and so the ratio of RRs  
10  
11 429 could not be as precisely estimated. We found no evidence of a clinically important  
12  
13 430 difference in the magnitude of effect between studies with industry ties or authors with a COI  
14  
15 431 compared to those with no industry ties or no COI for other outcomes.  
16  
17 432  
18 433

19 434 For every study, the overall risk of bias was classified as high (meaning either serious or  
20  
21 435 critical). Therefore, differences in the risk of bias across studies with and without industry  
22  
23 436 ties would not seem to provide an explanation for our findings. However, the version of the  
24  
25 437 ROBINS-E tool that we used may not have been able to adequately discriminate across the  
26  
27 438 studies, as perhaps is indicated by the uniformity in risk of bias classification.<sup>26</sup> Therefore, we  
28  
29 439 cannot rule out the possibility that differences in bias across studies with and without industry  
30  
31 440 ties may partly explain our findings.  
32  
33 441

### 34 442 **Strengths and limitations of this review**

35  
36 443 Our review was prospectively registered in Prospero.<sup>19</sup> We followed explicit inclusion and  
37  
38 444 exclusion criteria, conducted a comprehensive search across multiple databases and hand  
39  
40 445 searched reference lists for the included studies.  
41  
42 446

43 447 For those studies missing a funding or author COI disclosure, we did not contact the authors  
44  
45 448 and we therefore may be underestimating the number of studies with industry ties. The tool  
46  
47 449 that we used to assess the risk of bias is still under development, however it is unlikely any  
48  
49 450 future changes to the tool will affect the risk of bias ratings.<sup>22</sup> We did not analyse studies of  
50  
51 451 low and full fat dairy separately. Industry ties may have different effects on studies of low or  
52  
53 452 full fat dairy foods.  
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## 456 **Agreements and disagreements with other studies or reviews**

457 The observed greater benefit of dairy on CVD outcomes in industry sponsored studies  
458 compared to non-industry sponsored studies corroborates previous research that has  
459 demonstrated studies sponsored by the food industry reported smaller harmful effect sizes for  
460 soft drink consumption, compared with non-industry sponsored studies.<sup>17</sup> It is not consistent,  
461 however, with a recent meta-analysis funded by the Israel Dairy Board that found non  
462 statistically significant differences in the estimated associations between industry and non-  
463 industry funded studies.<sup>18</sup> The differences in the results of our current review and this  
464 previous study can be attributed to a number of important factors in how the studies were  
465 conducted, including how the exposures were classified, the outcomes selected for the meta-  
466 analyses and the analysis method used. For the exposures, our review included yogurt and  
467 cheese, as well as ‘total dairy’ and milk, whereas the Dairy Board study included only ‘total  
468 dairy’ and milk as exposures. We included all outcomes related to CVD, and the Dairy Board  
469 study included only CVD and stroke, as well as Type 2 diabetes. For the analysis method, we  
470 fitted separate meta-analyses for studies that had measured the association using HRs and  
471 those that had used either RRs or ORs, while the Dairy Board study only measured the  
472 associations using RRs.

473

474 The lack of difference in the risks of bias between studies with industry ties and those with no  
475 industry ties, is consistent with a previous review that examined the association of industry  
476 ties with outcomes of studies examining the effect of wholegrain foods on CVD and mortality  
477 that used the same tool to assess risk of bias.<sup>16</sup> These findings have also been shown in  
478 pharmaceutical and tobacco research that have demonstrated industry sponsored studies are  
479 of equal or better internal validity than studies with no sponsorship.<sup>12, 13, 15, 27, 28</sup>

480

## 481 **Implications for clinicians, policy makers and future research**

482 As dietary guidelines depend on an evidence base that should be as free as possible of bias,  
483 the difference in the magnitude of effects between industry sponsored studies compared to  
484 non-industry sponsored studies is concerning. Therefore, the dairy intake recommendations  
485 made in dietary guidelines should account for the potential influence of industry sponsorship  
486 on evidence of health effects.

487

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3 488 Industry sponsors may bias research via different mechanisms, including the design and  
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5 489 conduct of a study, the selective reporting of results and by spinning conclusions,<sup>11</sup> as well as  
6  
7 490 how the questions are asked.<sup>29</sup> It has been suggested that the dairy industry may preferentially  
8  
9 491 fund research on topics which will provide them with more favourable outcomes.<sup>30</sup> The  
10  
11 492 influence of the food industry on the research agenda has been demonstrated in an  
12  
13 493 examination of research topics covered by samples of randomised controlled trials included  
14  
15 494 in systematic reviews of nutrition studies and obesity.<sup>31</sup> It was shown that most food industry  
16  
17 495 studies focused on the manipulations of specific nutrients, and not on dietary behaviours,  
18  
19 496 therefore limiting the public health relevance of rigorous evidence available for use in both  
20  
21 497 systematic reviews and dietary guidelines.<sup>31</sup> The topics examined in cohort studies on the  
22  
23 498 relationship of nutrition and obesity, which tend to focus on more complex exposures than  
24  
25 499 trials, did not demonstrate a similar influence of funding source. However, the disclosure of  
26  
27 500 food industry sponsorship was low, making a comparison difficult.<sup>32</sup>

501

502

### 503 **Conclusion**

504 There was no clear evidence of an association between studies with food industry ties and the  
505 reporting of favourable results and conclusions compared with studies without industry ties.  
506 However, the statistically significant difference in the magnitude of effects identified in  
507 industry sponsored studies compared to non-industry sponsored studies is important in  
508 quantifying industry influence on studies included in dietary guidelines.

1  
2  
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7 511

8  
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11 abstract screening and full article screening for final study inclusion. NC, AF, JD, AL and  
12 SMc conducted data collection and cleaning, LB supervised. NC and JMc undertook all data  
13 analysis. LB advised on methods, statistical analyses, and interpretation of findings. All  
14 authors contributed to the final manuscript. NC and LB are guarantors.  
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35 525 **Data sharing statement:** Available from The University of Sydney data repository. DOI to  
36 be determined.  
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42 528 **Patient consent for publication:** Not required.  
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610 **Figures**

611 **Figure 1. Study Flow Diagram**

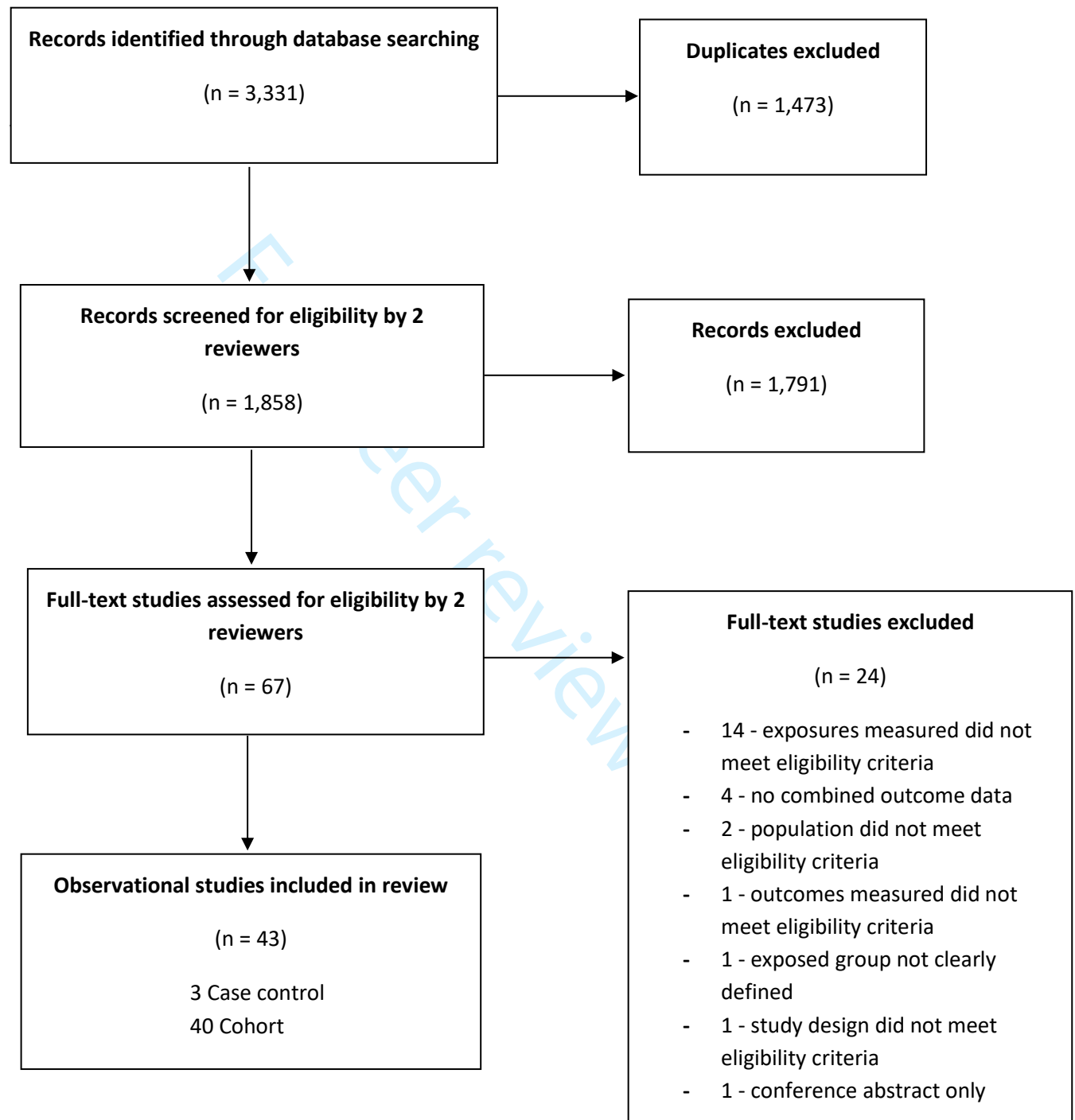
612 **Figure 2. Risk of Bias in Included Studies**

613 **Figure 3. Effect Size, Cardiovascular Disease: Industry sponsorship vs no industry**  
614 **sponsorship, Hazard Ratio**

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For peer review only

**Figure 1. Study Flow Diagram**

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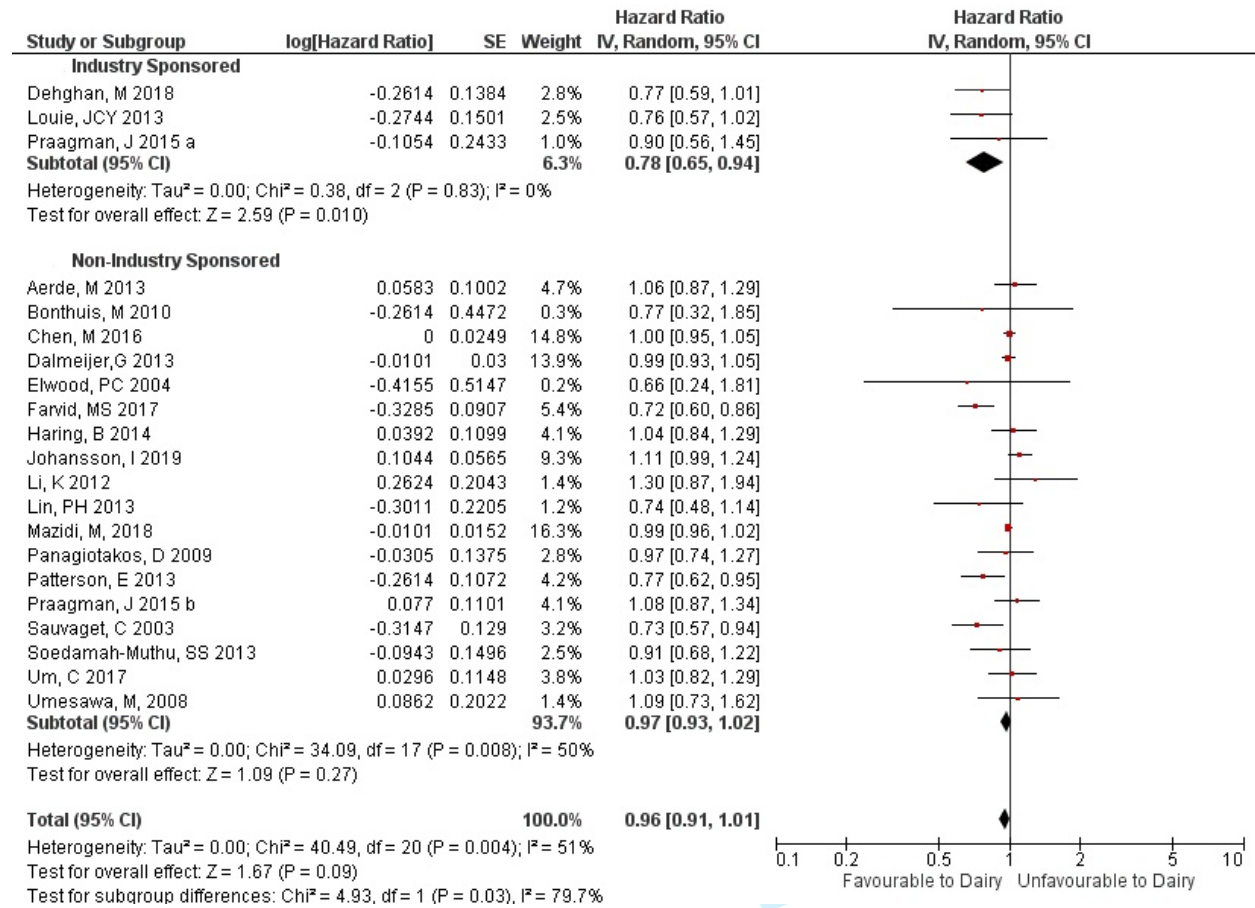
	Confounding	Selection of participants	Classification of exposures	Deviations from intended exposures	Missing data	Measurement of outcomes	Selection of the reported result	Overall bias
Aerde, M 2013	●	○	○	○	○	○	○	●
Al-Delaimy, WK 2003	○	○	○	●	●	●	○	○
Alonso A, 2005	●	○	○	○	○	○	○	●
Altorf-van der Kuil, W 2012	●	○	○	○	○	○	○	●
Avalos, EE 2013	●	○	●	●	○	○	○	●
Bernstein, AM 2012	○	○	○	●	●	○	○	○
Biong, A 2008	○	●	○	●	○	○	○	○
Bonthuis, M 2010	●	○	●	○	○	●	○	●
Buendia, JR 2018	○	○	○	●	○	○	○	○
Chen, M 2016	●	○	○	●	●	●	○	●
Dalmeijer, G 2013	●	○	○	○	○	○	○	●
Dauchet, L 2007	●	○	○	○	●	○	○	●
Dehghan, M 2018	●	○	○	○	○	○	○	●
Elwood, PC 2004	●	○	○	○	○	●	○	●
Engberink, MF 2009	●	○	○	○	○	○	○	●
Farvid, MS 2017	●	○	○	○	○	●	○	●
Haring, B 2014	●	○	○	○	●	○	○	●
He, K 2003	○	○	○	○	●	○	○	○
Heraclides, A 2012	●	○	○	○	○	○	○	●
Johansson, I 2018	●	○	○	○	●	●	○	●
Johansson, I 2019	●	○	○	○	●	●	○	●
Kim, D 2017	●	○	○	○	○	●	○	●

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Larsson, S 2009								
Larsson, SC 2012								
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Lin, PH 2013								
Lockheart, MSK 2007								
Louie, JCY 2013								
Mazidi, M, 2018								
Nettleton, J 2008								
Panagiotakos, D 2009								
Patterson, E 2013								
Praagman, J 2015								
Praagman, J 2015								
Sauvaget, C 2003								
Snijder, MB 2008								
Soedamah-Muthu, SS 2013								
Steffen, LM 2005								
Tavani, A 2002								
Um, C 2017								
Umesawa, M, 2008								
Wang, L 2008								



Figure 3. Effect Size, Cardiovascular Disease, Industry sponsorship vs no Industry sponsorship, Hazard Ratio



## PROSPERO

### International prospective register of systematic reviews

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## Systematic review

Please complete all mandatory fields below (marked with an asterisk \*) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below or click on the icon to see guidance on completing each section.

This record cannot be edited because it has been rejected

### 1. \* Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

The association of food industry ties with findings of studies examining the effect of dairy foods intake with cardiovascular disease and mortality: Systematic review and Meta-analysis: protocol registration:

### 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.

01/09/2016

### 4. \* Anticipated completion date.

Give the date by which the review is expected to be completed.

01/06/2019

### 5. \* Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

## PROSPERO

### International prospective register of systematic reviews

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
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 (e.g. Funded proposal, protocol not yet finalised).

#### 6. \* Named contact.

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

Nicholas Chartres

#### Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr Chartres

#### 7. \* Named contact email.

Give the electronic mail address of the named contact.

ngar0960@uni.sydney.edu.au

#### 8. Named contact address

Give 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.

Give the telephone number for the named contact, including international dialling 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.

University of Sydney

#### Organisation web address:

#### 11. \* Review team members and their organisational affiliations.

## PROSPERO

### International prospective register of systematic reviews

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**

Mr Nicholas Chartres. University of Sydney

Dr Alice Fabbri. The University of Sydney

Agnes Lau. University of California

Dr Joanna Diong. The University of Sydney

Assistant/Associate Professor Joanne Mckenzie. Monash University

Professor Lisa Bero. 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. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

Nicholas Chartres is a scholarship recipient (James Milner PhD scholarship in Pharmacy) from the University of Sydney.

#### Grant number(s)

#### 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.

None

#### 14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

#### 15. \* Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

The objective of this study is to determine if the presence of food industry sponsorship in primary nutrition studies examining the association of dairy 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 primary nutrition studies assessing the association of dairy foods with cardiovascular outcomes with industry sponsorship differ in their risk of bias compared with studies with no or other sources of sponsorship.

#### 16. \* Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

We will search the following databases from 2000-March 2019: Ovid MEDLINE; CINAHL; PubMed;

Cochrane Library; and ScienceDirect. No language restrictions will be applied



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#### 17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy. Do NOT provide links to your search results.

[https://www.crd.york.ac.uk/PROSPEROFILES/129659\\_STRATEGY\\_20190322.pdf](https://www.crd.york.ac.uk/PROSPEROFILES/129659_STRATEGY_20190322.pdf)

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

#### 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.

To determine whether industry sponsorship and/or study methods are associated with the results and/or conclusions of primary nutrition studies assessing the association of dairy foods and cardiovascular outcomes.

#### 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.

We will include primary research studies of any design that quantitatively examine the association of dairy foods with cardiovascular outcomes in healthy adults.

#### 20. \* Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

- The study quantitatively measures the effects of dairy consumption in humans.
- The study evaluates the effectiveness, efficacy or harms of dairy consumption.
- The study compares dairy food to control OR dairy food to other foods OR different levels of dairy consumption
- The study evaluates cow, goat or sheep milk, yogurt, cheese or custard. We will include and use the studies definition of dairy it is broader than milk, yogurt, cheese or custard.
- The study evaluates skim, low or full fat dairy products
- The study evaluates the effect of nutrients, e.g calcium and vitamin D when consumed within a dairy product

#### 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). The preferred format includes details of both inclusion and exclusion criteria.

Dairy vs Dairy (different doses) Dairy vs Dairy (different fat content) Dairy vs No dairy Dairy vs Other food

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### International prospective register of systematic reviews

Other (mixed intervention)

#### 22. \* Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

RCTs, Controlled Trials, Cohort, Case-control, Pre/Post, Other/Various

#### 23. Context.

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

- The study has a test of interest (e.g. risk ratio/hazard ratio) of cardiovascular mortality, nonfatal heart attack, stroke, etc.) and/or the surrogate outcomes of Blood Pressure (mmHg)

#### 24. \* Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

a. Primary Outcome 1 and 2

- o Statistical significance of results
- o Effect size of outcomes

For each study, the result reported for each primary outcome will be categorized as:

(1) Favourable if the result are statistically significant ( $p < 0.05$  or 95% confidence interval [CI] excluding no difference) and in the direction of dairy being more efficacious, less harmful or no more harmful than the comparator;

(2) Unfavourable if the result was statistically significant (e.g.  $P < 0.05$  or 95% confidence interval including the possibility of no difference) in the direction of the comparator being more efficacious or less harmful.

We will also extract the effect estimates for primary outcomes.

We will classify the results of the study as favourable if the stated primary outcome is reported as favourable.

If the study has multiple primary outcomes we will report the study as favourable if at least one of the outcomes is reported as favourable.

b. Primary Outcome 3 (Conclusions)

The conclusions reported in the published papers will be categorized as:

(1) Favourable if the dairy intervention was preferred to comparator

(2) Unfavourable if the comparator intervention was preferred to the test one OR if the test intervention

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showed a risk increase.

#### \* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

As this is not relevant to our study, we have nothing to include.

#### 25. \* Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

We used the QUOROM (Risk of Bias) tool for randomised studies (15) 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-I tool for non-randomized studies (ROBINS-I)(16), which also measures bias across 7 domains.

#### d. Secondary Outcome 2 (Concordance between results and conclusions)

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'

#### \* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

As this is not relevant to our study, we have nothing to include.

#### 26. \* Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

##### Selection Process

Two investigators (NC & AF) will independently screen the titles and abstracts of all retrieved records for obvious exclusions. Two investigators (NC & AF) will then assess the remaining papers based on full text, applying the aforementioned inclusion criteria for included studies. Agreement will be reached on any discrepancies by consensus between the two assessors. If agreement cannot be reached, a third assessor (LB) will make a decision. The reasons for the eligible papers being excluded will be described in

## PROSPERO

### International prospective register of systematic reviews

'Characteristics of excluded papers' table.

Data collection process

- a) Title of the paper
- b) Year of publication
- c) Study design
- d) Comparisons:
- e) Sample size of study
- f) Mean age of participants
- g) Intervention or observation period
- h) Definition of intervention and exposure
- i) Risk of Bias
- j) Primary Hypothesis of the study (Verbatim)
- k) Primary outcomes measures
- l) Conclusion
- m) Concordance between conclusions and results
- n) Industry Sponsorship
- o) Role of the Funder: Information about the role of the sponsor as stated in the study
- p) The institutional affiliation of the corresponding author will be obtained from the article and classified into the following categories
- q) Country of origin (verbatim)
- r) Author COI

#### 27. \* Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

We will use the Cochrane Risk of Bias tool for randomised studies (15) 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-I tool for non-randomized studies (ROBINS-I)(16), which also measures bias across 7 domains.

#### 28. \* Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

To test our hypothesis that studies with dairy industry sponsorship will be more likely to have favourable

## PROSPERO

### International prospective register of systematic reviews

1 results, we will compare the risk of dairy industry sponsored studies having a favourable result with the risk  
2 of non-dairy industry funded studies having a favorable result. Using Rev Manager we will calculate the  
3 pooled risk ratio (RR) and its 95% confidence interval using the Mantel-Haenszel fixed-effect model.

4 However, when substantial heterogeneity is observed, we will use an inverse variance DerSimonian-Laird  
5 random-effects model. We will assess heterogeneity using  $I^2$  and use a random-effects model when  
6 statistical heterogeneity is substantial, defined as an  $I^2$  50%.

7 To test our hypothesis that effect estimates will differ between studies with dairy industry sponsorship and  
8 those without sponsorship, we will compare the pooled effect estimates from dairy vs. non-dairy sponsored  
9 studies. We will pool the effect estimates of homogenous studies measuring dichotomous outcomes, (e.g.  
10 RR, HR, OR for all-cause mortality, CVD mortality, cardiovascular events, etc) calculating pooled risk ratios  
11 as described above. Blood pressure is a continuous outcome, so we will attempt to pool homogeneous  
12 studies and measure the mean difference from baseline measures.

13 To test our hypothesis that studies with dairy industry sponsorship would be more likely to have favourable  
14 conclusions we will compare the risk of dairy industry sponsored studies having favourable conclusions with  
15 the risk of non-dairy industry funded studies having a favorable conclusion. We will calculate the pooled risk  
16 ratio (RR) and its 95% confidence interval using the Mantel-Haenszel fixed-effect model. However, when  
17 substantial heterogeneity is observed, we will use an inverse variance DerSimonian-Laird random-effects  
18 model. We will assess heterogeneity using  $I^2$  and use a random-effects model when statistical heterogeneity  
19 is substantial, defined as an  $I^2$  50%.

#### 29. \* Analysis of subgroups or subsets.

20 State any planned investigation of 'subgroups'. Be clear and specific about which type of study or  
21 participant will be included in each group or covariate investigated. State the planned analytic approach.

22 We will conduct an a priori subgroup analysis on low fat and full fat dairy products to determine if studies  
23 measuring the effects of low fat products have different results from studies that measure full fat dairy  
24 products.

25 We will conduct an a priori subgroup analysis by the risks of bias of the included studies to determine if  
26 studies that have a high risk of bias have different results from studies that have a low risk of bias. We  
27 hypothesize that industry sponsored studies will have the same level of risk of bias as non-industry  
28 sponsored studies.

#### 30. \* Type and method of review.

29 Select the type of review and the review method from the lists below. Select the health area(s) of interest for  
30 your review.

##### 31 Type of review

32 Cost effectiveness

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**International prospective register of systematic reviews**

1  
 2  
 3  
 4 No  
 5 Diagnostic  
 6 No  
 7 Epidemiologic  
 8 No  
 9 Individual patient data (IPD) meta-analysis  
 10 No  
 11 Intervention  
 12 No  
 13  
 14 Meta-analysis  
 15 Yes  
 16 Methodology  
 17 No  
 18 Narrative synthesis  
 19 No  
 20  
 21 Network meta-analysis  
 22 No  
 23 Pre-clinical  
 24 No  
 25 Prevention  
 26 No  
 27 Prognostic  
 28 No  
 29  
 30 Prospective meta-analysis (PMA)  
 31 No  
 32 Review of reviews  
 33 No  
 34 Service delivery  
 35 No  
 36  
 37 Synthesis of qualitative studies  
 38 No  
 39 Systematic review  
 40 Yes  
 41 Other  
 42 No  
 43  
 44  
 45 **Health area of the review**  
 46 Alcohol/substance misuse/abuse  
 47 No  
 48  
 49 Blood and immune system  
 50 No  
 51 Cancer  
 52 No  
 53 Cardiovascular  
 54 Yes  
 55  
 56 Care of the elderly  
 57 No  
 58 Child health  
 59 No  
 60 Complementary therapies

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4 No  
5 Crime and justice  
6 No  
7 Dental  
8 No  
9 Digestive system  
10 No  
11 Ear, nose and throat  
12 No  
13 Education  
14 No  
15 Endocrine and metabolic disorders  
16 No  
17 Eye disorders  
18 No  
19 General interest  
20 No  
21 Genetics  
22 No  
23 Health inequalities/health equity  
24 No  
25 Infections and infestations  
26 No  
27 International development  
28 No  
29 Mental health and behavioural conditions  
30 No  
31 Musculoskeletal  
32 No  
33 Neurological  
34 No  
35 Nursing  
36 No  
37 Obstetrics and gynaecology  
38 No  
39 Oral health  
40 No  
41 Palliative care  
42 No  
43 Perioperative care  
44 No  
45 Physiotherapy  
46 No  
47 Pregnancy and childbirth  
48 No  
49 Public health (including social determinants of health)  
50 Yes  
51 Rehabilitation  
52 No  
53 Respiratory disorders  
54 No  
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## PROSPERO

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Service delivery

No

Skin disorders

No

Social care

No

Surgery

No

Tropical Medicine

No

Urological

No

Wounds, injuries and accidents

No

Violence and abuse

No

### 31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.

English

There is not an English language summary

### 32. \* Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Australia

### 33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

### 34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

**No I do not make this file publicly available until the review is complete**

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

### 35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.



## PROSPERO

### International prospective register of systematic reviews

#### Do you intend to publish the review on completion?

Yes

#### 36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

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

#### 37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

CRD42017055841 The association of industry sponsorship with outcomes of studies examining the effect of intake of wholegrain foods with cardiovascular disease and mortality: protocol

#### 38. \* Current review status.

Review status should be updated when the review is completed and when it is published. For new registrations the review must be Ongoing.

Please provide anticipated publication date

Review\_Ongoing

#### 39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

#### 40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

**Supplementary file 2.** Search Strategy OVID Medline: Dairy, CVD, Adults

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1. Randomized controlled trial\*.tw.

2. experimental design.tw.

3. intervention\*.tw.

4. (RCT\* or rct\*).tw.

5. random\* control\* trial\*.tw.

6. clinical trial\*.tw.

7. field trial\*.tw.

8. community trial\*.tw.

9. controlled clinical trial\*.tw.

10. pragmatic trial\*.tw.

11. observational stud\*.tw.

12. cohort stud\*.tw.

13. prospective cohort\*.tw.

14. retrospective cohort\*.tw.

15. case control\*.tw.

16. ecological stud\*.tw.

17. time series analys?s\*.tw.

18. before-after stud\*.tw.

19. pre-post stud\*.tw.

20. follow up stud\*.tw.

21. comparative stud\*.tw.

22. evaluation stud\*.tw.

23. dairy.mp.

24. dairy intake\*.mp.

- 1
- 2
- 3 25. dairy consumption.mp.
- 4
- 5 26. dairy food\*.mp.
- 6
- 7 27. Dairy Products/ or dairy product\*.mp.
- 8
- 9 28. dairy serv\*.mp.
- 10
- 11 29. dairy type\*.mp.
- 12
- 13 30. dairy source\*.mp.
- 14
- 15
- 16 31. (calcium adj15 food sourc\*).mp. [mp=title, abstract, original title, name of substance word,
- 17 subject heading word, keyword heading word, protocol supplementary concept word, rare
- 18 disease supplementary concept word, unique identifier]
- 19
- 20 32. (vitamin D adj15 food sourc\*).mp. [mp=title, abstract, original title, name of substance word,
- 21 subject heading word, keyword heading word, protocol supplementary concept word, rare
- 22 disease supplementary concept word, unique identifier]
- 23
- 24 33. (milk and (cow or goat or sheep)).mp. [mp=title, abstract, original title, name of substance
- 25 word, subject heading word, keyword heading word, protocol supplementary concept word, rare
- 26 disease supplementary concept word, unique identifier]
- 27
- 28 34. yogurt.mp. or Yogurt/
- 29
- 30 35. cheese.mp. or Cheese/
- 31
- 32 36. custard.mp.
- 33
- 34
- 35 37. (milk and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of
- 36 substance word, subject heading word, keyword heading word, protocol supplementary concept
- 37 word, rare disease supplementary concept word, unique identifier]
- 38
- 39 38. (yogurt and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of
- 40 substance word, subject heading word, keyword heading word, protocol supplementary concept
- 41 word, rare disease supplementary concept word, unique identifier]
- 42
- 43 39. Milk/
- 44
- 45 40. 23 or 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
- 46 39
- 47
- 48 41. cardiovascular disease.mp. or exp Cardiovascular Diseases/
- 49
- 50 42. coronary\*.tw.
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- 3 43. heart\*.tw.
- 4
- 5 44. cardia\*.tw.
- 6
- 7 45. cardio\*.tw.
- 8
- 9 46. myocard\*.tw.
- 10
- 11 47. isch?em\*.tw.
- 12
- 13 48. angina\*.tw.
- 14
- 15 49. ventric\*.tw.
- 16
- 17 50. tachycardi\*.tw.
- 18
- 19 51. pericard\*.tw.
- 20
- 21 52. endocardi\*.tw.
- 22
- 23 53. atrial fibrillat\*.tw.
- 24
- 25 54. arrhythmi\*.tw.
- 26
- 27 55. athero\*.tw.
- 28
- 29 56. arterio\*.tw.
- 30
- 31 57. exp Atherosclerosis/
- 32
- 33 58. exp Arteriosclerosis/
- 34
- 35 59. HDL.tw.
- 36
- 37 60. LDL.tw.
- 38
- 39 61. VLDL.tw.
- 40
- 41 62. lipid\*.tw.
- 42
- 43 63. lipoprotein\*.tw.
- 44
- 45 64. triacylglycerol\*.tw.
- 46
- 47 65. exp Hyperlipidemias/
- 48
- 49 66. hyperlipid\*.tw.
- 50
- 51 67. hypercholesterol\*.tw.
- 52
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- 3 68. hypercholester?emia\*.tw.
- 4
- 5 69. hypertriglycerid?emia\*.tw.
- 6
- 7 70. exp Cholesterol/
- 8
- 9 71. cholesterol\*.tw.
- 10
- 11 72. exp Stroke/
- 12
- 13 73. stroke\*.tw.
- 14
- 15 74. CVA.tw.
- 16
- 17 75. cerebrovasc\*.tw.
- 18
- 19 76. "vascular accident".tw.
- 20
- 21 77. TIA.tw.
- 22
- 23 78. cerebral vascular.tw.
- 24
- 25 79. thrombo\*.tw.
- 26
- 27 80. emboli\*.tw.
- 28
- 29 81. apoplexy.tw.
- 30
- 31 82. (brain adj2 accident\*).tw.
- 32
- 33 83. ((brain\* or cerebral or lacunar) adj2 infarct\*).tw.
- 34
- 35 84. Hypertension/
- 36
- 37 85. exp Blood Pressure/
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- 39 86. hypertensi\*.tw.
- 40
- 41 87. blood pressure\*.tw.
- 42
- 43 88. systolic blood pressure.tw.
- 44
- 45 89. diastolic blood pressure.tw.
- 46
- 47 90. peripheral arter\* disease\*.tw.
- 48
- 49 91. (coronar\$ adj5 (bypas\$ or graft\$ or disease\$ or event\$)).tw.
- 50
- 51 92. (cerebrovasc\$ or cardiovasc\$ or mortal\$ or angina\$ or stroke or strokes).tw.
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3 93. (myocardi\$ adj5 (infarct\$ or revascular\$ or ischaemi\$ or ischemi\$)).tw.  
4

5 94. (morbid\$ adj5 (heart\$ or coronar\$ or ischaem\$ or ischem\$ or myocard\$)).tw.  
6

7 95. (vascular\$ adj5 (peripheral\$ or disease\$ or complication\$)).tw.  
8

9 96. (heart\$ adj5 (disease\$ or attack\$ or bypass\$)).tw.  
10

11 97. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or  
12 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73  
13 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or  
14 90 or 91 or 92 or 93 or 94 or 95 or 96  
15

16 98. 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  
17 19 or 20 or 21 or 22  
18

19 99. 40 and 97 and 98  
20

21 100. limit 99 to yr="2000 - 2019"  
22

23 101. limit 100 to humans  
24

25 102. limit 101 to "all adult (19 plus years)"  
26  
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## Supplementary file 3: List of excluded studies and reasons for exclusion

Author	Title	Reason for Exclusion
Akbaraly, T 2013 <sup>1</sup>	Does overall diet in midlife predict future aging phenotypes? A cohort study	Dietary patterns only were assessed, not dairy foods
Anderson, LA 2011 <sup>2</sup>	Dietary Patterns and Survival of Older Adults	No relevant outcomes were measured
Baylin, A 2003 <sup>3</sup>	High 18:2 trans-fatty acids in adipose tissue are associated with increased risk of nonfatal acute myocardial infarction in Costa Rican adults	Effects of dairy foods not measured
Beydoun, MA 2018 <sup>4</sup>	Dairy product consumption and its association with metabolic disturbance in a prospective study of urban adults	Groups exposed to dairy not clearly defined
Biong, AS 2006 <sup>5</sup>	Intake of milk fat, reflected in adipose tissue fatty acids and risk of myocardial infarction: a case-control study	Effects of dairy foods not measured
Chen, y 2013 <sup>6</sup>	Prospective investigation of major dietary patterns and risk of cardiovascular mortality in Bangladesh	Dietary patterns only were assessed, not dairy foods
Ding, M 2017 <sup>7</sup>	Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study	Not an observational design study
Eguchi, E 2012 <sup>8</sup>	Healthy lifestyle behaviours and cardiovascular mortality among Japanese men and women: the Japan collaborative cohort study	Dietary patterns only were assessed, not dairy foods
Geleijnse, JM 2017 <sup>9</sup>	Dietary Patterns in Relation to Cardiovascular Disease Incidence and Risk Markers in a Middle-Aged British Male Population: Data from the Caerphilly Prospective Study	Dietary patterns only were assessed, not dairy foods
Goldbohm, RA 2011 <sup>10</sup>	Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands	No combined outcome data
Julián-Almárcegui, C 2016 <sup>11</sup>	Association of heart rate and blood pressure among European adolescents with usual food consumption: The HELENA study	Participants were adolescents, not adults
Larsson, SC 2018 <sup>12</sup>	Dietary patterns, food groups, and incidence of aortic valve stenosis: A prospective cohort study	Dietary patterns only were assessed, not dairy foods
Lupton, BS 2003 <sup>13</sup>	The Finnmark Intervention Study: is it possible to change CVD risk factors by community-based intervention in an Arctic village in crisis?	No combined outcome data
Meyer, J 2011 <sup>14</sup>	Dietary patterns, subclinical inflammation, incident coronary heart disease and mortality	Dietary patterns only were assessed, not dairy foods

	in middle-aged men from the MONICA/KORA Augsburg cohort study	
Michaelsson, K 2013 <sup>15</sup>	Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study	Dietary calcium only was assessed, not dairy foods
Oomen, CM 2000 <sup>16</sup>	Arginine intake and risk of coronary heart disease mortality in elderly men	Effects of dairy foods not measured
Paillard, F 2015 <sup>17</sup>	Cardiovascular risk and lifestyle habits of consumers of a phytosterol-enriched yogurt in a real-life setting	Yogurt was enriched with phytosterols
Praagman, J 2016 <sup>18</sup>	The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort	Effects of dairy foods not measured
Streppel, MT 2014 <sup>19</sup>	Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study	Dietary patterns only were assessed, not dairy foods
Umesawa, M 2006 <sup>20</sup>	Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study	No combined outcome data
van der Pols, J C 2009 <sup>21</sup>	Childhood dairy and calcium intake and cardiovascular mortality in adulthood: 65-year follow-up of the Boyd Orr cohort	Participants were children, not adults
Warensjo, E 2009 <sup>22</sup>	Stroke and plasma markers of milk fat intake – a prospective nested case-control study	Effects of dairy foods not measured
Warensjo, E 2009 <sup>23</sup>	Milk Fat Biomarkers and the Risk of a First Ever Acute Myocardial Infarction - A Prospective Nested Case-Control Study. <i>Journal of the American Dietetic Association.</i> 2009;1	Poster presentation only, full study not available
Warensjo, E 2010 <sup>24</sup>	Biomarkers of milk fat and the risk of myocardial infarction in men and women: a prospective, matched case-control study	No combined outcome data

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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 dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Aerde, M 2013 <sup>(1)</sup>	Cohort	12.4 years	1,956 men & women	61.6 years	Total Dairy, 271 g/day per SD of the mean intake for Total dairy (all dairy products except butter)		Fatal CVD	Non-Industry <sup>1</sup>	Yes <sup>a</sup>
Al-Delaiimy, WK 2003 <sup>(2)</sup>	Cohort	12 years	39,800 men	40-75 years	Dairy Calcium Q5, 819 mg/day (median) (dairy calcium intake summed the calcium intake from whole milk, skim or low-fat milk, yogurt, ice cream, cottage cheese, and other cheese was summed)	Q1, 106 mg/day	Fatal Ischemic Heart Disease	Non Industry <sup>2</sup>	No <sup>b</sup>
Alonso A, 2005 <sup>(3)</sup>	Cohort	27 months	5,880 men & women	37 years	Dairy Q 5, 798.8 g/day (whole-fat milk, partially skim milk, skim milk, condensed milk, whipped cream, yogurt, skim yogurt, milk-shake, cottage cheese or junket, petit Suisse cheese, spreadable cheese wedges, soft unripened cheese, other cheese, custard, and ice cream)	Q 1, 155.6 g/day	Hypertension	Non-industry <sup>3</sup>	No <sup>c</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Altorf-van der Kuil, W2012 <sup>(4)</sup>	Cohort	Mean follow up 7.5 years	3,588 men & women	44 years	Dairy Protein T3, $\geq 27$ g/day (dairy protein was calculated as protein from milk, yogurt, coffee creamer, curd, pudding, porridge, custard, whipped cream and cheese)	T1, $\leq 19$ g/day	Hypertension	Industry <sup>4</sup>	Yes <sup>d</sup>
Avalos, EE 2013 <sup>(5)</sup>	Cohort	Mean follow up 16.2 years	1,759 men & women	70.6 years men, 70.1 women	Whole Milk, Non-Fat Milk, Yogurt & Cheese, Sometimes/often (included daily, 4–6 times/week, 1–3 times/week and 1–3 times/months)	Rarely/never (included never & 1–11 times/year)	Incident CHD	Non-industry <sup>5</sup>	No <sup>e</sup>
Bernstein, AM 2012 <sup>(6)</sup>	2 Cohorts	26 and 22 years of follow-up in women and men, respectively	127,160 (43 150 men 84 010 women)	Men 40 to 75 years, Woman 30 to 55 years	Whole Fat Q 5, Men 2.55 servings/day, Woman 2.81 servings/day (whole milk, ice cream, hard cheese, full fat cheese, cream, sour cream, cream cheese, butter)  Low Fat Q5, Men 2.64 servings/day, Women 2.20 servings/day (skim/low-fat milk, 1% and 2% milk, yogurt, cottage and ricotta cheeses, low-fat cheese, sherbet)	Q 1, Men 0.21 servings/day, Woman 0.34 servings/day.  Low Fat Q1, Men 0.11 servings/day, Women 0.07 servings/day	Total Stroke	Non-industry <sup>6</sup>	Yes <sup>f</sup>
Biong, A 2008 <sup>(7)</sup>	Case Control		218 men & women	62.4 years	Dairy Fat, $> 34.1$ g/day	$<14.6$ g/day	First Myocardial Infarction	Industry <sup>7</sup>	Yes <sup>g</sup>

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Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Bonthuis, M 2010 <sup>(8)</sup>	Cohort	Mean 14.4 years	1,529 men & women	25–78 years	Total Dairy T3, 599 g/day (median) ('low-fat dairy products was computed by adding daily servings (in grams) of skim milk, low-fat milk, low-fat yoghurt, cottage or ricotta cheese, whereas the food group 'high-fat/unmodified dairy' included whole milk, cream, ice cream, yoghurt, full-fat cheese and custard. Total dairy intake was the sum of intake of all these dairy foods)	T1, 174 g/day	Cardiovascular Disease Mortality	Non-Industry <sup>8</sup>	No <sup>h</sup>
Buendia, JR 2018 <sup>(9)</sup>	3 Cohorts	30 years of follow-up in NHS, 20 years in NHS II, 24 years in the HPFS	NHS (N=69298), NHS II (N=84368), HPFS (N=30512)	Mean baseline ages in the 3 cohorts were 44.6, 35.8, and 50.7 years, respectively	Total Dairy Q4, 3 - <6 servings/day (total dairy intake included: milk (skim, low-fat, whole), ice cream, sherbet/ frozen yogurt, cheese (cottage, ricotta, hard, sliced), and yogurt (all types)	Q1, <0.5 servings/day	High Blood Pressure	Industry <sup>9</sup>	No <sup>i</sup>
Chen, M 2016 <sup>(10)</sup>	3 Cohorts	24 years in the HPFS, 32 years NHS, 20 years in NHS II	222,234 - 43,652 men HPFS, 87,907 women NHS, 90,675 women NHS II	40–75 years HPFS, 30–55 years NHS, 25–42 y NHS II	Dairy Fat, Q5	Q1	CVD	Non-Industry <sup>10</sup>	No <sup>i</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Dalmeijer, G 2013 <sup>(11)</sup>	Cohort	13 years	33,625 men & women	49.0 years	Total dairy and its subtypes were evaluated as continuous variables per standard deviation of the mean intake which is 265 g/d for total dairy (total dairy included all dairy food products except for butter and ice cream. Milk and milk products included all kinds of milk, yogurt, coffee creamers, curd, pudding, porridge, custard, and whipping cream)		Incident of Coronary Heart Disease & Incident Stroke	Non-Industry <sup>11</sup>	Yes <sup>k</sup>
Dauchet, L 2007 <sup>(12)</sup>	Cohort	5.4 years	2,341 men & women	Men 52.7 years, Women 46.9 years	Dairy Q4, 456 g/day (dairy products including milk, cheese, yogurt, and other dairy products)	Q1, 84 g/day	Systolic & Diastolic Blood Pressure	Non-Industry <sup>12</sup>	No <sup>l</sup>

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Study ID	Study Deign	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Dehghan, M 2018 <sup>(13)</sup>	Cohort	9.1 yrs	136,384 men & women	50·1 years	Dairy Q4, >2 servings/day (median) (dairy comprised milk, yoghurt, various types of cheese, yoghurt drink, and mixed dishes prepared with dairy. Mixed dishes prepared with dairy were dis- aggregated into their constituents and a proportional weight was assigned to each component. Then each component was included in the related dairy group.	Q1, 0 servings/day	Cardiovascular Mortality or Major Events	Industry <sup>13</sup>	No <sup>m</sup>
Elwood, PC 2004 <sup>(14)</sup>	Cohort	20-24 years	2,403 men	45-59 years	Milk Q4, >1 pint per day	Q1, None	Vascular Event	Non-Industry <sup>14</sup>	No disclosure

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Engberink, MF 2009 <sup>(15)</sup>	Cohort	6 years	2,245 men & women	>55 years	Dairy Q4, 691 g/day (i.e. 4.5 servings/day) (median intake) (calculated total dairy intake by summing the intake of individual dairy items, except butter and ice cream. The category "milk and milk products" included all kinds of milk, yogurt, coffee creamer, curd, pudding, porridge, custard, and whipped cream. The category "cheese" included all kinds of cheese products, ie, soft cheese, hard cheese, and cheese spreads)	Q1, 164 g/day (i.e. 1 serving/day) (median intake)	Hypertension	No disclosure	No <sup>a</sup>
Farvid, MS 2017 <sup>(16)</sup>	Cohort	8 years	42,403 men & women	51.6 years	Total Dairy Q5, 2.4 servings/day (median) (total dairy product items listed in the food frequency questionnaire included milk, cheese, yogurt, liquid yogurt (doogh), dried yogurt paste (kashk), and cream)	Q1, 0.4 servings/day (median)	Cardiovascular Disease Mortality	Non-Industry <sup>15</sup>	No <sup>a</sup>
Haring, B 2014 <sup>(17)</sup>	Cohort	22 years (median)	12,066 men & women	45-64 years	Dairy Protein Q5, 2.9 servings/day	Q1, 0.1 median servings/day	Coronary Heart Disease	Non-Industry <sup>16</sup>	No <sup>a</sup>
He, K 2003 <sup>(18)</sup>	Cohort	14 years	43,732 men	40-75 years	High Fat Dairy Q5, $\geq 1$ /day	Q1, <1/week	Ischaemic & Haemorrhagic Stroke	Non-Industry <sup>17</sup>	No <sup>a</sup>



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Study ID	Study Deign	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Heraclides, A 2012 <sup>(19)</sup>	Cohort	10 years	1,750 men & women	Men 43 years, Women 53 years	Total Dairy T3, 309.0 g/day (median) (full-fat milk; semi-skimmed milk; skimmed milk; milk-containing beverages (full fat, semi-skimmed and skimmed); full-fat cheese; low-fat cheese; full-fat yoghurt; low-fat yoghurt; fruit-flavoured yoghurt (full fat and low fat); and milk-based puddings)	T1, 224.1 g/day	Incident Hypertension	Non-Industry <sup>18</sup>	Yes <sup>r</sup>
Johansson, I 2018 <sup>(20)</sup>	Cohort	8-12 years	27,682 men & women	29-65 years	Dairy Q 5, 7.1 servings/day (median)	Q1, 1.6 servings/day (median)	Blood Pressure	Non-Industry <sup>19</sup>	No <sup>s</sup>
Johansson, I 2019 <sup>(21)</sup>	Cohort	14.2 years	108,065 men & women	calculated mean = 52.5 years *	High Fat & Low Fat Non-Fermented Milk & Cheese Q 4, high dose	Q1, low dose	Myocardial Infarction & Stroke	Non-Industry <sup>20</sup>	No <sup>t</sup>
Kim, D 2017 <sup>(22)</sup>	Cohort	67·4 months	4,335 men & women	40-69 years	Total Dairy Q 5, >7 servings/week	Q 1, <1 servings/week	Blood Pressure	Non-Industry <sup>21</sup>	No <sup>u</sup>
Larsson,S 2009 <sup>(23)</sup>	Cohort	13.6 years	26,556 men	50-69 years	Dairy Q5, 1295.6 g/day (median) (including low-fat milk, whole milk, sour milk, yogurt, cheese, cream, ice cream, and butter)	Q1 286.5 g/day	Cerebral Infarction, Intracerebral Haemorrhage, Subarachnoid Hemorrhage	Non-Industry <sup>22</sup>	No disclosure

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Larsson, SC 2012 <sup>(24)</sup>	Cohort	10.2 years	74,961 men & women	45-83 years	Dairy Q5, 9.3 servings/day (median) (dairy foods included low-fat milk (0.5% fat), medium-fat milk (1.5% fat), full-fat milk (3% fat), milk in pancakes, low-fat sour milk/yogurt (0.5% fat), full-fat sour milk/yogurt (3% fat), cottage cheese (4% fat), low-fat cheese (10%-17% fat), full-fat cheese (approximately 28% fat), ice cream, cream, and creme fraiche)	Q1, 2.3 servings/day	Total Stroke	Non-Industry <sup>23</sup>	No <sup>v</sup>
Li, K 2012 <sup>(25)</sup>	Cohort	11 years	23,980 men & women	35-64 years	Dairy Calcium Q4, 780 mg/day	Q1, 188 mg/day	CVD Mortality	Non-Industry <sup>24</sup>	No <sup>w</sup>
Lin, PH 2013 <sup>(26)</sup>	Cohort	12 years	2,061 men & women	45.8 years (no information for stroke group)	Dairy T3, (dairy milk of any kind, cheese, yogurt).	T1	Total Stroke	Non-Industry <sup>25</sup>	No <sup>x</sup>
Lockheart, MSK 2007 <sup>(27)</sup>	Case Control		211 men & women	62.5 years cases and 62.2 years controls	Low Fat Dairy T3, 618 g/day (Low-fat milk, skimmed milk, light sour cream)	T 1, 48 g/day	First Myocardial Infarction	Industry <sup>26</sup>	No disclosure
Louie, JCY 2013 <sup>(28)</sup>	Cohort	15 years	2,625 men & women	49-97 years	Total Dairy T3, 2.9 servings/day (median) (included all dairy foods)	T1, 0.6 servings/day	Total CVD	Industry <sup>27</sup>	No disclosure
Mazidi, M, 2018 <sup>(29)</sup>	Cohort	76.4 months	24,474 men & women	47.6 years	Total Dairy Q4, 3.08 cup equivalent servings/day (total dairy, milk, cheese, and yogurt)	Q1, 0.25 cup equivalent servings/day	CHD Mortality & Cerebrovascular Disease mortality	Non-Industry <sup>28</sup>	No <sup>y</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Ness, AR 2001 <sup>(30)</sup>	Cohort	25 years	5,765 men	35-64 years	Milk T3, > 1 pint (= 0.568 liters)	T1, None	Cardiovascular Disease Deaths	Non-Industry <sup>29</sup>	No <sup>z</sup>
Nettleton, J 2008 <sup>(31)</sup>	Cohort	13.3 years	14,153 men & women	45 to 64 years	High Fat Dairy, per 1 daily serving difference in food group intake		Incident Heart Failure	Non Industry <sup>30</sup>	No <sup>aa</sup>
Panagiotakos, D 2009 <sup>(32)</sup>	Cohort	5 years	3,042 men & women	18-89 years	Low Fat Dairy, 1-unit increase in components' scores (0%, 2% or total fat), like cheese, yogurt, milk)		CVD Events	Non-Industry <sup>31</sup>	No disclosure
Patterson, E 2013 <sup>(33)</sup>	Cohort	11.6 years	33,636 women	48-83 years	Total Dairy, Q5 8.4 servings/day (median) (total dairy intake was the sum of milk [full-fat ( $\geq 3.0\%$ fat), semi-skimmed ( $\leq 1.5\%$ fat), skimmed (0.5% fat), and pancakes], cultured milk/yogurt [full-fat ( $\geq 3.0\%$ fat) and low-fat ( $\leq 1.5\%$ fat)], cheese [full-fat ( $> 17\%$ fat), low-fat ( $\leq 17\%$ fat), and cottage cheese/ quark], cream and creme fariche (full fat and low fat) intakes)	Q1, 2.2 servings/day	Myocardial Infarction	Non Industry <sup>32</sup>	No <sup>bb</sup>
Praagman, J 2015 (a) <sup>(34)</sup>	Cohort	13.3 years (median)	4,235 men & women	66.9 years	Total Dairy, T3 >400g/day (total dairy included milk, buttermilk, yogurt, coffee creamer, curd, pudding, porridge, custard, whipped cream, ice cream, and cheese, but not butter)	Total Dairy, T 1 <200 g/day	Fatal Stroke & Fatal CHD	Industry <sup>33</sup>	Yes <sup>cc</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Praagman, J 2015 (b) <sup>(35)</sup>	Cohort	15 years	34,409 men & women	Men 51 years & women 43 years	Total Yogurt & Cheese Q4, (fermented dairy foods)	Q1	CVD Mortality	Non-Industry <sup>34</sup>	Yes <sup>dd</sup>
Sauvaget, C 2003 <sup>(36)</sup>	Cohort	16 years	37,130 men & women	56 years	Dairy Q4, Almost Daily (dairy products (butter and cheese, excluding margarine))	Q1, Never	Total Stroke	Non-Industry <sup>35</sup>	No disclosure
Snijder, MB 2008 <sup>(37)</sup>	Cohort	6.4 years	1,124 men & women	50–75 years	Dairy Q4, 5.75-17.24 servings/day (range) (total dairy consumption was categorized as low-fat dairy ( $\leq 2\%$ fat) or high-fat dairy ( $> 2\%$ fat). The variable dairy desserts included yoghurt, curds, and custard. The variable milk included low-fat, skim, and, whole milk. The variable yoghurt included all low-fat, skim, and whole yoghurts)	Q1 0-2.97 servings/day (range)	Systolic & Diastolic Blood Pressure	Industry <sup>36</sup>	Yes <sup>ee</sup>
Soedamah-Muthu, SS 2013 <sup>(38)</sup>	Cohort	10.8 years	4,255 men & women	56 years	Dairy, T3 575 g/day (median) (all dairy products, except butter and ice cream)	T1, 246 g/day (median)	Fatal & Non-Fatal CHD	Non-Industry <sup>37</sup>	Yes <sup>ff</sup>
Steffen, LM 2005 <sup>(39)</sup>	Cohort	15 years	4,304 men & women	18-30 years	Dairy Foods Q5, $> 3.4$ times/day (dairy foods, including milk, cheese, yogurt, and dairy desserts)	Q1, $< 1.1$ times/day	Blood Pressure	Non-Industry <sup>38</sup>	No <sup>gg</sup>

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Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Tavani, A 2002 <sup>(40)</sup>	Case Control		985 men & women	61 years (median)	Total milk >7 cups/week, Yogurt >= 7 portions/week, Cheese >=350g/week	Total milk 0 cups/week, Yogurt 0 portions/week, Cheese <200g/week	Acute Myocardial Infarction	Non-Industry <sup>39</sup>	No <sup>hh</sup>
Um, C 2017 <sup>(41)</sup>	Cohort	5.7 years of follow-up	21,427 men & women	calculated mean = 64.8 years**	Total Dairy Q5, 17.8 servings/day (dairy products (milk, cream, fermented dairy products, ice cream, butter, cheeses))	Q1, 0.9 servings/day	CVD Mortality	Non-Industry <sup>40</sup>	No <sup>ii</sup>
Umesawa, M, 2008 <sup>(42)</sup>	Cohort	12.9-year follow-up	41,526 men & women	40-59 years	Dairy Calcium, Q5, 116 mg/day (median) (to calculate dairy calcium intake, we specified 2 kinds of dairy products, ie, cheese and dairy products except cheese, for the baseline questionnaire, and 4 kinds, ie, whole milk, low fat milk, cheese, and yogurt, for the 5-year follow-up questionnaire)	Q1, 0 mg/day	Total Stroke & CHD	Non-Industry <sup>41</sup>	No <sup>jj</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Wang,L 2008 <sup>(43)</sup>	Cohort	10 years	28,886 women	53.8 years	Total Dairy Q5, 3.69 servings/day (median) (total dairy product intake was calculated by summing the intake of individual dairy items: low-fat dairy items include skim or low-fat milk, sherbet, yogurt, and cottage/ricotta cheese, high-fat dairy items include whole milk, cream, sour cream, ice cream, cream cheese, and other cheese)	Q1, 0.56 servings/day (median)	Hypertension	Non-Industry <sup>42</sup>	No <sup>kk</sup>

\* We calculated the mean age score of participants by summing Non-cases, T2D, MI and stroke cases at baseline and dividing them by 4

\*\*We calculated the mean age score of participants by summing all quintiles 1, 3, & 5 (they were the only ones available) at baseline and dividing them by 5

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- 9
- 10 d) Altorf-van der Kuil W, Engberink MF, Geleijnse JM - Top Institute Food and Nutrition, PO Box 557, 6700 AN, Wageningen, The
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- 23
- 24 h) The authors declare no conflict of interest.
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- 34
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- 37 n) There were no conflicts of interest.
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- 42
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- t) The authors declare no conflict of interest
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## Supplementary File 5. Risk of bias in included studies

Funding Source, n (%<sup>a</sup>)

Characteristic	Category	Total N = 43	Sponsorship		COI		Industry Ties	
			Industr y N= 8	Non- Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non- Industry/ No COI N = 29
<b>Risk of Bias Assessment</b>								
	Serious/Critical Bias due to confounding	43 (100)	8 (100)	35 (100)	10 (100)	33 (100)	14 (100)	29 (100)
	Serious/Critical Bias in selection of participants into the study	6 (14)	1 (13)	5 (14)	1 (10)	5 (15)	2 (14)	4 (14)
	Serious/Critical Bias in classification of exposures	16 (37)	3 (38)	13 (37)	2 (20)	14 (42)	3 (21)	13 (44)
	Serious/Critical Bias due to deviations from exposures	21 (49)	3 (38)	18 (51)	6 (60)	15 (45)	7 (50)	14 (48)
	Serious/Critical Bias due to missing data	10 (23)	2 (25)	8 (23)	3 (30)	7 (21)	3 (21)	7 (24)

	Serious/Critical Bias in measurement of outcomes	6 (14)	2 (25)	4 (11)	1 (10)	5 (15)	2 (14)	4 (14)
	Serious/Critical Bias in selection of reported results	4 (9)	1 (13)	3 (9)	2 (20)	2 (6)	2 (14)	2 (7)
	Serious/Critical overall risk of bias	43 (100)	8 (100)	35 (100)	10 (100)	33 (100)	14 (100)	29 (100)

<sup>a</sup> Percentages may not add to 100 due to rounding



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Supplementary File 6: Favorable Outcomes by Industry Ties v No Industry Ties, Industry Sponsorship v No Industry Sponsorship and Conflicts of Interest v No Conflicts of Interest

Industry Ties: Industry Sponsorship and/or Author Conflicts of Interest					No Industry Ties: No Industry Sponsorship and No Author Conflicts of Interest				
Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable	Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable
Aerde, M 2013	Non-Industry	Yes	U	U	Al-Delaimy, WK 2003	Non Industry	No	U	U
Altorf-van der Kuil, W2012	Industry	Yes	U	U	Alonso A, 2005	Non-industry	No	U	U
Bernstein, AM 2012	Non-industry	Yes	U	U	Avalos, EE 2013	Non-industry	No	U	U
Biong, A 2008	Industry	Yes	U	F	Bonthuis, M 2010	Non-Industry	No	U	U
Buendia, JR 2018	Industry	No	F	F	Chen, M 2016	Non-Industry	No	U	F
Dalmeijer, G 2013	Non-Industry	Yes	U	F	Dauchet, L 2007	Non-Industry	No	U	U
Dehghan, M 2018	Industry	No	U	F	Elwood, PC 2004	Non-Industry	No disclosure	U	U
Heraclides, A 2012	Non-Industry	Yes	U	U	Engberink, MF 2009	No disclosure	No	U	F
Lockheart, MSK 2007	Industry	No disclosure	U	U	Farvid, MS 2017	Non-Industry	No	F	F
Louie, JCY 2013	Industry	No disclosure	U	U	Haring, B 2014	Non-Industry	No	U	U
Praagman, J 2015	Industry	Yes	U	U	He, K 2003	Non-Industry	No	U	U

Industry Ties: Industry Sponsorship and/or Author Conflicts of Interest					No Industry Ties: No Industry Sponsorship and No Author Conflicts of Interest				
Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable	Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable
Praagman J, 2015	Non-Industry	Yes	U	U	Johansson, I 2018	Non-Industry	No	U	U
Snijder, MB 2008	Industry	Yes	U	U	Johansson, I 2019	Non-Industry	No	U	U
Soedamah-Muthu, SS 2013	Non-Industry	Yes	U	U	Kim, D 2017	Non-Industry	No	F	F
					Larsson,S 2009	Non-Industry	No disclosure	U	U
					Larsson, SC 2012	Non-Industry	No	U	U
					Li, K 2012	Non-Industry	No	U	U
					Lin, PH 2013	Non-Industry	No	U	U
					Mazidi, M, 2018	Non-Industry	No	F	F
					Ness, AR 2001	Non-Industry	No	U	U
					Nettleton, J 2008	Non-Industry	No	U	U
					Panagiotakos, D 2009	Non-Industry	No disclosure	U	U
					Patterson, E 2013	Non-Industry	No	F	F
					Sauvaget, C 2003	Non-Industry	No disclosure	F	F
					Steffen, LM 2005	Non-Industry	No	U	U

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Industry Ties: Industry Sponsorship and/or Author Conflicts of Interest					No Industry Ties: No Industry Sponsorship and No Author Conflicts of Interest				
Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable	Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable
					Tavani, A 2002	Non-Industry	No	F	F
					Um, C 2017	Non-Industry	No	U	F
					Umesawa, M, 2008	Non-Industry	No	F	F
					Wang,L 2008	Non-Industry	No	F	F

**Favourable results - Statistical significance: Industry ties vs no industry ties; industry sponsorship vs no sponsorship; COI v no COI**

**Industry Ties**

	Industry/COI	Non-Industry/No COI
Favourable	1	8
Unfavourable	13	21

RR= 0.26 (95% CI 0.04, 1.87)

**Industry Sponsorship**

	Industry	Non-Industry
Favourable	1	8
Unfavourable	7	27

RR = 0.55 (95% CI 0.08, 3.77)

### Conflicts of Interest

	COI	No/COI
Favourable	0	9
Unfavourable	10	24

RR= 0.16 (95% CI 0.01, 2.57)

**Favourable conclusions: Industry ties vs no industry ties; industry sponsorship vs no sponsorship; COI v no COI**

### Industry Ties

	Industry/COI	Non-Industry/NO COI
Favourable	4	11
Unfavourable	10	18

RR = 0.75 (95% CI 0.29, 1.95)

### Industry Sponsorship

	Industry	Non-Industry
Favourable	3	12
Unfavourable	5	23

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RR= 1.09 (95% CI 0.40, 2.99)

**Conflicts of Interest**

	COI	No COI
Favourable	2	13
Unfavourable	8	20

RR =0.51 (95% 0.14, 1.88)

**Concordance between study results and conclusions: Industry ties vs no industry ties; industry sponsorship vs no sponsorship; COI v no**

**COI Industry Ties**

**Industry Ties**

	Industry/COI	Non-Industry/NO COI
Discord	3	3
Concord	11	26

RR = 2.07 (95% CI 0.48, 8.99)

**Industry Sponsorship**

	Industry	Non-Industry
Discord	2	4
Concord	6	31

RR = 2.19 (95% CI 0.48, 9.94)

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**Conflicts of Interest**

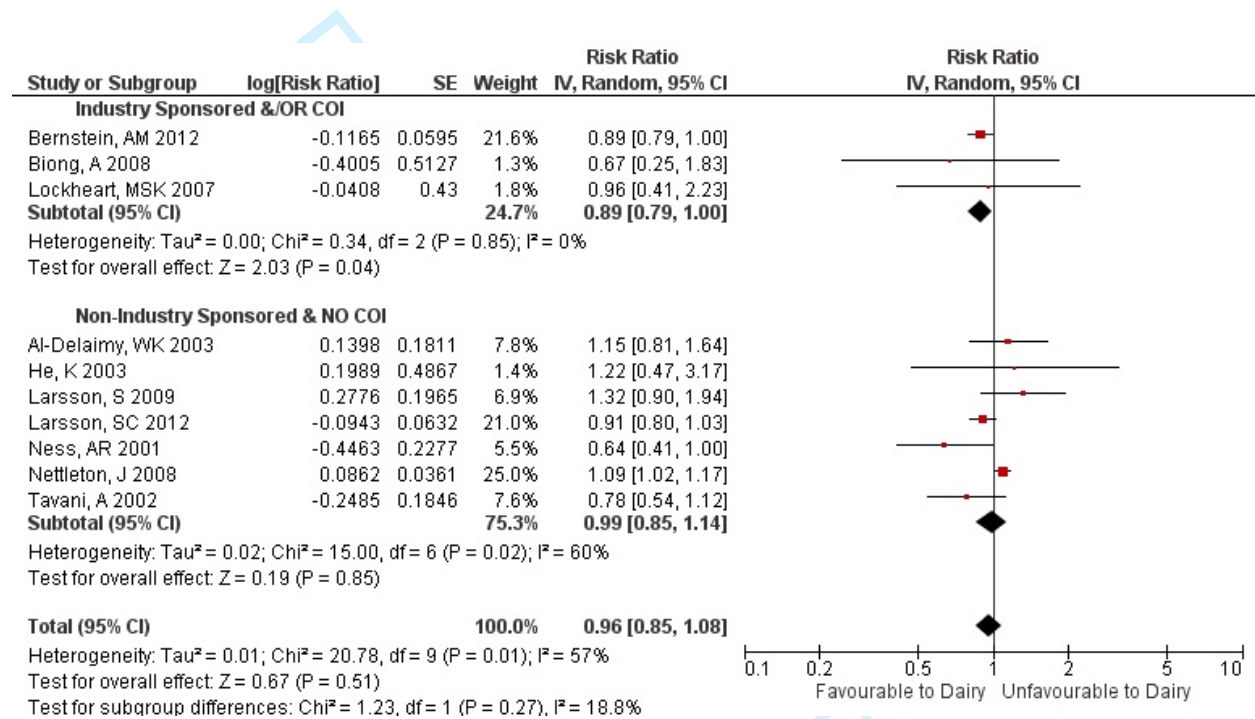
	COI	No/COI
Favourable	2	4
Unfavourable	8	29

RR = 1.65 (95% CI 0.35, 7.72)

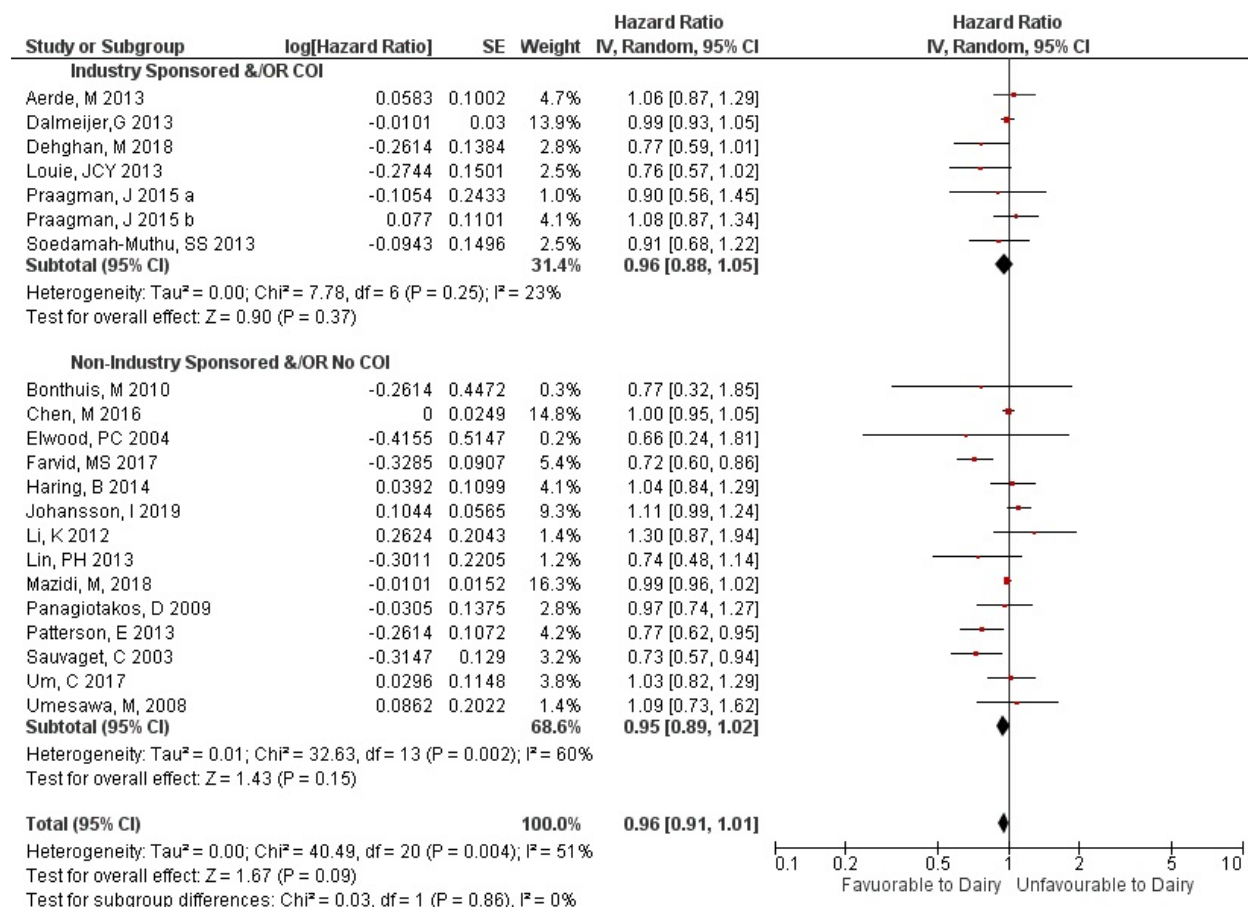
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## Supplementary File 7. Results for each of the meta-analyses conducted

## Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Risk Ratio

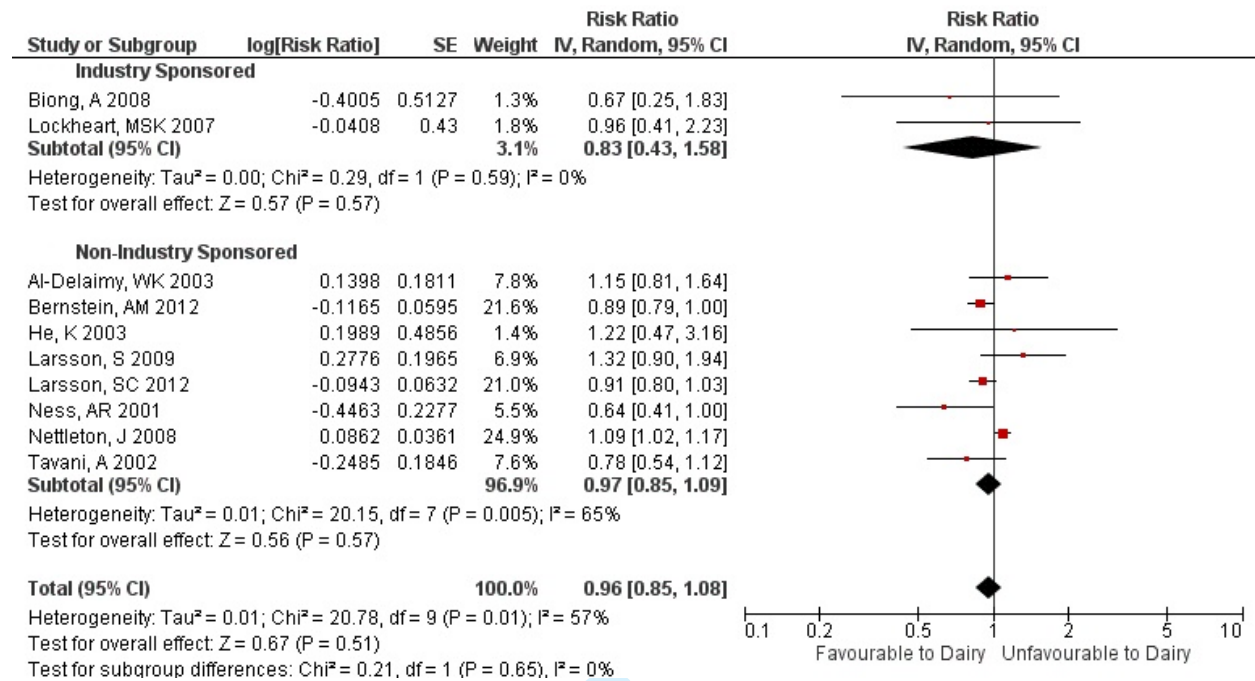


Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Hazard Ratio

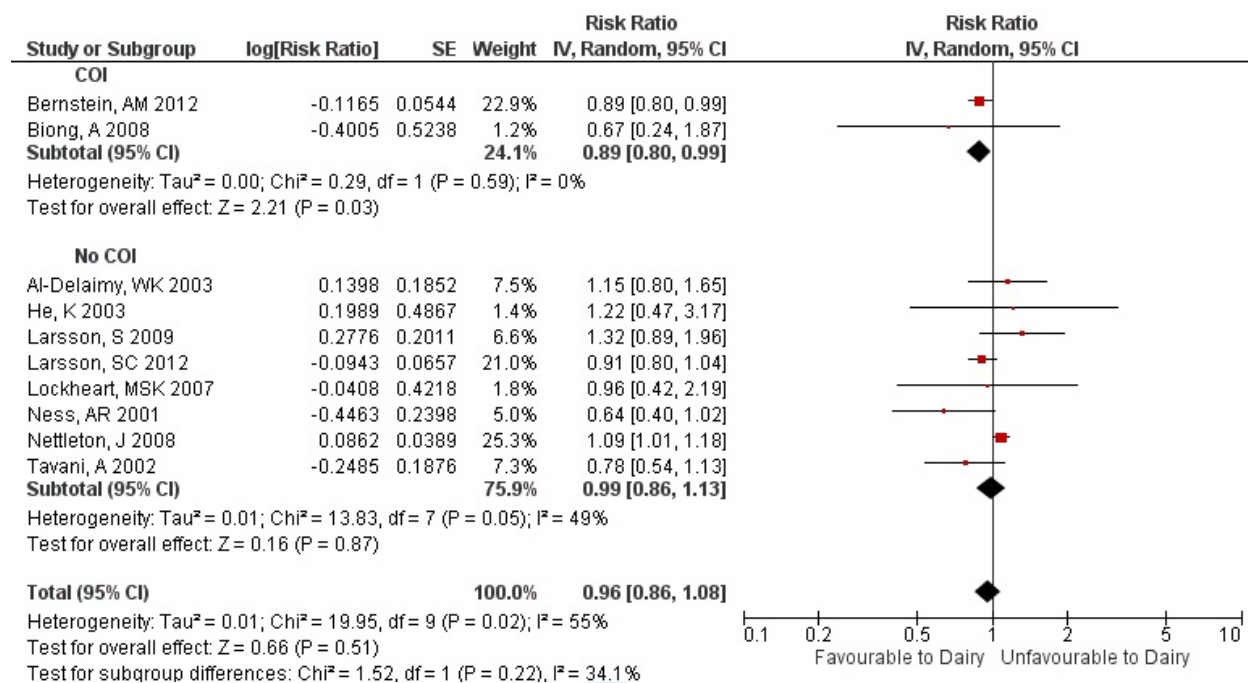




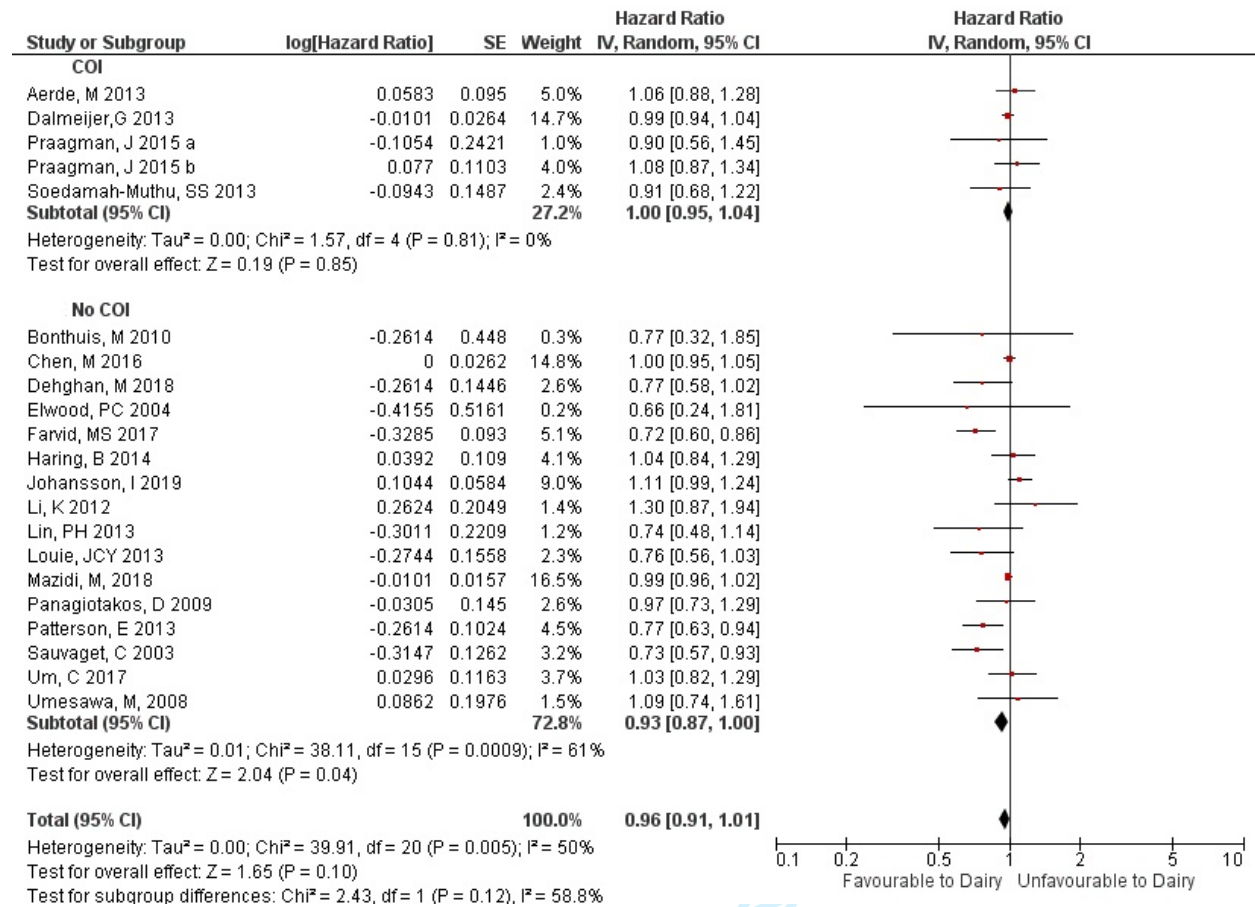
## Effect Size, Cardiovascular Disease: Industry sponsorship vs no industry sponsorship, Risk Ratio



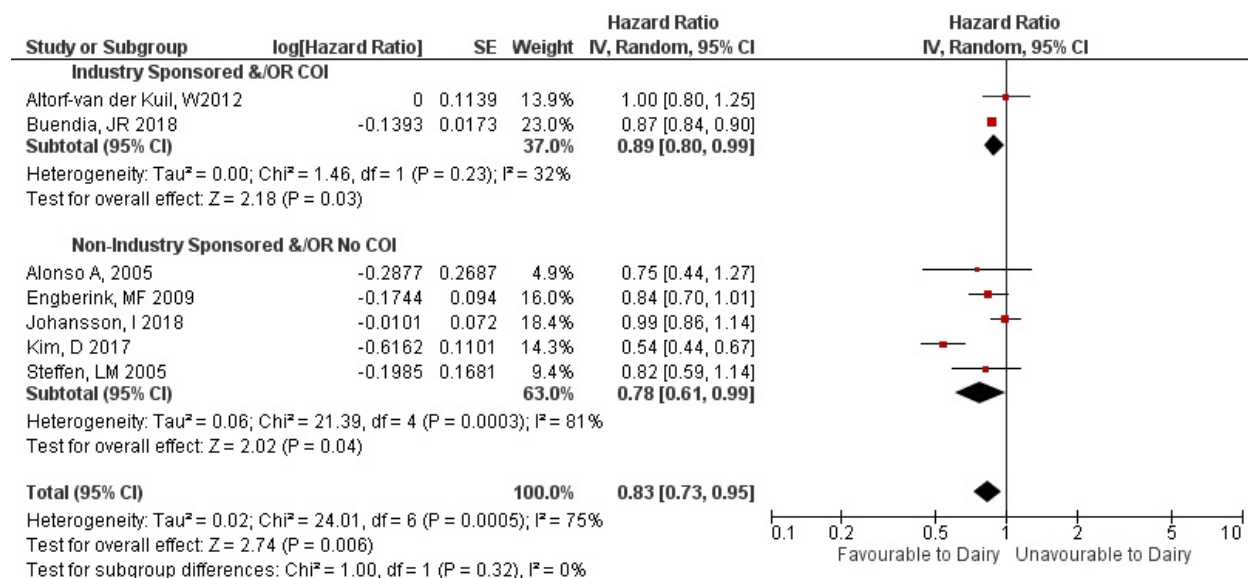
Effect Size, Cardiovascular Disease: COI vs No COI, Risk Ratio



## Effect Size, Cardiovascular Disease: COI vs no COI, Hazard Ratio



Effect Size, Elevated Blood Pressure / Hypertension: Industry ties v no industry ties





# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Supp file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7 & 10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6 & 10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ for each meta-analysis).	10



# PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11, Figure 1, Supp file 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supp file 4
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13, Supp File 5, Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-15, Supp file 6 & 7, Figure 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13, Supp file 5, Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16



# PRISMA 2009 Checklist

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Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

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# BMJ Open

## The association of food industry ties with findings of studies examining the effect of dairy foods intake on cardiovascular disease and mortality: Systematic review and Meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039036.R1
Article Type:	Original research
Date Submitted by the Author:	16-Sep-2020
Complete List of Authors:	Chartres, Nicholas; The University of Sydney, Charles Perkins Centre Fabbri, Alice; University of Insubria, Centre for Research in Medical Pharmacology McDonald, Sally ; The University of Sydney, ; the University of Sydney Diong, Joanna; The University of Sydney Faculty of Medicine and Health McKenzie, Joanne; Monash University Bero, Lisa; University of Sydney Faculty of Health Sciences, Pharmacy
<b>Primary Subject Heading</b>:	Research methods
Secondary Subject Heading:	Public health, Epidemiology, Health policy, Nutrition and metabolism
Keywords:	STATISTICS & RESEARCH METHODS, NUTRITION & DIETETICS, PUBLIC HEALTH

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3 1 **The association of food industry ties with findings of studies examining the effect of**  
4 **dairy foods intake on cardiovascular disease and mortality: Systematic review and**  
5 **Meta-analysis**  
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## 20 Abstract

21 **Objective:** To determine if the association of dairy foods with cardiovascular disease  
22 outcomes differs between studies with food industry ties versus those without industry ties.

23 To determine whether studies with or without industry ties differ in their risk of bias.

24 **Eligibility criteria:** We included cohort and case control studies that estimated the  
25 association of dairy foods with cardiovascular disease (CVD) outcomes in healthy adults.

26 **Information sources:** We searched eight databases on February 1, 2019 from 2000-2019 and  
27 hand searched reference lists

28 **Risk of bias:** We used the Risk of Bias in Non-Randomized Studies-of Exposure (ROBINS-  
29 E) tool.

30 **Included studies:** 43 studies (3 case controls, 40 cohorts).

31 **Synthesis of results:** There was no clear evidence of an association between studies with  
32 industry ties (1/14) vs. no industry ties (8/29) and the reporting of favourable results, RR=  
33 0.26 (95% CI 0.04, 1.87; n=43 studies) and studies with industry ties (4/14) vs. no industry  
34 ties (11/29) and favourable conclusions, RR= 0.75 (95% CI 0.29, 1.95; n=43).. Studies with  
35 industry sponsorship, (HR =0.78; n= 3 studies) showed a decreased magnitude of risk of  
36 CVD outcomes compared to studies with no industry sponsorship (HR=0.97; n=18) (ratio of  
37 HRs 0.80 (95% CI 0.66, 0.97)) P=0.03.

38 **Strengths and Limitations of evidence:** Every study had an overall high risk of bias rating;  
39 this was primarily due to confounding.

40 **Interpretation:** There was no clear evidence of an association between studies with food  
41 industry ties and the reporting of favourable results and conclusions compared with studies  
42 without industry ties. The statistically significant difference in the magnitude of effects  
43 identified in industry sponsored studies compared to non-industry sponsored studies,  
44 however, is important in quantifying industry influence on studies included in dietary  
45 guidelines.

46 **Funding:** This work was supported by Australian Health and Medical Research Council  
47 Project Grant APP 1139997.

48 **Registration:** Prospero ID CRD42019129659

51 **Keywords:** Industry Sponsorship, Conflicts of Interest, Bias, Dietary Guidelines

53 **Strengths and limitations of this study**

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4 54 • This is the first systematic review and meta-analysis to evaluate the association of  
5 55 food industry ties (industry sponsorship and / or author conflicts of interest (COI))  
6 56 with the results, conclusions and risk of bias of primary nutrition studies examining  
7 57 the association of dairy foods with cardiovascular disease outcomes and mortality.  
8  
9 58 • We conducted a comprehensive search and followed explicit and well-defined  
10 59 inclusion and exclusion criteria for the included studies.  
11  
12 60 • For studies missing a funding or author COI disclosure, we did not contact the  
13 61 authors; thus we may be underestimating the number of studies with industry ties.  
14  
15 62 • The tool that we used to assess the risk of bias is still under modification, however it  
16 63 is unlikely any future changes to the tool will affect the risk of bias ratings.  
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18 64 • We did not analyse studies of low and full fat dairy separately. Industry ties may have  
19 65 different effects on studies of low or full fat dairy foods.  
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## 67 INTRODUCTION

68 The effect of dairy foods on cardiovascular disease (CVD) is unclear. Recent systematic  
69 reviews and meta-analyses of observational studies have reported conflicting results between  
70 the association of total dairy consumption and risk of CVD, with some showing decreased  
71 risk and some showing no clear evidence.<sup>1-4</sup> The beneficial effects of decreasing blood  
72 pressure, however, appear more consistent.<sup>4,5</sup> Further, dairy intake recommendations made in  
73 dietary guidelines around the world vary. Although the Australian Dietary Guidelines  
74 concluded that there is a probable association between dairy food consumption and a reduced  
75 risk of cardiovascular events,<sup>6</sup> recent amendments to the Eatwell guidelines by Public Health  
76 England recommend a significant reduction in the daily intake of dairy foods.<sup>7</sup>

78 Food industry sponsors and authors with a conflict of interest (COI) with the food industry  
79 may gain financially from finding that dairy foods have health benefits, since such a finding  
80 can be used to market dairy products. Such a driver may lead industry sponsors to magnify  
81 (or bias) the health benefits of dairy foods by influencing the research agenda, design and  
82 conduct of the study, or reporting of the results.<sup>8-11</sup> Prior examinations of pharmaceutical and  
83 tobacco research have identified that even when controlling for methodological biases,  
84 studies sponsored by industry were more likely to have results that favoured the sponsor than  
85 studies with other sources of sponsorship.<sup>12-14</sup>

87 The effects of food industry sponsorship or author COI with the food industry on study  
88 results needs further examination.<sup>15</sup> A systematic review assessing the association of  
89 wholegrain foods with CVD and mortality found that studies with food industry ties more  
90 often have favourable results and conclusions compared to those with no industry ties, but the  
91 association was uncertain.<sup>16</sup> One study has demonstrated an association of food industry  
92 sponsorship with the magnitude of effect estimates.<sup>17</sup> In this examination, studies of soft  
93 drink consumption sponsored by the food industry reported significantly smaller harm effect  
94 estimates than those with no food industry sponsorship. A recent dairy industry funded meta-  
95 analysis of observational studies found that studies without food industry sponsorship showed  
96 that dairy consumption was associated with a statistically significant decreased risk of  
97 developing CVD and Type 2 diabetes, while studies with food industry sponsorship did not.<sup>18</sup>

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2  
3 98 The primary objective of this systematic review and meta-analysis is to determine whether:  
4  
5 99 • Studies of observational design examining the associations of dairy foods with CVD  
6  
7 100 with food industry ties (industry sponsorship and / or authors with a COI) are more  
8  
9 101 likely to have results and / or conclusions that are favourable to industry than those  
10  
11 102 with no industry ties.

12 103  
13  
14 104 The secondary objectives of this review are to determine whether observational studies with  
15  
16 105 food industry ties compared with no industry ties:

- 17  
18 106 I. differ in their risk of bias;  
19  
20 107 II. have a higher level of discordance between study results and conclusions, with the  
21  
22 108 conclusions more likely to be favourable compared to the results.  
23  
24  
25 109

## 26 27 110 **METHODS**

28  
29 111 We conducted a systematic review of observational studies examining the effect of dairy  
30  
31 112 consumption on CVD. Our study is registered with Prospero ID CRD42019129659 (see  
32  
33 113 Supplementary file 1).<sup>19</sup>  
34  
35 114

### 36 115 **Search Strategy**

37  
38 116 The search included terms to locate observational studies and randomised control trials, the  
39  
40 117 latter of which are for a separate systematic review. The search used was based on the  
41  
42 118 Process Manual used to develop the 2013 Australian Dietary Guidelines and the guidance of  
43  
44 119 an information specialist.<sup>20</sup> The search dates used were to ensure that we identified the  
45  
46 120 studies used to inform the recommendations in these guidelines. We therefore searched the  
47  
48 121 following databases from January 2000-February 2019: MEDLINE; CINAHL; PubMed;  
49  
50 122 PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy  
51  
52 123 used for Ovid MEDLINE on February 1, 2019 is shown in Supplementary file 2. We adapted  
53  
54 124 this strategy for the other databases. We hand searched references lists of the identified  
55  
56 125 studies and reviews.  
57  
58 126  
59 127  
60 128

## 129 **Eligibility Criteria**

130 We included studies of cohort or case control designs that estimated the effects of dairy  
131 consumption on CVD outcomes in healthy adults. We focused on these study designs as they  
132 are often used to assess the association of diet with long term health outcomes.

133

134 We included studies with no restriction on the authors' definition of dairy. For example, some  
135 authors' defined dairy as milk, yogurt and cheese, while others defined dairy as 'whole fat'  
136 milk, yogurt and cheese. We included studies that compared dairy foods to other foods or  
137 compared various levels of dairy consumption.

138

139 We included studies that measured any clinical outcome of CVD, defined as either mortality  
140 related to specific CVD events, and / or CVD events, (e.g., first myocardial infarction, total  
141 stroke etc.) or incidence of elevated blood pressure / hypertension.

142

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

145

## 146 **Types of Outcome Measures**

### 147 **Primary Outcomes**

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

151 1. Statistical significance of results favourable to dairy

152 Favourable results were defined as those that were in the direction of showing a health  
153 benefit of dairy product(s), and were statistically significant at the 0.05 level (two tailed),  
154 such as a statistically significant decreased risk of CVD compared to the comparator (i.e.  
155 another food or lower dairy consumption). Otherwise, results were classified as unfavourable.  
156 In the circumstance where a study reported multiple results (e.g. first myocardial infarction  
157 and total stroke), only one result needed to be 'favourable' for the study as a whole to be  
158 classified as 'favourable'.

159

160 2. Effect size of results

161 Effect size was defined as the risk ratio (RR), hazard ratio (HR) or odds ratio (OR) between  
162 dairy foods tested versus comparator on the CVD outcome.

163

### 3. Conclusions

Conclusions that suggested that the dairy consumption was beneficial to health by decreasing CVD were considered favourable. Otherwise, the conclusions were considered unfavourable. In the circumstance where a study reported multiple results (e.g. first myocardial infarction and total stroke), only one conclusion needed to be 'favourable' for the study as a whole to be classified as 'favourable'.

170

#### **Secondary Outcomes**

We assessed two secondary outcomes:

##### 1. The risk of bias of the included studies

To evaluate the risk of bias of included observational studies, we used an adapted version of the Cochrane Collaboration's 'Risk of Bias in Non-Randomized Studies-of Interventions' (ROBINS-I) tool,<sup>21</sup> the ROBINS-E<sup>22</sup>. Bias is assessed across seven domains ('Bias due to confounding', 'Bias in selection of participants', 'Bias in classification of exposures', 'Bias due to deviations from exposures', 'Bias due to missing data', 'Bias in measurement of outcomes', 'Bias in selection of reported results'), with each domain classified low, moderate, serious, critical risk of bias, or no information. The first step in using the ROBINS-E tool is to identify all possible confounders that a study should control. We developed this list of confounders by searching the literature for the most recent systematic reviews on possible confounders and having this list reviewed by expert Professors in nutrition at The University of Sydney (see Supplementary file 3 for list of confounder). An overall risk of bias rating for the study is given based on the domain with the highest risk of bias rating. For example, if a study is rated as being at a 'critical' risk of bias in one domain, the overall risk of bias rating is 'critical.' In the circumstance where a study reported multiple results (e.g. stroke and myocardial infarction), the risk of bias was only assessed for one randomly selected outcome.

190

##### 2. Concordance between study results and conclusions

Results unfavourable to the sponsor with conclusions favourable to the sponsor, were considered discordant. Otherwise, the results and conclusions were considered concordant.

194

#### **Selection of studies**

195



1  
2  
3 196 Three investigators (NC, SMC & AF), working independently in pairs, screened the titles and  
4  
5 197 abstracts of all records for obvious exclusions. If both investigators agreed on excluding the  
6  
7 198 study, the full text was not retrieved. Three investigators (NC, SMC & AF) working  
8  
9 199 independently in pairs, assessed the full text of potentially eligible studies against the  
10  
11 200 inclusion criteria. If agreement could not be reached, a fourth investigator (LB) resolved the  
12  
13 201 conflict.

### 15 203 **Selection of results for meta-analysis**

17 204 If total dairy consumption had been assessed in the study, we included this as our only  
18  
19 205 exposure. If total dairy consumption had not been assessed, we included any type of dairy  
20  
21 206 consumption (e.g. milk, yogurt, and cheese; or low fat, high fat) other than fermented milk as  
22  
23 207 our exposure. We included the results comparing the highest level of dairy consumption to  
24  
25 208 the lowest level of dairy consumption (e.g., 'yes' to dairy consumption vs. 'no' to dairy  
26  
27 209 consumption, tertile 3 vs. tertile 1, quartile 4 vs. quartile 1, quintile 5 vs. quintile 1). For the  
28  
29 210 meta-analyses if our pre-specified rules for selecting results did not allow us to uniquely  
30  
31 211 identify one exposure for inclusion, we randomly selected one result.

32  
33 213 If 'cardiovascular disease mortality/death/s' (verbatim) had been assessed, we included this  
34  
35 214 as our only outcome. If not, we included any type of CVD mortality (e.g., coronary heart  
36  
37 215 disease mortality, stroke mortality etc.) as our outcome. If there were no mortality outcomes  
38  
39 216 assessed in the study, we included any CVD event or incidence of elevated blood pressure /  
40  
41 217 hypertension as our outcome. If a study used a composite outcome, which was a combination  
42  
43 218 of multiple outcomes, the result pertaining to the composite outcome was selected. For the  
44  
45 219 meta-analyses if our pre-specified rules for selecting results did not allow us to uniquely  
46  
47 220 identify one outcome for inclusion, we randomly selected one result.

### 48 222 **Data Collection**

49  
50 223 From each study we extracted:

- 51 224 • Year of publication
- 53 225 • Study design (cohort or case control)
- 55 226 • Sample size of study
- 57 227 • Age of participants (combined or if reported, separately)
- 59 228 • Exposure duration or observation period

- 1  
2  
3 229 • How the study defined dairy (verbatim)  
4  
5 230 • Disclosure of funding source (no disclosure, yes and there is a sponsor, the authors  
6  
7 231 state they received no funding for their work)  
8  
9 232 • Name of the funders of the study (verbatim)  
10  
11 233 • Role of the funders (role of the sponsor not mentioned, sponsor not involved in study  
12  
13 234 design and analyses, sponsor involved, N/A)  
14  
15 235 • Disclosure of author COI (no disclosure, yes (if at least 1 author had a COI), the authors  
16  
17 236 state they had no conflicts of interest to declare)  
18  
19 237 • Authors COI statement (verbatim)  
20  
21 238 • Outcomes assessed in the study (any CVD death and/or event or blood  
22  
23 239 pressure/hypertension)  
24  
25 240 • The numerical results of the study (e.g., OR, HR, RR)  
26  
27 241

28 242 All extracted data from the included studies was stored in REDcap, a secure web-based  
29  
30 243 application for the collection and management of data.<sup>23</sup> Five investigators (NC, SMc, AF,  
31  
32 244 AL & JD) working independently in pairs extracted data from the included studies.  
33  
34 245 Discrepancies in data extraction were resolved by consensus. If agreement could not be  
35  
36 246 reached, a sixth investigator (LB) resolved the discrepancy.  
37  
38 247

### 39 248 **Classification of industry sponsorship and author conflicts of interest**

40 249 Sponsorship was categorized as 1) industry or 2) non-industry. Industry sponsored studies  
41  
42 250 were defined as those that declared any sponsorship from the food industry, including 'Big  
43  
44 251 Food' (i.e. Danone, Kraft, Unilever etc), trade associations (i.e. dairy associations and  
45  
46 252 organisations) and dairy industry (i.e. primary producers). Studies with food industry  
47  
48 253 sponsorship plus any other sponsorship were classified as industry. Any study that did not  
49  
50 254 contain a funding disclosure statement was classified as 'non-industry'.  
51  
52 255

53 256 Studies with at least one author with any disclosed financial tie with the food industry were  
54  
55 257 classified as having a conflict of interest (COI). Author COI were categorised as 1) COI or 2)  
56  
57 258 no COI. Studies with no authors with disclosed financial ties with the food industry were  
58  
59 259 classified as 'no conflict of interest'.  
60  
60 260

1  
2  
3 261 Since the number of studies with industry sponsorship or author COI was small, we also  
4 262 categorized studies as having “industry ties” for analysis. Studies classified as having an  
5 263 industry tie were industry sponsored and / or had an author COI. Otherwise, they were  
6 264 classified as having no industry ties.  
7  
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10 265

## 11 266 **Analysis**

12 267 We report the frequencies and percentages of the study characteristics across all studies, and  
13 268 separately, by sponsorship, COI and industry ties. We visually present the risk of bias rating  
14 269 for each domain and overall across each study.  
15  
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19 270

20 271 To quantify the association between industry ties, food industry sponsorship, or authors with  
21 272 a conflict of interest with the food industry and (i) favourable results, (ii) favourable  
22 273 conclusions, (iii) overall risk of bias across each study, and (iv) level of concordance, we  
23 274 calculated RR (and 95% confidence intervals). To analyse the risk of bias rating for each  
24 275 study, we dichotomised the overall risk of bias ratings as low (low or moderate) or high  
25 276 (serious or critical).  
26  
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31 277

32 278 We conducted meta-analysis to examine whether studies with food industry ties, food  
33 279 industry sponsorship, or authors with a conflict of interest with the food industry modified the  
34 280 magnitude of effect of dairy on CVD outcomes.. For each outcome, we combined effect  
35 281 estimates using a random effects meta-analysis model using the inverse variance method.  
36 282 DerSimonian and Laird’s method of moments estimator was used to estimate between study  
37 283 heterogeneity. We fitted separate meta-analyses for studies that had measured the association  
38 284 using HRs and those that had used either RRs or ORs. It is not recommended to combine HRs  
39 285 with RRs and ORs in a meta-analysis, as HRs represent instantaneous risk over the study time  
40 286 period, whereas RRs and ORs estimate risk/odds at a fixed time point.<sup>24</sup> We considered that  
41 287 the ORs approximated RRs given CVD events were rare.  
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51 289 We undertook a fixed-effects test for subgroup differences (defined by industry sponsorship /  
52 290 authors conflict of interest) using the Chi<sup>2</sup> test and calculated the ratio of RRs (ORs) or HRs  
53 291 along with 95% confidence intervals. Analyses were undertaken in Review Manager 5.3.<sup>25</sup>  
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2  
3 293 We planned to use sensitivity analysis to assess the influence of risk of bias by restricting the  
4 294 analysis to studies at ‘low risk of bias’ overall (i.e. an overall risk of bias rating of low or  
5 295 moderate). However, as the overall risk of bias was high across all studies, this was not  
6 296 undertaken.  
7  
8  
9

10 297

## 11 298 **Patient and Public Involvement**

12 299 No patient involved  
13  
14  
15

16 300

## 17 301 **RESULTS**

18 302 As shown in Figure 1, there were 1, 858 studies screened for inclusion and 43 studies were  
19 303 included (3 case controls, 40 cohorts). See Supplementary file 4 for ‘List of excluded studies  
20 304 and reasons for exclusion’.  
21  
22  
23

24 305

### 25 306 **Characteristics of included Studies**

26 307 All studies were published between 2001 and 2019. All but one contained a funding  
27 308 disclosure. Eight studies disclosed food industry sponsorship, but only two of these studies  
28 309 described the role of the sponsor. Six studies did not contain an author COI disclosure  
29 310 statement. Ten studies contained an author with a COI with the food industry. Fourteen  
30 311 studies were classified as having industry ties, disclosing food industry sponsorship and / or  
31 312 an author with a COI.  
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38 313

39 314 As shown in Table 1, most characteristics were similarly distributed across studies with  
40 315 industry ties or no industry ties. Studies with industry ties (64%) were more likely to have  
41 316 sample sizes <5000 than non-industry sponsored studies (34%). A greater proportion of  
42 317 industry sponsored studies (100%) than non-industry sponsored studies (83%) focused on  
43 318 total dairy intake rather than a specific food. Details of the individual studies are in  
44 319 Supplementary file 5.  
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325 **Table 1. Characteristics of the included studies by sponsorship, author conflict of**  
 326 **interest and industry ties**

327 Funding Source, n (%<sup>a</sup>)

Characteristic	Category	Total N = 43	Sponsorship		COI		Industry Ties	
			Industr y N= 8	Non- Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non- Industry/ No COI N = 29
<b>Sex</b>	Male	5 (12)	0 (0)	5 (14)	0 (0)	5 (15)	0 (0)	5 (17)
	Female	2 (5)	0 (0)	2 (6)	0 (0)	2 (6)	0 (0)	2 (7)
	Both	36 (84)	8 (100)	28 (80)	10 (100)	26 (79)	14 (100)	22 (76)
<b>Sample Size</b>	<5000	19 (44)	6 (75)	13 (37)	7 (70)	12 (36)	9 (64)	10 (34)
	5000-50,000	18 (42)	0 (0)	18 (51)	2 (20)	16 (48)	2 (14)	16 (55)
	>50,000	6 (14)	2 (25)	4 (11)	1 (10)	5 (15)	3 (21)	3 (10)
<b>Length of Follow up</b>	N/A*	3 (7)	2 (25)	1 (3)	1 (10)	2 (6)	2 (14)	1 (3)
	<10 years	11 (26)	3 (38)	8 (23)	2 (20)	9 (27)	3 (21)	8 (28)
	10-15 years	21 (49)	2 (25)	19 (54)**	6 (60)	15 (45)**	7 (50)	14 (48)
	>15 years	8 (19)	1 (13)	7 (20)	1 (10)	7 (21)	2 (14)	6 (21)
<b>Type of Dairy</b>	Total Dairy Intake***	37 (86)	8 (100)	29 (83)	9 (90)	28 (85)	13 (93)	24 (83)
	Individual Dairy Foods****	6 (14)	0 (0)	6 (17)	1 (10)	5 (15)	1 (7)	5 (17)

328 <sup>a</sup> Percentages may not add to 100 due to rounding

329 \* Follow up is not applicable for case control studies

330 \*\* Follow up for Johansson, I 2018 described the follow up as '8-12 years', we took the median of 10 years

331 \*\*\* This includes studies that looked at nutrients e.g calcium, fat & protein by measuring total dairy intake

332 \*\*\*\*Individual foods included milk, cheese & yogurt

### 333 **Risk of bias in included studies**

334 Every study was classified as having an overall high risk of bias, with 10 assessed as having a  
335 serious risk of bias and 33 as having a critical risk of bias (Figure 2). Most studies were  
336 assessed as having a critical risk of bias rating for the domain 'Bias due to confounding'. An  
337 example of one of the several confounders we identified that studies needed to control for was  
338 fruit and vegetable intake. If these confounders were not controlled for appropriately when  
339 measuring the effect of dairy intake on a CVD outcome, the study was classified as having a  
340 risk of bias for the confounding domain.

341

342 Studies without industry ties or without an author with a COI were more likely to have a  
343 serious or critical risk of bias rating for 'Bias in classification of exposures'. For example, if a  
344 study did not use a validated food frequency questionnaire to measure the dietary intake of  
345 dairy, the study was classified as having a risk of bias for the domain of classification of  
346 exposures. For all other domains, the risk of bias classifications were similarly distributed  
347 across studies with industry ties, industry sponsorship or COI vs no industry ties, industry  
348 sponsorship or COI, respectively (see Supplementary file 6).

349

### 350 **Favourable results - Statistical significance: Industry ties vs no industry ties; industry** 351 **sponsorship vs no sponsorship; COI v no COI**

352 There was no clear evidence of an association between the reporting of favourable results and  
353 studies with industry ties (1/14) compared to those with no industry ties (8/29), RR= 0.26  
354 (95% CI 0.04, 1.87; n=43 studies) (Supplementary file 7). When comparing studies with  
355 industry sponsorship (1/8) with those with no industry sponsorship (8/35), there was no clear  
356 evidence of an association, RR = 0.55 (95% CI 0.08, 3.77; n=43 studies). There was again no  
357 clear evidence of an association between the reporting of favourable results and studies with  
358 an author with a COI (0/10) than those with no COI (9/33), RR= 0.16 (95% CI 0.01, 2.57;  
359 n=43 studies).

360

### 361 **Effect Size, Cardiovascular Disease: Industry ties v no industry ties; industry** 362 **sponsorship vs no industry sponsorship; COI v no COI**

363 For studies that quantified the association between dairy consumption and CVD outcomes  
364 using a RR, we found no important difference in the magnitude of the effect in studies with  
365 industry ties (RR = 0.89; n=3 studies) compared with those studies with no industry ties, (RR

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2  
3 366 = 0.99; n=7 studies) (ratio of RRs 0.90 (95% CI 0.74, 1.09)); P=0.27 (Supplementary file 8).  
4  
5 367 For studies that had quantified the association using HRs, we similarly did not find an  
6  
7 368 important difference in the magnitude of HRs between studies with industry ties, (HR=0.96;  
8  
9 369 n=7 studies) and those studies with no industry ties, (HR=0.95; n=14 studies) (ratio of HRs  
10 370 1.01 (95% CI 0.90, 1.13)); P=0.86.  
11

371

12  
13 372 In our analysis comparing studies with industry sponsorship, (RR 0.83; n=2 studies) and  
14 373 those with no industry sponsorship, (RR 0.97; n=8 studies) we again did not find an  
15 374 important difference in the magnitude of RRs (ratio of RRs 0.86 (95% CI 0.44, 1.66));  
16  
17 375 P=0.65 (Supplementary file 8). However, when we compared industry sponsored studies,  
18  
19 376 (HR =0.78; n=3 studies) and non-industry sponsored studies, (HR=0.97; n=18 studies) that  
20 377 measured the association using HRs, we found a statistically significant difference in the  
21  
22 378 magnitude of the HRs (ratio of HRs 0.80 (95%CI 0.66, 0.97)); P=0.03 (Figure 3).  
23  
24  
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26  
27 380 In our analysis comparing studies with an author with a COI (RR 0.89; n=2 studies) and those  
28 381 with no COI, (RR 0.99; n= 8 studies) we found no important difference in the magnitude of  
29 382 RRs (ratio of RRs 0.90 (95% CI 0.76-1.07)); P=0.22 (Supplementary file 8). When we  
30 383 compared studies with a COI, (HR =1.00; n= 5 studies) and studies with no COI, (HR=0.93;  
31 384 n=16 studies) that measured the association using HRs, we again found no difference in the  
32 385 magnitude of the HRs (ratio of HRs 1.08 (95% CI 0.99, 1.17)); P=0.12.  
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387 **Effect Size, Elevated Blood Pressure / Hypertension: Industry ties v no industry ties,**  
388 **and industry sponsorship vs no sponsorship**

389 We found no important difference in the magnitude of the HRs for elevated blood pressure /  
390 hypertension in studies with industry ties, (HR = 0.89; n =2) and those studies with no  
391 industry ties, (HR = 0.78; n= 5) (ratio of HRs 1.14 (95% CI 0.88, 1.49); P=0.32  
392 (Supplementary file 8).  
393

394

395 All of these studies with industry ties also had industry sponsorship, so the ratio of HRs was  
396 the same.  
397

398

399 **Favourable conclusions: Industry ties vs no industry ties; industry sponsorship vs no**  
400 **sponsorship; COI v no COI**

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2  
3 399 There was no clear evidence of an association between the reporting of favourable  
4  
5 400 conclusions and studies with industry ties (4/14) compared to those with no industry ties  
6  
7 401 (11/29), RR= 0.75 (95% CI 0.29, 1.95; n=43) (Supplementary file 7). When we compared  
8  
9 402 studies only by industry sponsorship, there was no clear evidence of an association between  
10  
11 403 industry sponsored studies (3/8), compared to studies with no sponsorship (12/35), RR = 1.09  
12  
13 404 (95% CI 0.40, 2.99; n=43). There was again no clear evidence of an association between the  
14  
15 405 reporting of favourable conclusions and studies with an author with a COI (2/10) than those  
16  
17 406 without a COI (13/33), RR= 0.51 (95% CI 0.14, 1.88; n=43 studies).

17 407

### 18 408 **Risk of Bias Assessment by Industry Ties**

19 409 As every study had an overall high (serious or critical) risk of bias rating, there was no  
20  
21 410 difference in the proportion of studies at a high risk of bias between those with industry ties,  
22  
23 411 industry sponsorship or COI and those without industry ties, sponsorship or COI.

24 412

### 25 413 **Concordance between study results and conclusions**

26 414 Six (of 43) studies, all with unfavorable results, overemphasized the benefits of the dairy  
27  
28 415 exposure in their conclusions and thus were coded as 'favourable' conclusions.

29 416 There was no clear evidence of an association between discordant results and conclusions and  
30  
31 417 studies with industry ties (3/14) than those with no industry ties (3/29), RR = 2.07 (95% CI  
32  
33 418 0.48, 8.99; n=43) (Supplementary file 7). There was no clear evidence of an association when  
34  
35 419 comparing studies with industry sponsorship (2/8) to those with no industry sponsorship  
36  
37 420 (4/35), RR = 2.19 (95% CI 0.48-9.94). There was again no clear evidence of an association  
38  
39 421 between studies with an author with a COI (2/10) than those with no COI (4/33), RR = 1.65  
40  
41 422 (95% CI 0.35, 7.72; n=43).

42 423

## 43 424 **DISCUSSION**

44 425 There was no clear evidence of an association between studies with food industry ties and the  
45  
46 426 reporting of favourable results and conclusions of observational studies measuring the  
47  
48 427 associations of dairy foods with cardiovascular disease outcomes. The 'mixed' group of  
49  
50 428 funders we identified in the industry sponsored studies may influence these results, as the  
51  
52 429 funding effect may be diluted by this heterogeneous group of sponsors. Unlike in drug  
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3 430 studies,<sup>12</sup> the funders in the studies included in this review were extremely diverse, with Big  
4 431 Food and trade association jointly sponsoring several studies. Thus, dairy foods are not their  
5 432 sole interest.  
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9 433 The meta-analysis of hazard ratios of CVD outcomes found that studies with industry  
10 434 sponsorship showed a greater benefit from dairy than studies without industry sponsorship,  
11 435 and this difference was statistically significant. The meta-analysis of risk ratios of CVD  
12 436 outcomes found a similar estimate; however, this was not statistically significant. The likely  
13 437 reason for this was that the meta-analysis of RRs had fewer studies, and so the ratio of RRs  
14 438 could not be as precisely estimated. We found no evidence of a clinically important  
15 439 difference in the magnitude of effect between studies with industry ties or authors with a COI  
16 440 compared to those with no industry ties or no COI for other outcomes.  
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24  
25 442 For every study, the overall risk of bias was classified as high (meaning either serious or  
26 443 critical). Therefore, differences in the risk of bias across studies with and without industry  
27 444 ties would not seem to provide an explanation for our findings. However, the version of the  
28 445 ROBINS-E tool that we used may not have been able to adequately discriminate across the  
29 446 studies, as perhaps is indicated by the uniformity in risk of bias classification.<sup>26</sup> Therefore, we  
30 447 cannot rule out the possibility that differences in bias across studies with and without industry  
31 448 ties may partly explain our findings.  
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#### 40 450 **Strengths and limitations of this review**

41  
42 451 Our review was prospectively registered in Prospero.<sup>19</sup> We followed explicit inclusion and  
43 452 exclusion criteria, conducted a comprehensive search across multiple databases and hand  
44 453 searched reference lists for the included studies.  
45  
46  
47

48 454

49 455 For those studies missing a funding or author COI disclosure, we did not contact the authors  
50 456 and we therefore may be underestimating the number of studies with industry ties. The tool  
51 457 that we used to assess the risk of bias is still under development, however it is unlikely any  
52 458 future changes to the tool will affect the risk of bias ratings.<sup>22</sup> We did not analyse studies of  
53 459 low and full fat dairy or other types of dairy products separately. Industry ties may have  
54 460 different effects on studies of low or full fat dairy foods or other foods and drinks.  
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#### 60 461 **Agreements and disagreements with other studies or reviews**

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2  
3 462 The observed greater benefit of dairy on CVD outcomes in industry sponsored studies  
4  
5 463 compared to non-industry sponsored studies corroborates previous research that has  
6  
7 464 demonstrated studies sponsored by the food industry reported smaller harmful effect sizes for  
8  
9 465 soft drink consumption, compared with non-industry sponsored studies.<sup>17</sup> It is not consistent,  
10  
11 466 however, with a recent meta-analysis funded by the Israel Dairy Board that found non  
12  
13 467 statistically significant differences in the estimated associations between industry and non-  
14  
15 468 industry funded studies.<sup>18</sup> The differences in the results of our current review and this  
16  
17 469 previous study can be attributed to a number of important factors in how the studies were  
18  
19 470 conducted, including how the exposures were classified, the outcomes selected for the meta-  
20  
21 471 analyses and the analysis method used. For the exposures, our review included yogurt and  
22  
23 472 cheese, as well as ‘total dairy’ and milk, whereas the Dairy Board study included only ‘total  
24  
25 473 dairy’ and milk as exposures. We included all outcomes related to CVD, and the Dairy Board  
26  
27 474 study included only CVD and stroke, as well as Type 2 diabetes. For the analysis method, we  
28  
29 475 fitted separate meta-analyses for studies that had measured the association using HRs and  
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31 476 those that had used either RRs or ORs, while the Dairy Board study only measured the  
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33 477 associations using RRs.

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35 478  
36  
37 479 The lack of difference in the risks of bias between studies with industry ties and those with no  
38  
39 480 industry ties, is consistent with a previous review that examined the association of industry  
40  
41 481 ties with outcomes of studies examining the effect of wholegrain foods on CVD and mortality  
42  
43 482 that used the same tool to assess risk of bias.<sup>16</sup> These findings have also been shown in  
44  
45 483 pharmaceutical and tobacco research that have demonstrated industry sponsored studies are  
46  
47 484 of equal or better internal validity than studies with no sponsorship.<sup>12, 13, 15, 27, 28</sup>

### 485 486 **Implications for clinicians, policy makers and future research**

487  
488 As dietary guidelines depend on an evidence base that should be as free as possible of bias,  
49  
50 489 the difference in the magnitude of effects between industry sponsored studies compared to  
51  
52 490 non-industry sponsored studies is concerning. Therefore, the dairy intake recommendations  
53  
54 491 made in dietary guidelines should account for the potential influence of industry sponsorship  
55  
56 492 on evidence of health effects. Nutrition studies included in systematic reviews used in the  
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58 493 development of dietary guidelines should be assessed using empirical methods to identify  
59  
60 494 factors associated with study results. Current risk of bias tools should therefore be amended  
or supplemented to include industry sponsorship and author COI as a separate risk of bias

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2  
3 495 domain. The University of California, San Francisco's Navigation Guide assesses both author  
4  
5 496 conflicts of interest and funding sources as a risk of bias in human and animal studies.<sup>29</sup> As  
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7 497 the study designs used in nutrition are the same as those used to evaluate the harms of an  
8  
9 498 exposure in environmental health, dietary guideline committees could consider adopting this  
10  
11 499 tool to evaluate the risk of bias of the studies included in the systematic reviews used to  
12  
13 500 develop dietary guidelines.

14 501

15 502 Industry sponsors may bias research via different mechanisms, including the design and  
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17 503 conduct of a study, the selective reporting of results, how they code events, analyse data, by  
18  
19 504 spinning conclusions,<sup>11</sup> as well as framing how the questions are asked.<sup>30-32</sup> It has been  
20  
21 505 suggested that the dairy industry may preferentially fund research on topics which will  
22  
23 506 provide them with more favourable outcomes.<sup>33</sup> The influence of the food industry on the  
24  
25 507 research agenda has been demonstrated in an examination of research topics covered by  
26  
27 508 samples of randomised controlled trials included in systematic reviews of nutrition studies  
28  
29 509 and obesity.<sup>34</sup> It was shown that most food industry studies focused on the manipulations of  
30  
31 510 specific nutrients, and not on dietary behaviours, therefore limiting the public health  
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33 511 relevance of rigorous evidence available for use in both systematic reviews and dietary  
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35 512 guidelines.<sup>34</sup> The topics examined in cohort studies on the relationship of nutrition and  
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37 513 obesity, which tend to focus on more complex exposures than trials, did not demonstrate a  
38  
39 514 similar influence of funding source. However, the disclosure of food industry sponsorship  
40  
41 515 was low, making a comparison difficult.<sup>35</sup>

42 516

43 517 This present study has also demonstrated that there is significant funding for nutrition  
44  
45 518 research that comes from non-industry sources, including academia and government. In this  
46  
47 519 study, only eight studies had food industry sponsorship, while 34 had a non-food industry  
48  
49 520 sponsorship. A similar rate was seen in a study that assessed the association of industry ties  
50  
51 521 with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease  
52  
53 522 and mortality, with only five industry sponsored studies and 17 non-industry sponsored  
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55 523 studies.<sup>16</sup> To eliminate this risk of bias from nutrition research, investigators should use only  
56  
57 524 non-industry sources to fund their research.

58 525

59 526

60 527 **Conclusion**

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3 528 There was no clear evidence of an association between studies with food industry ties and the  
4 reporting of favourable results and conclusions compared with studies without industry ties.  
5 529  
6 However, the statistically significant difference in the magnitude of effects identified in  
7 530  
8 industry sponsored studies compared to non-industry sponsored studies is important in  
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10 532 quantifying industry influence on studies included in dietary guidelines.  
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4  
5 534 assistance with data collection.  
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10  
11 537 strategy and undertook the literature search. NC, AF and SMc, conducted the title and  
12  
13 538 abstract screening and full article screening for final study inclusion. NC, AF, JD, AL and  
14  
15 539 SMc conducted data collection and cleaning, LB supervised. NC and JMc undertook all data  
16  
17 540 analysis. LB advised on methods, statistical analyses, and interpretation of findings. All  
18  
19 541 authors contributed to the final manuscript. NC and LB are guarantors.  
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22  
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24  
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26  
27 545 Scholarship in Pharmacy from the University of Sydney.  
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31 547 **Competing interests:** None declared.  
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35 549 **Data sharing statement:** Available from The University of Sydney data repository. DOI to  
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37 550 be determined.  
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42 552 **Patient consent for publication:** Not required.  
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3 648 **Figures**  
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5 649 **Figure 1. Study Flow Diagram**  
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8 650 **Figure 2. Risk of Bias in Included Studies**  
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10 651 **Figure 3. Effect Size, Cardiovascular Disease: Industry sponsorship vs no industry**  
11 **sponsorship, Hazard Ratio**  
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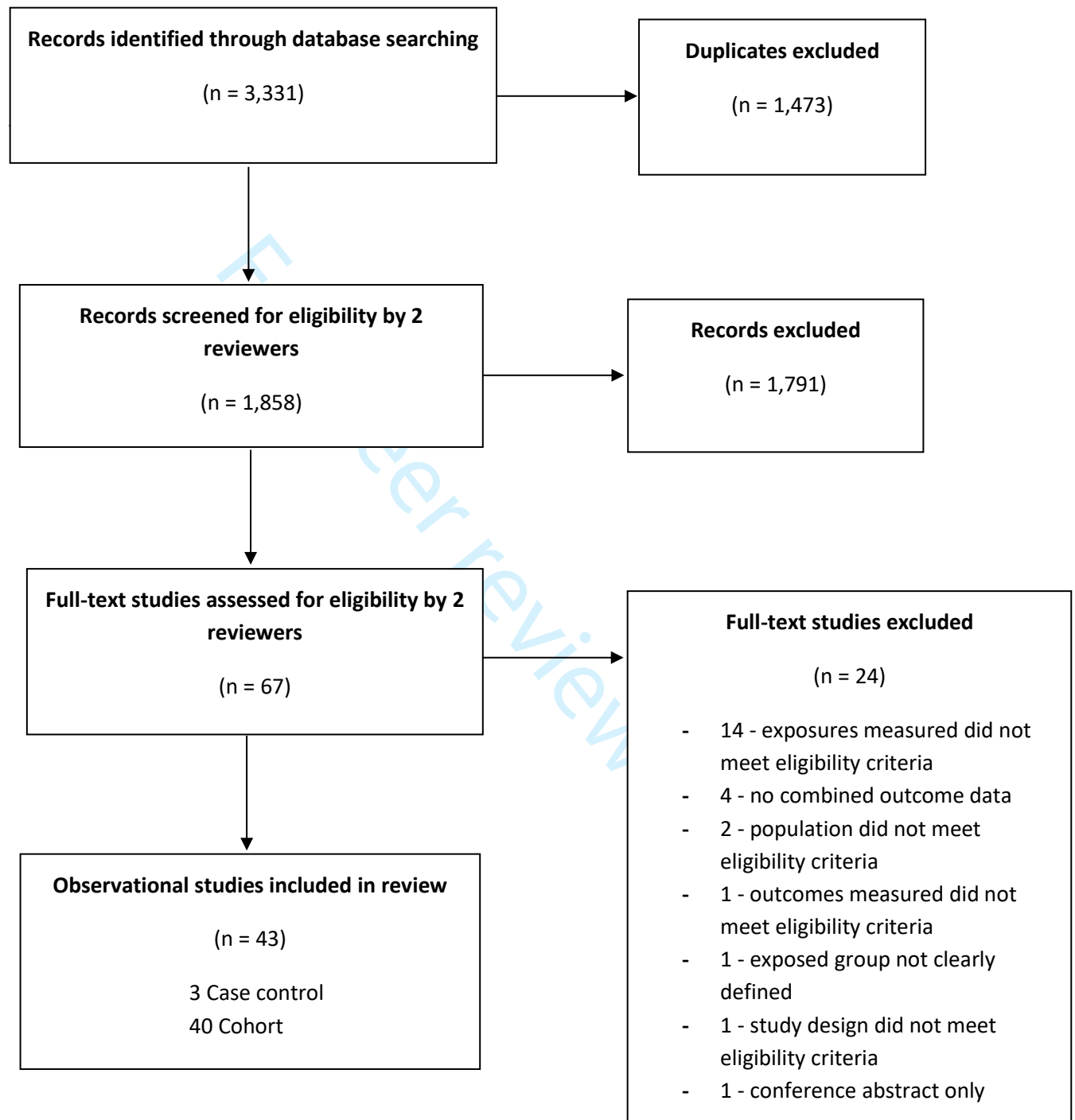
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Figure 1. Study Flow Diagram



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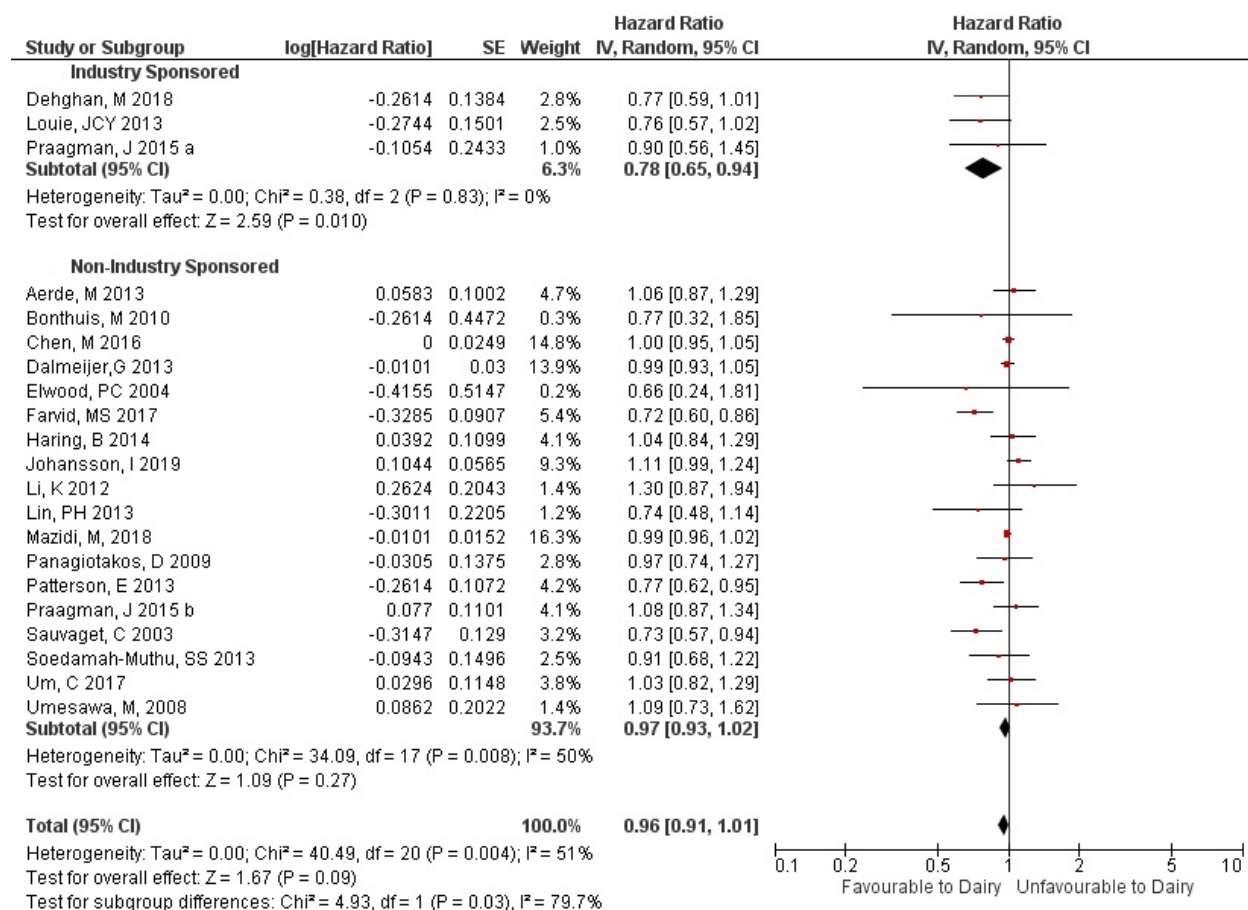
	Confounding	Selection of participants	Classification of exposures	Deviations from intended exposures	Missing data	Measurement of outcomes	Selection of the reported result	Overall bias
Aerde, M 2013	●	○	○	○	○	○	○	●
Al-Delaimy, WK 2003	○	○	○	●	●	●	○	○
Alonso A, 2005	●	○	○	○	○	○	○	●
Altorf-van der Kuil, W 2012	●	○	○	○	○	○	○	●
Avalos, EE 2013	●	○	●	●	○	○	○	●
Bernstein, AM 2012	○	○	○	●	●	○	○	○
Biong, A 2008	○	●	○	●	○	○	○	○
Bonthuis, M 2010	●	○	●	○	○	●	○	●
Buendia, JR 2018	○	○	○	●	○	○	○	○
Chen, M 2016	●	○	○	●	●	●	○	●
Dalmeijer, G 2013	●	○	○	○	○	○	○	●
Dauchet, L 2007	●	○	○	○	●	○	○	●
Dehghan, M 2018	●	○	○	○	○	○	○	●
Elwood, PC 2004	●	○	○	○	○	●	○	●
Engberink, MF 2009	●	○	○	○	○	○	○	●
Farvid, MS 2017	●	○	○	○	○	●	○	●
Haring, B 2014	●	○	○	○	●	○	○	●
He, K 2003	○	○	○	○	●	○	○	○
Heraclides, A 2012	●	○	○	○	○	○	○	●
Johansson, I 2018	●	○	○	○	●	●	○	●
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Kim, D 2017	●	○	○	○	○	●	○	●

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Larsson, S 2009								
Larsson, SC 2012								
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Lin, PH 2013								
Lockheart, MSK 2007								
Louie, JCY 2013								
Mazidi, M, 2018								
Nettleton, J 2008								
Panagiotakos, D 2009								
Patterson, E 2013								
Praagman, J 2015								
Praagman, J 2015								
Sauvaget, C 2003								
Snijder, MB 2008								
Soedamah-Muthu, SS 2013								
Steffen, LM 2005								
Tavani, A 2002								
Um, C 2017								
Umesawa, M, 2008								
Wang, L 2008								

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Figure 3. Effect Size, Cardiovascular Disease, Industry sponsorship vs no Industry sponsorship, Hazard Ratio



**PROSPERO**  
International prospective register of systematic reviews

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Centre for Reviews and Dissemination

## Systematic review

Please complete all mandatory fields below (marked with an asterisk \*) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below or click on the icon to see guidance on completing each section.

This record cannot be edited because it has been rejected

### 1. \* Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

The association of food industry ties with findings of studies examining the effect of dairy foods intake with cardiovascular disease and mortality: Systematic review and Meta-analysis: protocol registration:

### 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.

01/09/2016

### 4. \* Anticipated completion date.

Give the date by which the review is expected to be completed.

01/06/2019

### 5. \* Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

## PROSPERO

### International prospective register of systematic reviews

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
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 (e.g. Funded proposal, protocol not yet finalised).

#### 6. \* Named contact.

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

Nicholas Chartres

#### Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr Chartres

#### 7. \* Named contact email.

Give the electronic mail address of the named contact.

ngar0960@uni.sydney.edu.au

#### 8. Named contact address

Give 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.

Give the telephone number for the named contact, including international dialling 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.

University of Sydney

#### Organisation web address:

#### 11. \* Review team members and their organisational affiliations.

## PROSPERO

### International prospective register of systematic reviews

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**

Mr Nicholas Chartres. University of Sydney

Dr Alice Fabbri. The University of Sydney

Agnes Lau. University of California

Dr Joanna Diong. The University of Sydney

Assistant/Associate Professor Joanne Mckenzie. Monash University

Professor Lisa Bero. 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. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

Nicholas Chartres is a scholarship recipient (James Milner PhD scholarship in Pharmacy) from the University of Sydney.

#### Grant number(s)

#### 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.

None

#### 14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

#### 15. \* Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

The objective of this study is to determine if the presence of food industry sponsorship in primary nutrition studies examining the association of dairy 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 primary nutrition studies assessing the association of dairy foods with cardiovascular outcomes with industry sponsorship differ in their risk of bias compared with studies with no or other sources of sponsorship.

#### 16. \* Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

We will search the following databases from 2000-March 2019: Ovid MEDLINE; CINAHL; PubMed;

Cochrane Library; and ScienceDirect. No language restrictions will be applied

## PROSPERO

### International prospective register of systematic reviews

#### 17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy. Do NOT provide links to your search results.

[https://www.crd.york.ac.uk/PROSPEROFILES/129659\\_STRATEGY\\_20190322.pdf](https://www.crd.york.ac.uk/PROSPEROFILES/129659_STRATEGY_20190322.pdf)

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

#### 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.

To determine whether industry sponsorship and/or study methods are associated with the results and/or conclusions of primary nutrition studies assessing the association of dairy foods and cardiovascular outcomes.

#### 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.

We will include primary research studies of any design that quantitatively examine the association of dairy foods with cardiovascular outcomes in healthy adults.

#### 20. \* Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

- The study quantitatively measures the effects of dairy consumption in humans.
- The study evaluates the effectiveness, efficacy or harms of dairy consumption.
- The study compares dairy food to control OR dairy food to other foods OR different levels of dairy consumption
- The study evaluates cow, goat or sheep milk, yogurt, cheese or custard. We will include and use the studies definition of dairy it is broader than milk, yogurt, cheese or custard.
- The study evaluates skim, low or full fat dairy products
- The study evaluates the effect of nutrients, e.g calcium and vitamin D when consumed within a dairy product

#### 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). The preferred format includes details of both inclusion and exclusion criteria.

Dairy vs Dairy (different doses) Dairy vs Dairy (different fat content) Dairy vs No dairy Dairy vs Other food



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Other (mixed intervention)

#### 22. \* Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

RCTs, Controlled Trials, Cohort, Case-control, Pre/Post, Other/Various

#### 23. Context.

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

- The study has a test of interest (e.g. risk ratio/hazard ratio) of cardiovascular mortality, nonfatal heart attack, stroke, etc.) and/or the surrogate outcomes of Blood Pressure (mmHg)

#### 24. \* Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

a. Primary Outcome 1 and 2

- o Statistical significance of results
- o Effect size of outcomes

For each study, the result reported for each primary outcome will be categorized as:

(1) Favourable if the result are statistically significant ( $p < 0.05$  or 95% confidence interval [CI] excluding no difference) and in the direction of dairy being more efficacious, less harmful or no more harmful than the comparator;

(2) Unfavourable if the result was statistically significant (e.g.  $P < 0.05$  or 95% confidence interval including the possibility of no difference) in the direction of the comparator being more efficacious or less harmful.

We will also extract the effect estimates for primary outcomes.

We will classify the results of the study as favourable if the stated primary outcome is reported as favourable.

If the study has multiple primary outcomes we will report the study as favourable if at least one of the outcomes is reported as favourable.

b. Primary Outcome 3 (Conclusions)

The conclusions reported in the published papers will be categorized as:

(1) Favourable if the dairy intervention was preferred to comparator

(2) Unfavourable if the comparator intervention was preferred to the test one OR if the test intervention

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showed a risk increase.

#### \* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

As this is not relevant to our study, we have nothing to include.

#### 25. \* Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

~~We used the Cochrane Risk of Bias tool (15) 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-I tool for non-randomized studies (ROBINS-I)(16), which also measures bias across 7 domains.~~

#### d. Secondary Outcome 2 (Concordance between results and conclusions)

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'

#### \* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

As this is not relevant to our study, we have nothing to include.

#### 26. \* Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

##### Selection Process

Two investigators (NC & AF) will independently screen the titles and abstracts of all retrieved records for obvious exclusions. Two investigators (NC & AF) will then assess the remaining papers based on full text, applying the aforementioned inclusion criteria for included studies. Agreement will be reached on any discrepancies by consensus between the two assessors. If agreement cannot be reached, a third assessor (LB) will make a decision. The reasons for the eligible papers being excluded will be described in

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'Characteristics of excluded papers' table.

Data collection process

- a) Title of the paper
- b) Year of publication
- c) Study design
- d) Comparisons:
- e) Sample size of study
- f) Mean age of participants
- g) Intervention or observation period
- h) Definition of intervention and exposure
- i) Risk of Bias
- j) Primary Hypothesis of the study (Verbatim)
- k) Primary outcomes measures
- l) Conclusion
- m) Concordance between conclusions and results
- n) Industry Sponsorship
- o) Role of the Funder: Information about the role of the sponsor as stated in the study
- p) The institutional affiliation of the corresponding author will be obtained from the article and classified into the following categories
- q) Country of origin (verbatim)
- r) Author COI

#### 27. \* Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

We will use the Cochrane Risk of Bias tool for randomised studies (15) 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-I tool for non-randomized studies (ROBINS-I)(16), which also measures bias across 7 domains.

#### 28. \* Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

To test our hypothesis that studies with dairy industry sponsorship will be more likely to have favourable

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results, we will compare the risk of dairy industry sponsored studies having a favourable result with the risk of non-dairy industry funded studies having a favorable result. Using Rev Manager we will calculate the pooled risk ratio (RR) and its 95% confidence interval using the Mantel-Haenszel fixed-effect model.

However, when substantial heterogeneity is observed, we will use an inverse variance DerSimonian-Laird random-effects model. We will assess heterogeneity using  $I^2$  and use a random-effects model when statistical heterogeneity is substantial, defined as an  $I^2$  50%.

To test our hypothesis that effect estimates will differ between studies with dairy industry sponsorship and those without sponsorship, we will compare the pooled effect estimates from dairy vs. non-dairy sponsored studies. We will pool the effect estimates of homogenous studies measuring dichotomous outcomes, (e.g. RR, HR, OR for all-cause mortality, CVD mortality, cardiovascular events, etc) calculating pooled risk ratios as described above. Blood pressure is a continuous outcome, so we will attempt to pool homogeneous studies and measure the mean difference from baseline measures.

To test our hypothesis that studies with dairy industry sponsorship would be more likely to have favourable conclusions we will compare the risk of dairy industry sponsored studies having favourable conclusions with the risk of non-dairy industry funded studies having a favorable conclusion. We will calculate the pooled risk ratio (RR) and its 95% confidence interval using the Mantel-Haenszel fixed-effect model. However, when substantial heterogeneity is observed, we will use an inverse variance DerSimonian-Laird random-effects model. We will assess heterogeneity using  $I^2$  and use a random-effects model when statistical heterogeneity is substantial, defined as an  $I^2$  50%.

#### 29. \* Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

We will conduct an a priori subgroup analysis on low fat and full fat dairy products to determine if studies measuring the effects of low fat products have different results from studies that measure full fat dairy products.

We will conduct an a priori subgroup analysis by the risks of bias of the included studies to determine if studies that have a high risk of bias have different results from studies that have a low risk of bias. We hypothesize that industry sponsored studies will have the same level of risk of bias as non-industry sponsored studies.

#### 30. \* Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

##### Type of review

Cost effectiveness

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1  
2  
3  
4 No  
5 Diagnostic  
6 No  
7 Epidemiologic  
8 No  
9 Individual patient data (IPD) meta-analysis  
10 No  
11 Intervention  
12 No  
13  
14 Meta-analysis  
15 Yes  
16 Methodology  
17 No  
18 Narrative synthesis  
19 No  
20  
21 Network meta-analysis  
22 No  
23 Pre-clinical  
24 No  
25 Prevention  
26 No  
27 Prognostic  
28 No  
29  
30 Prospective meta-analysis (PMA)  
31 No  
32 Review of reviews  
33 No  
34 Service delivery  
35 No  
36  
37 Synthesis of qualitative studies  
38 No  
39 Systematic review  
40 Yes  
41 Other  
42 No  
43  
44  
45  
46 **Health area of the review**  
47 Alcohol/substance misuse/abuse  
48 No  
49 Blood and immune system  
50 No  
51 Cancer  
52 No  
53 Cardiovascular  
54 Yes  
55  
56 Care of the elderly  
57 No  
58 Child health  
59 No  
60 Complementary therapies

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1 No  
2  
3  
4 Crime and justice  
5 No  
6 Dental  
7 No  
8 Digestive system  
9 No  
10 Ear, nose and throat  
11 No  
12 Education  
13 No  
14 Endocrine and metabolic disorders  
15 No  
16 Eye disorders  
17 No  
18 General interest  
19 No  
20 Genetics  
21 No  
22 Health inequalities/health equity  
23 No  
24 Infections and infestations  
25 No  
26 International development  
27 No  
28 Mental health and behavioural conditions  
29 No  
30 Musculoskeletal  
31 No  
32 Neurological  
33 No  
34 Nursing  
35 No  
36 Obstetrics and gynaecology  
37 No  
38 Oral health  
39 No  
40 Palliative care  
41 No  
42 Perioperative care  
43 No  
44 Physiotherapy  
45 No  
46 Pregnancy and childbirth  
47 No  
48 Public health (including social determinants of health)  
49 Yes  
50 Rehabilitation  
51 No  
52 Respiratory disorders  
53 No  
54  
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56  
57  
58  
59  
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## PROSPERO

### International prospective register of systematic reviews

Service delivery

No

Skin disorders

No

Social care

No

Surgery

No

Tropical Medicine

No

Urological

No

Wounds, injuries and accidents

No

Violence and abuse

No

### 31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.  
English

There is not an English language summary

### 32. \* Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Australia

### 33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

### 34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

**No I do not make this file publicly available until the review is complete**

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

### 35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

## PROSPERO

### International prospective register of systematic reviews

#### Do you intend to publish the review on completion?

Yes

#### 36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

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

#### 37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

CRD42017055841 The association of industry sponsorship with outcomes of studies examining the effect of intake of wholegrain foods with cardiovascular disease and mortality: protocol

#### 38. \* Current review status.

Review status should be updated when the review is completed and when it is published. For new registrations the review must be Ongoing.

Please provide anticipated publication date

Review\_Ongoing

#### 39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

#### 40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.



**Supplementary file 2.** Search Strategy OVID Medline: Dairy, CVD, Adults

1. Randomized controlled trial\*.tw.
2. experimental design.tw.
3. intervention\*.tw.
4. (RCT\* or rct\*).tw.
5. random\* control\* trial\*.tw.
6. clinical trial\*.tw.
7. field trial\*.tw.
8. community trial\*.tw.
9. controlled clinical trial\*.tw.
10. pragmatic trial\*.tw.
11. observational stud\*.tw.
12. cohort stud\*.tw.
13. prospective cohort\*.tw.
14. retrospective cohort\*.tw.
15. case control\*.tw.
16. ecological stud\*.tw.
17. time series analys?s\*.tw.
18. before-after stud\*.tw.
19. pre-post stud\*.tw.
20. follow up stud\*.tw.
21. comparative stud\*.tw.
22. evaluation stud\*.tw.
23. dairy.mp.
24. dairy intake\*.mp.

- 1
- 2
- 3 25. dairy consumption.mp.
- 4
- 5 26. dairy food\*.mp.
- 6
- 7 27. Dairy Products/ or dairy product\*.mp.
- 8
- 9 28. dairy serv\*.mp.
- 10
- 11 29. dairy type\*.mp.
- 12
- 13 30. dairy source\*.mp.
- 14
- 15
- 16 31. (calcium adj15 food sourc\*).mp. [mp=title, abstract, original title, name of substance word,
- 17 subject heading word, keyword heading word, protocol supplementary concept word, rare
- 18 disease supplementary concept word, unique identifier]
- 19
- 20
- 21 32. (vitamin D adj15 food sourc\*).mp. [mp=title, abstract, original title, name of substance word,
- 22 subject heading word, keyword heading word, protocol supplementary concept word, rare
- 23 disease supplementary concept word, unique identifier]
- 24
- 25
- 26 33. (milk and (cow or goat or sheep)).mp. [mp=title, abstract, original title, name of substance
- 27 word, subject heading word, keyword heading word, protocol supplementary concept word, rare
- 28 disease supplementary concept word, unique identifier]
- 29
- 30
- 31 34. yogurt.mp. or Yogurt/
- 32
- 33 35. cheese.mp. or Cheese/
- 34
- 35 36. custard.mp.
- 36
- 37 37. (milk and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of
- 38 substance word, subject heading word, keyword heading word, protocol supplementary concept
- 39 word, rare disease supplementary concept word, unique identifier]
- 40
- 41
- 42 38. (yogurt and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of
- 43 substance word, subject heading word, keyword heading word, protocol supplementary concept
- 44 word, rare disease supplementary concept word, unique identifier]
- 45
- 46
- 47 39. Milk/
- 48
- 49 40. 23 or 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
- 50 39
- 51
- 52 41. cardiovascular disease.mp. or exp Cardiovascular Diseases/
- 53
- 54 42. coronary\*.tw.
- 55
- 56
- 57
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- 59
- 60

- 1
- 2
- 3 43. heart\*.tw.
- 4
- 5 44. cardia\*.tw.
- 6
- 7 45. cardio\*.tw.
- 8
- 9 46. myocard\*.tw.
- 10
- 11 47. isch?em\*.tw.
- 12
- 13 48. angina\*.tw.
- 14
- 15 49. ventric\*.tw.
- 16
- 17 50. tachycardi\*.tw.
- 18
- 19 51. pericard\*.tw.
- 20
- 21 52. endocardi\*.tw.
- 22
- 23 53. atrial fibrillat\*.tw.
- 24
- 25 54. arrhythmi\*.tw.
- 26
- 27 55. athero\*.tw.
- 28
- 29 56. arterio\*.tw.
- 30
- 31 57. exp Atherosclerosis/
- 32
- 33 58. exp Arteriosclerosis/
- 34
- 35 59. HDL.tw.
- 36
- 37 60. LDL.tw.
- 38
- 39 61. VLDL.tw.
- 40
- 41 62. lipid\*.tw.
- 42
- 43 63. lipoprotein\*.tw.
- 44
- 45 64. triacylglycerol\*.tw.
- 46
- 47 65. exp Hyperlipidemias/
- 48
- 49 66. hyperlipid\*.tw.
- 50
- 51 67. hypercholesterol\*.tw.
- 52
- 53
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- 1  
2  
3 68. hypercholester?emia\*.tw.  
4  
5 69. hypertriglycerid?emia\*.tw.  
6  
7 70. exp Cholesterol/  
8  
9 71. cholesterol\*.tw.  
10  
11 72. exp Stroke/  
12  
13 73. stroke\*.tw.  
14  
15 74. CVA.tw.  
16  
17 75. cerebrovasc\*.tw.  
18  
19 76. "vascular accident".tw.  
20  
21 77. TIA.tw.  
22  
23 78. cerebral vascular.tw.  
24  
25 79. thrombo\*.tw.  
26  
27 80. emboli\*.tw.  
28  
29 81. apoplexy.tw.  
30  
31 82. (brain adj2 accident\*).tw.  
32  
33 83. ((brain\* or cerebral or lacunar) adj2 infarct\*).tw.  
34  
35 84. Hypertension/  
36  
37 85. exp Blood Pressure/  
38  
39 86. hypertensi\*.tw.  
40  
41 87. blood pressure\*.tw.  
42  
43 88. systolic blood pressure.tw.  
44  
45 89. diastolic blood pressure.tw.  
46  
47 90. peripheral arter\* disease\*.tw.  
48  
49 91. (coronar\$ adj5 (bypas\$ or graft\$ or disease\$ or event\$)).tw.  
50  
51 92. (cerebrovasc\$ or cardiovasc\$ or mortal\$ or angina\$ or stroke or strokes).tw.  
52  
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1  
2  
3 93. (myocardi\$ adj5 (infarct\$ or revascular\$ or ischaemi\$ or ischemi\$)).tw.  
4

5 94. (morbid\$ adj5 (heart\$ or coronar\$ or ischaem\$ or ischem\$ or myocard\$)).tw.  
6

7 95. (vascular\$ adj5 (peripheral\$ or disease\$ or complication\$)).tw.  
8

9 96. (heart\$ adj5 (disease\$ or attack\$ or bypass\$)).tw.  
10

11 97. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or  
12 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73  
13 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or  
14 90 or 91 or 92 or 93 or 94 or 95 or 96  
15  
16

17 98. 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  
18 19 or 20 or 21 or 22  
19  
20

21 99. 40 and 97 and 98  
22

23 100. limit 99 to yr="2000 - 2019"  
24

25 101. limit 100 to humans  
26

27 102. limit 101 to "all adult (19 plus years)"  
28  
29  
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## Supplementary File 3. List of confounders

Outcome	Confounders	Confounders (all outcomes)
1. CVD mortality	Fibre supplement (p) Red Meat (h) Sodium (Na+) (h)	Age Sex BMI
2. CVD events	Fibre supplement (p) Magnesium supplement (p)	Smoking Alcohol intake
3. CHD mortality (incident CVD)	Fibre supplement (p) Trans Fat (h) Polyunsaturated fat (n-6) (p) Sodium (+Na) (h)	History of co-morbidities Parenteral/Fhx MI < 60 yrs PA levels SES
4. CHD events (incident CHD)	Fibre supplement (p) Trans fat (h) Magnesium supplement (p) Polyunsaturated fat (n-6) (p)	Total energy intake Fruit & Vegetable intake  <i>Specialised Confounders</i>
5. Total MI	Aspirin (p) Vitamin E supplement (p)	Hormone therapy
6. Fatal MI	Vitamin E supplement (p)	
7. Non-fatal MI	Aspirin (p)	
8. Total stroke	Potassium supplement (p) Red Meat (h) Sodium (+Na) (h)	
9. Ischemic stroke	Aspirin (p) Polyunsaturated fat (LC n-3) (p) Red meat (h)	
10. Haemorrhagic stroke	Aspirin (h)	
11. Systolic BP	Magnesium supplement (p) Sodium (-Na) (p) Polyunsaturated fat (supplement) (LC n-3) (p) Potassium supplement (p)	
12. Diastolic BP	Magnesium supplement (p) Sodium (-Na) (p) Polyunsaturated fat (supplement) (LC n-3) (p) Potassium supplement (p)	

p = protective, h = harmful

**a) Not Confounders (inconclusive evidence)**

Outcome	Not a confounder (inconclusive)
1. CVD mortality	Aspirin Dietary Saturated Fat Folate supplement Monounsaturated Fat Multivitamin Polyunsaturated Fat Total Dietary Fat Vitamin E supplement
2. CVD events	Folate supplement Monounsaturated Fat Multivitamin Polyunsaturated Fat Sodium Total Dietary Fat Vitamin E supplement
3. CHD mortality	Dietary Saturated Fat Magnesium supplement
4. CHD events	Dietary Saturated Fat Sodium Red Meat
5. Total MI	Dietary Saturated Fat Folate supplement Magnesium supplement Multivitamin Polyunsaturated Fat Total Dietary Fat
6. Fatal MI	Folate supplement Multivitamin
7. Non-fatal MI	Dietary Saturated Fat Folate supplement Multivitamin Polyunsaturated Fat Total Dietary Fat Vitamin E supplement

8. Total stroke	Aspirin Dietary Saturated Fat Folate supplement Monounsaturated Fat Multivitamin Polyunsaturated Fat Total Dietary Fat Vitamin E supplement
9. Ischemic stroke	Dietary Saturated Fat Trans Fat
10. Haemorrhagic stroke	Polyunsaturated Fat Red Meat
11. Systolic BP	Polyunsaturated Fat (dietary)
12. Diastolic BP	Polyunsaturated Fat (dietary)



## Supplementary file 4: List of excluded studies and reasons for exclusion

<b>Author</b>	<b>Title</b>	<b>Reason for Exclusion</b>
Akbaraly, T 2013 <sup>1</sup>	Does overall diet in midlife predict future aging phenotypes? A cohort study	Dietary patterns only were assessed, not dairy foods
Anderson, LA 2011 <sup>2</sup>	Dietary Patterns and Survival of Older Adults	No relevant outcomes were measured
Baylin, A 2003 <sup>3</sup>	High 18:2 trans-fatty acids in adipose tissue are associated with increased risk of nonfatal acute myocardial infarction in Costa Rican adults	Effects of dairy foods not measured
Beydoun, MA 2018 <sup>4</sup>	Dairy product consumption and its association with metabolic disturbance in a prospective study of urban adults	Groups exposed to dairy not clearly defined
Biong, AS 2006 <sup>5</sup>	Intake of milk fat, reflected in adipose tissue fatty acids and risk of myocardial infarction: a case-control study	Effects of dairy foods not measured
Chen, y 2013 <sup>6</sup>	Prospective investigation of major dietary patterns and risk of cardiovascular mortality in Bangladesh	Dietary patterns only were assessed, not dairy foods
Ding, M 2017 <sup>7</sup>	Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study	Not an observational design study
Eguchi, E 2012 <sup>8</sup>	Healthy lifestyle behaviours and cardiovascular mortality among Japanese men and women: the Japan collaborative cohort study	Dietary patterns only were assessed, not dairy foods
Geleijnse, JM 2017 <sup>9</sup>	Dietary Patterns in Relation to Cardiovascular Disease Incidence and Risk Markers in a Middle-Aged British Male Population: Data from the Caerphilly Prospective Study	Dietary patterns only were assessed, not dairy foods
Goldbohm, RA 2011 <sup>10</sup>	Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands	No combined outcome data
Julián-Almárcegui, C 2016 <sup>11</sup>	Association of heart rate and blood pressure among European adolescents with usual food consumption: The HELENA study	Participants were adolescents, not adults
Larsson, SC 2018 <sup>12</sup>	Dietary patterns, food groups, and incidence of aortic valve stenosis: A prospective cohort study	Dietary patterns only were assessed, not dairy foods
Lupton, BS 2003 <sup>13</sup>	The Finnmark Intervention Study: is it possible to change CVD risk factors by community-based intervention in an Arctic village in crisis?	No combined outcome data
Meyer, J 2011 <sup>14</sup>	Dietary patterns, subclinical inflammation, incident coronary heart disease and mortality	Dietary patterns only were assessed, not dairy foods

	in middle-aged men from the MONICA/KORA Augsburg cohort study	
Michaelsson, K 2013 <sup>15</sup>	Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study	Dietary calcium only was assessed, not dairy foods
Oomen, CM 2000 <sup>16</sup>	Arginine intake and risk of coronary heart disease mortality in elderly men	Effects of dairy foods not measured
Paillard, F 2015 <sup>17</sup>	Cardiovascular risk and lifestyle habits of consumers of a phytosterol-enriched yogurt in a real-life setting	Yogurt was enriched with phytosterols
Praagman, J 2016 <sup>18</sup>	The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort	Effects of dairy foods not measured
Streppel, MT 2014 <sup>19</sup>	Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study	Dietary patterns only were assessed, not dairy foods
Umesawa, M 2006 <sup>20</sup>	Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study	No combined outcome data
van der Pols, J C 2009 <sup>21</sup>	Childhood dairy and calcium intake and cardiovascular mortality in adulthood: 65-year follow-up of the Boyd Orr cohort	Participants were children, not adults
Warensjo, E 2009 <sup>22</sup>	Stroke and plasma markers of milk fat intake – a prospective nested case-control study	Effects of dairy foods not measured
Warensjo, E 2009 <sup>23</sup>	Milk Fat Biomarkers and the Risk of a First Ever Acute Myocardial Infarction - A Prospective Nested Case-Control Study. <i>Journal of the American Dietetic Association.</i> 2009;1	Poster presentation only, full study not available
Warensjo, E 2010 <sup>24</sup>	Biomarkers of milk fat and the risk of myocardial infarction in men and women: a prospective, matched case-control study	No combined outcome data

1. Akbaraly T, Sabia S, Hagger-Johnson G, et al. Does overall diet in midlife predict future aging phenotypes? A cohort study. *The American journal of medicine.* 2013;126(5):411-419.e413.
2. Anderson AL, Harris TB, Tylavsky FA, et al. Dietary Patterns and Survival of Older Adults. *Journal of the American Dietetic Association.* 2011;111(1):84-91.
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## Supplementary file 5: 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 dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Aerde, M 2013 <sup>(1)</sup>	Cohort	12.4 years	1,956 men & women	61.6 years	Total Dairy, 271 g/day per SD of the mean intake for Total dairy (all dairy products except butter)		Fatal CVD	Non-Industry <sup>1</sup>	Yes <sup>a</sup>
Al-Delaimy, WK 2003 <sup>(2)</sup>	Cohort	12 years	39,800 men	40-75 years	Dairy Calcium Q5, 819 mg/day (median) (dairy calcium intake summed the calcium intake from whole milk, skim or low-fat milk, yogurt, ice cream, cottage cheese, and other cheese was summed)	Q1, 106 mg/day	Fatal Ischemic Heart Disease	Non Industry <sup>2</sup>	No <sup>b</sup>
Alonso A, 2005 <sup>(3)</sup>	Cohort	27 months	5,880 men & women	37 years	Dairy Q 5, 798.8 g/day (whole-fat milk, partially skim milk, skim milk, condensed milk, whipped cream, yogurt, skim yogurt, milk-shake, cottage cheese or junket, petit Suisse cheese, spreadable cheese wedges, soft unripened cheese, other cheese, custard, and ice cream)	Q 1, 155.6 g/day	Hypertension	Non-industry <sup>3</sup>	No <sup>c</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Altorf-van der Kuil, W2012 <sup>(4)</sup>	Cohort	Mean follow up 7.5 years	3,588 men & women	44 years	Dairy Protein T3, $\geq 27$ g/day (dairy protein was calculated as protein from milk, yogurt, coffee creamer, curd, pudding, porridge, custard, whipped cream and cheese)	T1, $\leq 19$ g/day	Hypertension	Industry <sup>4</sup>	Yes <sup>d</sup>
Avalos, EE 2013 <sup>(5)</sup>	Cohort	Mean follow up 16.2 years	1,759 men & women	70.6 years men, 70.1 women	Whole Milk, Non-Fat Milk, Yogurt & Cheese, Sometimes/often (included daily, 4–6 times/week, 1–3 times/week and 1–3 times/months)	Rarely/never (included never & 1–11 times/year)	Incident CHD	Non-industry <sup>5</sup>	No <sup>e</sup>
Bernstein, AM 2012 <sup>(6)</sup>	2 Cohorts	26 and 22 years of follow-up in women and men, respectively	127,160 (43 150 men 84 010 women)	Men 40 to 75 years, Woman 30 to 55 years	Whole Fat Q 5, Men 2.55 servings/day, Woman 2.81 servings/day (whole milk, ice cream, hard cheese, full fat cheese, cream, sour cream, cream cheese, butter)  Low Fat Q5, Men 2.64 servings/day, Women 2.20 servings/day (skim/low-fat milk, 1% and 2% milk, yogurt, cottage and ricotta cheeses, low-fat cheese, sherbet)	Q 1, Men 0.21 servings/day, Woman 0.34 servings/day.  Low Fat Q1, Men 0.11 servings/day, Women 0.07 servings/day	Total Stroke	Non-industry <sup>6</sup>	Yes <sup>f</sup>
Biong, A 2008 <sup>(7)</sup>	Case Control		218 men & women	62.4 years	Dairy Fat, $> 34.1$ g/day	$<14.6$ g/day	First Myocardial Infarction	Industry <sup>7</sup>	Yes <sup>g</sup>

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Study ID	Study Deign	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Bonthuis, M 2010 <sup>(8)</sup>	Cohort	Mean 14.4 years	1,529 men & women	25–78 years	Total Dairy T3, 599 g/day (median) ('low-fat dairy products was computed by adding daily servings (in grams) of skim milk, low-fat milk, low-fat yoghurt, cottage or ricotta cheese, whereas the food group 'high-fat/unmodified dairy' included whole milk, cream, ice cream, yoghurt, full-fat cheese and custard. Total dairy intake was the sum of intake of all these dairy foods)	T1, 174 g/day	Cardiovascular Disease Mortality	Non-Industry <sup>8</sup>	No <sup>h</sup>
Buendia, JR 2018 <sup>(9)</sup>	3 Cohorts	30 years of follow-up in NHS, 20 years in NHS II, 24 years in the HPFS	NHS (N=69298), NHS II (N=84368), HPFS (N=30512)	Mean baseline ages in the 3 cohorts were 44.6, 35.8, and 50.7 years, respectively	Total Dairy Q4, 3 - <6 servings/day (total dairy intake included: milk (skim, low-fat, whole), ice cream, sherbet/ frozen yogurt, cheese (cottage, ricotta, hard, sliced), and yogurt (all types)	Q1, <0.5 servings/day	High Blood Pressure	Industry <sup>9</sup>	No <sup>i</sup>
Chen, M 2016 <sup>(10)</sup>	3 Cohorts	24 years in the HPFS, 32 years NHS, 20 years in NHS II	222,234 - 43,652 men HPFS, 87,907 women NHS, 90,675 women NHS II	40–75 years HPFS, 30–55 years NHS, 25–42 y NHS II	Dairy Fat, Q5	Q1	CVD	Non-Industry <sup>10</sup>	No <sup>j</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Dalmeijer, G 2013 <sup>(11)</sup>	Cohort	13 years	33,625 men & women	49.0 years	Total dairy and its subtypes were evaluated as continuous variables per standard deviation of the mean intake which is 265 g/d for total dairy (total dairy included all dairy food products except for butter and ice cream. Milk and milk products included all kinds of milk, yogurt, coffee creamers, curd, pudding, porridge, custard, and whipping cream)		Incident of Coronary Heart Disease & Incident Stroke	Non-Industry <sup>11</sup>	Yes <sup>k</sup>
Dauchet, L 2007 <sup>(12)</sup>	Cohort	5.4 years	2,341 men & women	Men 52.7 years, Women 46.9 years	Dairy Q4, 456 g/day (dairy products including milk, cheese, yogurt, and other dairy products)	Q1, 84 g/day	Systolic & Diastolic Blood Pressure	Non-Industry <sup>12</sup>	No <sup>l</sup>



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Study ID	Study Deign	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Dehghan, M 2018 <sup>(13)</sup>	Cohort	9.1 yrs	136,384 men & women	50-1 years	Dairy Q4, >2 servings/day (median) (dairy comprised milk, yoghurt, various types of cheese, yoghurt drink, and mixed dishes prepared with dairy. Mixed dishes prepared with dairy were dis- aggregated into their constituents and a proportional weight was assigned to each component. Then each component was included in the related dairy group.	Q1, 0 servings/day	Cardiovascular Mortality or Major Events	Industry <sup>13</sup>	No <sup>m</sup>
Elwood, PC 2004 <sup>(14)</sup>	Cohort	20-24 years	2,403 men	45-59 years	Milk Q4, >1 pint per day	Q1, None	Vascular Event	Non-Industry <sup>14</sup>	No disclosure

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Engberink, MF 2009 <sup>(15)</sup>	Cohort	6 years	2,245 men & women	>55 years	Dairy Q4, 691 g/day (i.e. 4.5 servings/day) (median intake) (calculated total dairy intake by summing the intake of individual dairy items, except butter and ice cream. The category "milk and milk products" included all kinds of milk, yogurt, coffee creamer, curd, pudding, porridge, custard, and whipped cream. The category "cheese" included all kinds of cheese products, ie, soft cheese, hard cheese, and cheese spreads)	Q1, 164 g/day (i.e. 1 serving/day) (median intake)	Hypertension	No disclosure	No <sup>a</sup>
Farvid, MS 2017 <sup>(16)</sup>	Cohort	8 years	42,403 men & women	51.6 years	Total Dairy Q5, 2.4 servings/day (median) (total dairy product items listed in the food frequency questionnaire included milk, cheese, yogurt, liquid yogurt (doogh), dried yogurt paste (kashk), and cream)	Q1, 0.4 servings/day (median)	Cardiovascular Disease Mortality	Non-Industry <sup>15</sup>	No <sup>a</sup>
Haring, B 2014 <sup>(17)</sup>	Cohort	22 years (median)	12,066 men & women	45-64 years	Dairy Protein Q5, 2.9 servings/day	Q1, 0.1 median servings/day	Coronary Heart Disease	Non-Industry <sup>16</sup>	No <sup>a</sup>
He, K 2003 <sup>(18)</sup>	Cohort	14 years	43,732 men	40-75 years	High Fat Dairy Q5, $\geq 1$ /day	Q1, <1/week	Ischaemic & Haemorrhagic Stroke	Non-Industry <sup>17</sup>	No <sup>a</sup>

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Study ID	Study Deign	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Heraclides, A 2012 <sup>(19)</sup>	Cohort	10 years	1,750 men & women	Men 43 years, Women 53 years	Total Dairy T3, 309.0 g/day (median) (full-fat milk; semi-skimmed milk; skimmed milk; milk-containing beverages (full fat, semi-skimmed and skimmed); full-fat cheese; low-fat cheese; full-fat yoghurt; low-fat yoghurt; fruit-flavoured yoghurt (full fat and low fat); and milk-based puddings)	T1, 224.1 g/day	Incident Hypertension	Non-Industry <sup>18</sup>	Yes <sup>r</sup>
Johansson, I 2018 <sup>(20)</sup>	Cohort	8-12 years	27,682 men & women	29-65 years	Dairy Q 5, 7.1 servings/day (median)	Q1, 1.6 servings/day (median)	Blood Pressure	Non-Industry <sup>19</sup>	No <sup>s</sup>
Johansson, I 2019 <sup>(21)</sup>	Cohort	14.2 years	108,065 men & women	calculated mean = 52.5 years *	High Fat & Low Fat Non-Fermented Milk & Cheese Q 4, high dose	Q1, low dose	Myocardial Infarction & Stroke	Non-Industry <sup>20</sup>	No <sup>t</sup>
Kim, D 2017 <sup>(22)</sup>	Cohort	67-4 months	4,335 men & women	40-69 years	Total Dairy Q 5, >7 servings/week	Q 1, <1 servings/week	Blood Pressure	Non-Industry <sup>21</sup>	No <sup>u</sup>
Larsson,S 2009 <sup>(23)</sup>	Cohort	13.6 years	26,556 men	50-69 years	Dairy Q5, 1295.6 g/day (median) (including low-fat milk, whole milk, sour milk, yogurt, cheese, cream, ice cream, and butter)	Q1 286.5 g/day	Cerebral Infarction, Intracerebral Haemorrhage, Subarachnoid Hemorrhage	Non-Industry <sup>22</sup>	No disclosure

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Larsson, SC 2012 <sup>(24)</sup>	Cohort	10.2 years	74,961 men & women	45-83 years	Dairy Q5, 9.3 servings/day (median) (dairy foods included low-fat milk (0.5% fat), medium-fat milk (1.5% fat), full-fat milk (3% fat), milk in pancakes, low-fat sour milk/yogurt (0.5% fat), full-fat sour milk/yogurt (3% fat), cottage cheese (4% fat), low-fat cheese (10%-17% fat), full-fat cheese (approximately 28% fat), ice cream, cream, and creme fraiche)	Q1, 2.3 servings/day	Total Stroke	Non-Industry <sup>23</sup>	No <sup>v</sup>
Li, K 2012 <sup>(25)</sup>	Cohort	11 years	23,980 men & women	35-64 years	Dairy Calcium Q4, 780 mg/day	Q1, 188 mg/day	CVD Mortality	Non-Industry <sup>24</sup>	No <sup>w</sup>
Lin, PH 2013 <sup>(26)</sup>	Cohort	12 years	2,061 men & women	45.8 years (no information for stroke group)	Dairy T3, (dairy milk of any kind, cheese, yogurt).	T1	Total Stroke	Non-Industry <sup>25</sup>	No <sup>x</sup>
Lockheart, MSK 2007 <sup>(27)</sup>	Case Control		211 men & women	62.5 years cases and 62.2 years controls	Low Fat Dairy T3, 618 g/day (Low-fat milk, skimmed milk, light sour cream)	T 1, 48 g/day	First Myocardial Infarction	Industry <sup>26</sup>	No disclosure
Louie, JCY 2013 <sup>(28)</sup>	Cohort	15 years	2,625 men & women	49-97 years	Total Dairy T3, 2.9 servings/day (median) (included all dairy foods)	T1, 0.6 servings/day	Total CVD	Industry <sup>27</sup>	No disclosure
Mazidi, M, 2018 <sup>(29)</sup>	Cohort	76.4 months	24,474 men & women	47.6 years	Total Dairy Q4, 3.08 cup equivalent servings/day (total dairy, milk, cheese, and yogurt)	Q1, 0.25 cup equivalent servings/day	CHD Mortality & Cerebrovascular Disease mortality	Non-Industry <sup>28</sup>	No <sup>y</sup>

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Study ID	Study Deign	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Ness, AR 2001 <sup>(30)</sup>	Cohort	25 years	5,765 men	35-64 years	Milk T3, > 1 pint (= 0.568 liters)	T1, None	Cardiovascular Disease Deaths	Non-Industry <sup>29</sup>	No <sup>z</sup>
Nettleton, J 2008 <sup>(31)</sup>	Cohort	13.3 years	14,153 men & women	45 to 64 years	High Fat Dairy, per 1 daily serving difference in food group intake		Incident Heart Failure	Non Industry <sup>30</sup>	No <sup>aa</sup>
Panagiotakos, D 2009 <sup>(32)</sup>	Cohort	5 years	3,042 men & women	18-89 years	Low Fat Dairy, 1-unit increase in components' scores (0%, 2% or total fat), like cheese, yogurt, milk)		CVD Events	Non-Industry <sup>31</sup>	No disclosure
Patterson, E 2013 <sup>(33)</sup>	Cohort	11.6 years	33,636 women	48-83 years	Total Dairy, Q5 8.4 servings/day (median) (total dairy intake was the sum of milk [full-fat (≥3.0% fat), semi-skimmed (≤1.5% fat), skimmed (0.5% fat), and pancakes], cultured milk/yogurt [full-fat (≥3.0% fat) and low-fat (≤1.5% fat)], cheese [full-fat (>17% fat), low-fat (≤17% fat), and cottage cheese/ quark], cream and creme fariche (full fat and low fat) intakes)	Q1, 2.2 servings/day	Myocardial Infarction	Non Industry <sup>32</sup>	No <sup>bb</sup>
Praagman, J 2015 (a) <sup>(34)</sup>	Cohort	13.3 years (median)	4,235 men & women	66.9 years	Total Dairy, T3 >400g/day (total dairy included milk, buttermilk, yogurt, coffee creamer, curd, pudding, porridge, custard, whipped cream, ice cream, and cheese, but not butter)	Total Dairy, T 1 <200 g/day	Fatal Stroke & Fatal CHD	Industry <sup>33</sup>	Yes <sup>cc</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Praagman, J 2015 (b) <sup>(35)</sup>	Cohort	15 years	34,409 men & women	Men 51 years & women 43 years	Total Yogurt & Cheese Q4, (fermented dairy foods)	Q1	CVD Mortality	Non-Industry <sup>34</sup>	Yes <sup>dd</sup>
Sauvaget, C 2003 <sup>(36)</sup>	Cohort	16 years	37,130 men & women	56 years	Dairy Q4, Almost Daily (dairy products (butter and cheese, excluding margarine))	Q1, Never	Total Stroke	Non-Industry <sup>35</sup>	No disclosure
Snijder, MB 2008 <sup>(37)</sup>	Cohort	6.4 years	1,124 men & women	50–75 years	Dairy Q4, 5.75-17.24 servings/day (range) (total dairy consumption was categorized as low-fat dairy ( $\leq 2\%$ fat) or high-fat dairy ( $> 2\%$ fat). The variable dairy desserts included yoghurt, curds, and custard. The variable milk included low-fat, skim, and, whole milk. The variable yoghurt included all low-fat, skim, and whole yoghurts)	Q1 0-2.97 servings/day (range)	Systolic & Diastolic Blood Pressure	Industry <sup>36</sup>	Yes <sup>ee</sup>
Soedamah-Muthu, SS 2013 <sup>(38)</sup>	Cohort	10.8 years	4,255 men & women	56 years	Dairy, T3 575 g/day (median) (all dairy products, except butter and ice cream)	T1, 246 g/day (median)	Fatal & Non-Fatal CHD	Non-Industry <sup>37</sup>	Yes <sup>ff</sup>
Steffen, LM 2005 <sup>(39)</sup>	Cohort	15 years	4,304 men & women	18-30 years	Dairy Foods Q5, $> 3.4$ times/day (dairy foods, including milk, cheese, yogurt, and dairy desserts)	Q1, $< 1.1$ times/day	Blood Pressure	Non-Industry <sup>38</sup>	No <sup>gg</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Tavani, A 2002 <sup>(40)</sup>	Case Control		985 men & women	61 years (median)	Total milk >7 cups/week, Yogurt >= 7 portions/week, Cheese >=350g/week	Total milk 0 cups/week, Yogurt 0 portions/week, Cheese <200g/week	Acute Myocardial Infarction	Non-Industry <sup>39</sup>	No <sup>hh</sup>
Um, C 2017 <sup>(41)</sup>	Cohort	5.7 years of follow-up	21,427 men & women	calculated mean = 64.8 years**	Total Dairy Q5, 17.8 servings/day (dairy products (milk, cream, fermented dairy products, ice cream, butter, cheeses))	Q1, 0.9 servings/day	CVD Mortality	Non-Industry <sup>40</sup>	No <sup>ii</sup>
Umesawa, M, 2008 <sup>(42)</sup>	Cohort	12.9-year follow-up	41,526 men & women	40-59 years	Dairy Calcium, Q5, 116 mg/day (median) (to calculate dairy calcium intake, we specified 2 kinds of dairy products, ie, cheese and dairy products except cheese, for the baseline questionnaire, and 4 kinds, ie, whole milk, low fat milk, cheese, and yogurt, for the 5-year follow-up questionnaire)	Q1, 0 mg/day	Total Stroke & CHD	Non-Industry <sup>41</sup>	No <sup>jj</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Wang,L 2008 <sup>(43)</sup>	Cohort	10 years	28,886 women	53.8 years	Total Dairy Q5, 3.69 servings/day (median) (total dairy product intake was calculated by summing the intake of individual dairy items: low-fat dairy items include skim or low-fat milk, sherbet, yogurt, and cottage/ricotta cheese, high-fat dairy items include whole milk, cream, sour cream, ice cream, cream cheese, and other cheese)	Q1, 0.56 servings/day (median)	Hypertension	Non-Industry <sup>42</sup>	No <sup>kk</sup>

\* We calculated the mean age score of participants by summing Non-cases, T2D, MI and stroke cases at baseline and dividing them by 4

\*\*We calculated the mean age score of participants by summing all quintiles 1, 3, & 5 (they were the only ones available) at baseline and dividing them by 5



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- 7
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- 9
- 10 d) Altorf-van der Kuil W, Engberink MF, Geleijnse JM - Top Institute Food and Nutrition, PO Box 557, 6700 AN, Wageningen, The
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- 25
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- 38
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## Supplementary File 6. Risk of bias in included studies

Funding Source, n (%<sup>a</sup>)

Characteristic	Category	Total N = 43	Sponsorship		COI		Industry Ties	
			Industr y N= 8	Non- Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non- Industry/ No COI N = 29
<b>Risk of Bias Assessment</b>								
	Serious/Critical Bias due to confounding	43 (100)	8 (100)	35 (100)	10 (100)	33 (100)	14 (100)	29 (100)
	Serious/Critical Bias in selection of participants into the study	6 (14)	1 (13)	5 (14)	1 (10)	5 (15)	2 (14)	4 (14)
	Serious/Critical Bias in classification of exposures	16 (37)	3 (38)	13 (37)	2 (20)	14 (42)	3 (21)	13 (44)
	Serious/Critical Bias due to deviations from exposures	21 (49)	3 (38)	18 (51)	6 (60)	15 (45)	7 (50)	14 (48)
	Serious/Critical Bias due to missing data	10 (23)	2 (25)	8 (23)	3 (30)	7 (21)	3 (21)	7 (24)

	Serious/Critical Bias in measurement of outcomes	6 (14)	2 (25)	4 (11)	1 (10)	5 (15)	2 (14)	4 (14)
	Serious/Critical Bias in selection of reported results	4 (9)	1 (13)	3 (9)	2 (20)	2 (6)	2 (14)	2 (7)
	Serious/Critical overall risk of bias	43 (100)	8 (100)	35 (100)	10 (100)	33 (100)	14 (100)	29 (100)

<sup>a</sup> Percentages may not add to 100 due to rounding

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Supplementary File 7: Favorable Outcomes by Industry Ties v No Industry Ties, Industry Sponsorship v No Industry Sponsorship and Conflicts of Interest v No Conflicts of Interest

Industry Ties: Industry Sponsorship and/or Author Conflicts of Interest					No Industry Ties: No Industry Sponsorship and No Author Conflicts of Interest				
Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable	Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable
Aerde, M 2013	Non-Industry	Yes	U	U	Al-Delaimy, WK 2003	Non Industry	No	U	U
Altorf-van der Kuil, W2012	Industry	Yes	U	U	Alonso A, 2005	Non-industry	No	U	U
Bernstein, AM 2012	Non-industry	Yes	U	U	Avalos, EE 2013	Non-industry	No	U	U
Biong, A 2008	Industry	Yes	U	F	Bonthuis, M 2010	Non-Industry	No	U	U
Buendia, JR 2018	Industry	No	F	F	Chen, M 2016	Non-Industry	No	U	F
Dalmeijer, G 2013	Non-Industry	Yes	U	F	Dauchet, L 2007	Non-Industry	No	U	U
Dehghan, M 2018	Industry	No	U	F	Elwood, PC 2004	Non-Industry	No disclosure	U	U
Heraclides, A 2012	Non-Industry	Yes	U	U	Engberink, MF 2009	No disclosure	No	U	F
Lockheart, MSK 2007	Industry	No disclosure	U	U	Farvid, MS 2017	Non-Industry	No	F	F
Louie, JCY 2013	Industry	No disclosure	U	U	Haring, B 2014	Non-Industry	No	U	U
Praagman, J 2015	Industry	Yes	U	U	He, K 2003	Non-Industry	No	U	U

Industry Ties: Industry Sponsorship and/or Author Conflicts of Interest					No Industry Ties: No Industry Sponsorship and No Author Conflicts of Interest				
Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable	Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable
Praagman J, 2015	Non-Industry	Yes	U	U	Johansson, I 2018	Non-Industry	No	U	U
Snijder, MB 2008	Industry	Yes	U	U	Johansson, I 2019	Non-Industry	No	U	U
Soedamah-Muthu, SS 2013	Non-Industry	Yes	U	U	Kim, D 2017	Non-Industry	No	F	F
					Larsson,S 2009	Non-Industry	No disclosure	U	U
					Larsson, SC 2012	Non-Industry	No	U	U
					Li, K 2012	Non-Industry	No	U	U
					Lin, PH 2013	Non-Industry	No	U	U
					Mazidi, M, 2018	Non-Industry	No	F	F
					Ness, AR 2001	Non-Industry	No	U	U
					Nettleton, J 2008	Non-Industry	No	U	U
					Panagiotakos, D 2009	Non-Industry	No disclosure	U	U
					Patterson, E 2013	Non-Industry	No	F	F
					Sauvaet, C 2003	Non-Industry	No disclosure	F	F
					Steffen, LM 2005	Non-Industry	No	U	U

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Industry Ties: Industry Sponsorship and/or Author Conflicts of Interest					No Industry Ties: No Industry Sponsorship and No Author Conflicts of Interest				
Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable	Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable
					Tavani, A 2002	Non-Industry	No	F	F
					Um, C 2017	Non-Industry	No	U	F
					Umesawa, M, 2008	Non-Industry	No	F	F
					Wang,L 2008	Non-Industry	No	F	F

**Favourable results - Statistical significance: Industry ties vs no industry ties; industry sponsorship vs no sponsorship; COI v no COI**

**Industry Ties**

	Industry/COI	Non-Industry/No COI
Favourable	1	8
Unfavourable	13	21

RR= 0.26 (95% CI 0.04, 1.87)

**Industry Sponsorship**

	Industry	Non-Industry
Favourable	1	8
Unfavourable	7	27

RR = 0.55 (95% CI 0.08, 3.77)

### Conflicts of Interest

	COI	No/COI
Favourable	0	9
Unfavourable	10	24

RR= 0.16 (95% CI 0.01, 2.57)

**Favourable conclusions: Industry ties vs no industry ties; industry sponsorship vs no sponsorship; COI v no COI**

### Industry Ties

	Industry/COI	Non-Industry/NO COI
Favourable	4	11
Unfavourable	10	18

RR = 0.75 (95% CI 0.29, 1.95)

### Industry Sponsorship

	Industry	Non-Industry
Favourable	3	12
Unfavourable	5	23

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RR= 1.09 (95% CI 0.40, 2.99)

**Conflicts of Interest**

	COI	No COI
Favourable	2	13
Unfavourable	8	20

RR =0.51 (95% 0.14, 1.88)

**Concordance between study results and conclusions: Industry ties vs no industry ties; industry sponsorship vs no sponsorship; COI v no**

**COI Industry Ties**

**Industry Ties**

	Industry/COI	Non-Industry/NO COI
Discord	3	3
Concord	11	26

RR = 2.07 (95% CI 0.48, 8.99)

**Industry Sponsorship**

	Industry	Non-Industry
Discord	2	4
Concord	6	31

RR = 2.19 (95% CI 0.48, 9.94)

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**Conflicts of Interest**

	COI	No/COI
Favourable	2	4
Unfavourable	8	29

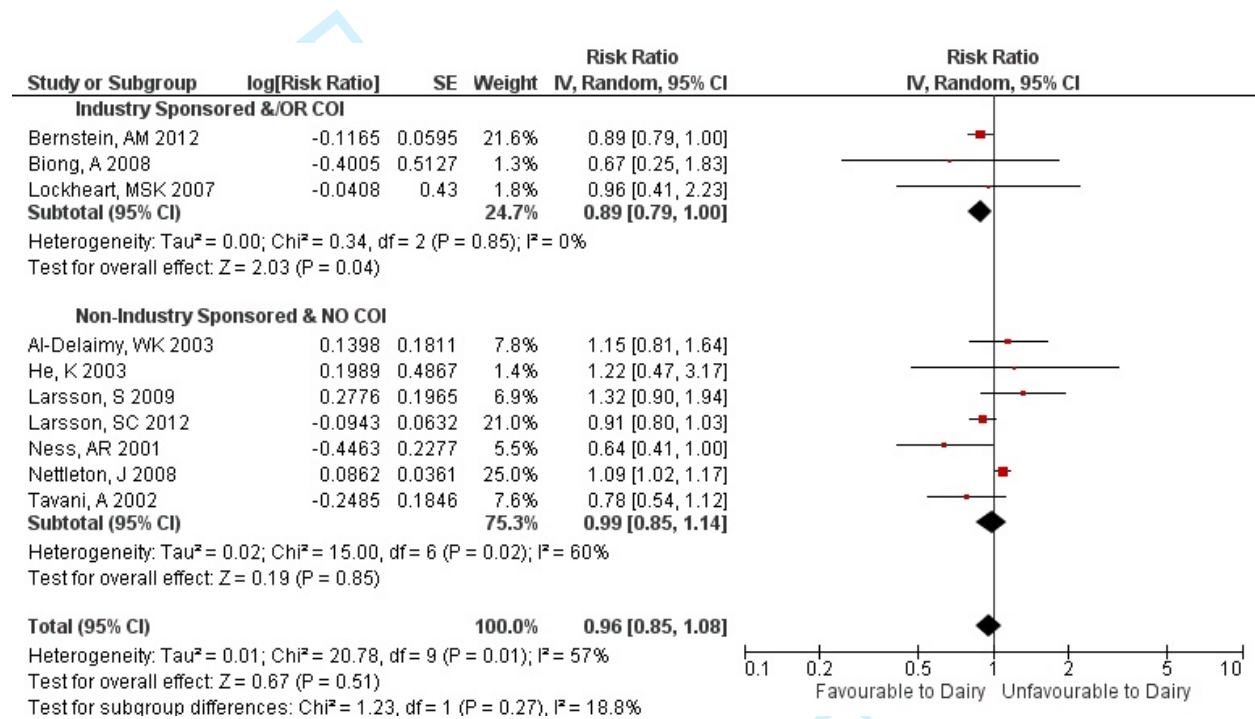
RR = 1.65 (95% CI 0.35, 7.72)

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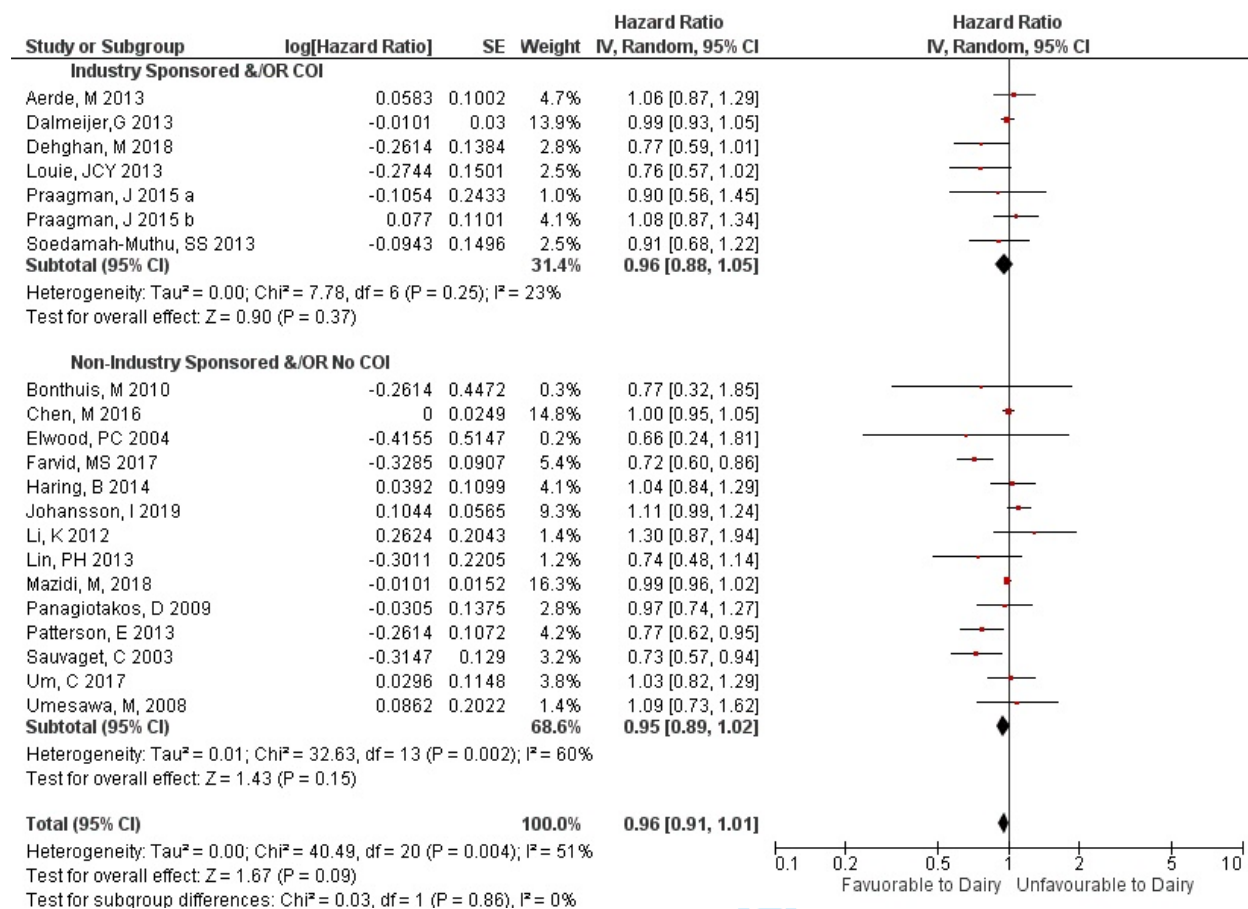


## Supplementary File 8. Results for each of the meta-analyses conducted

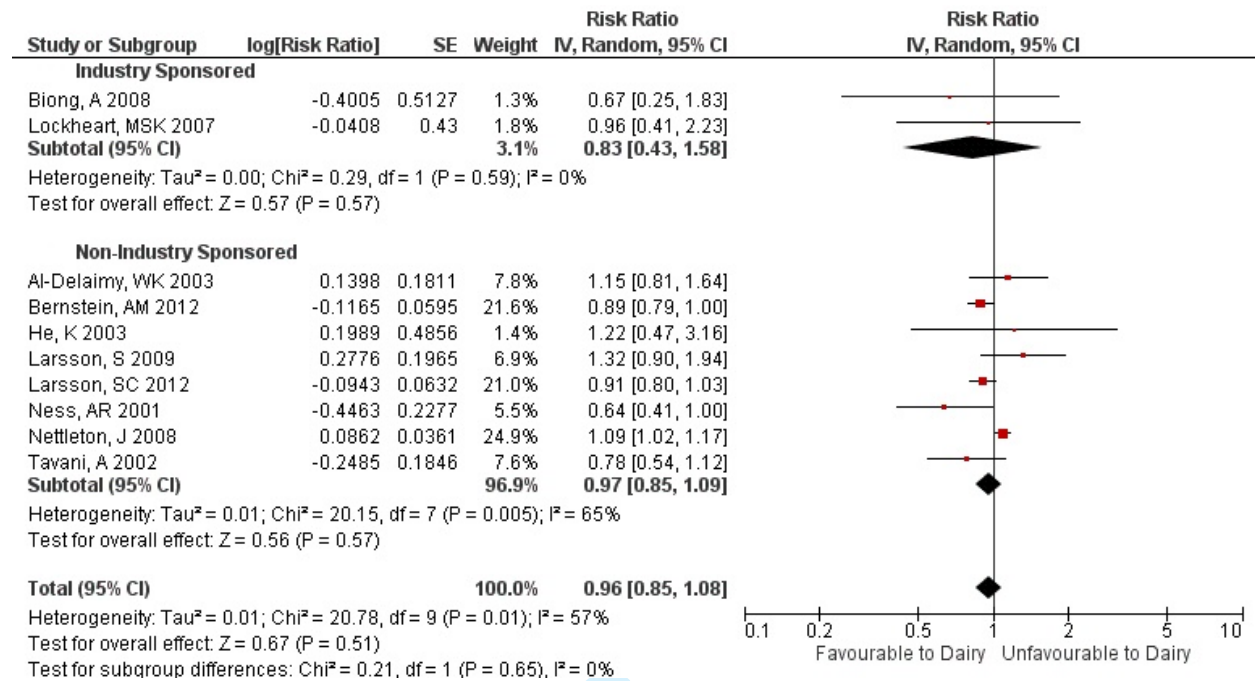
## Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Risk Ratio



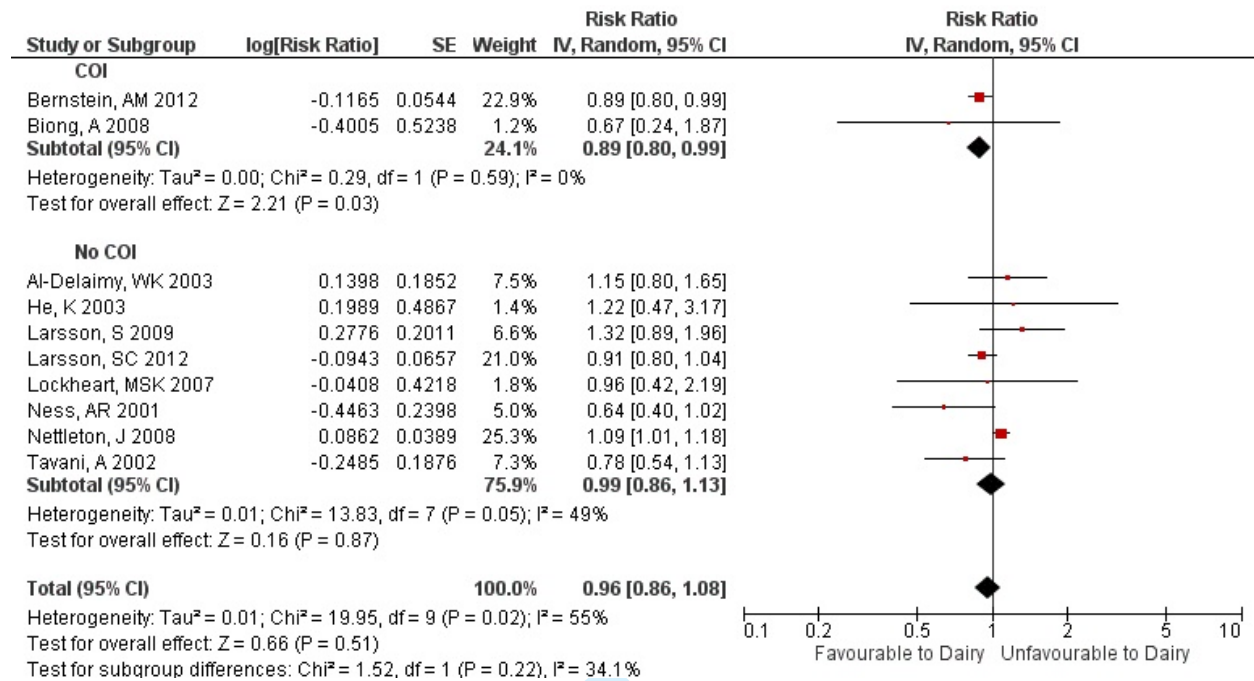
Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Hazard Ratio



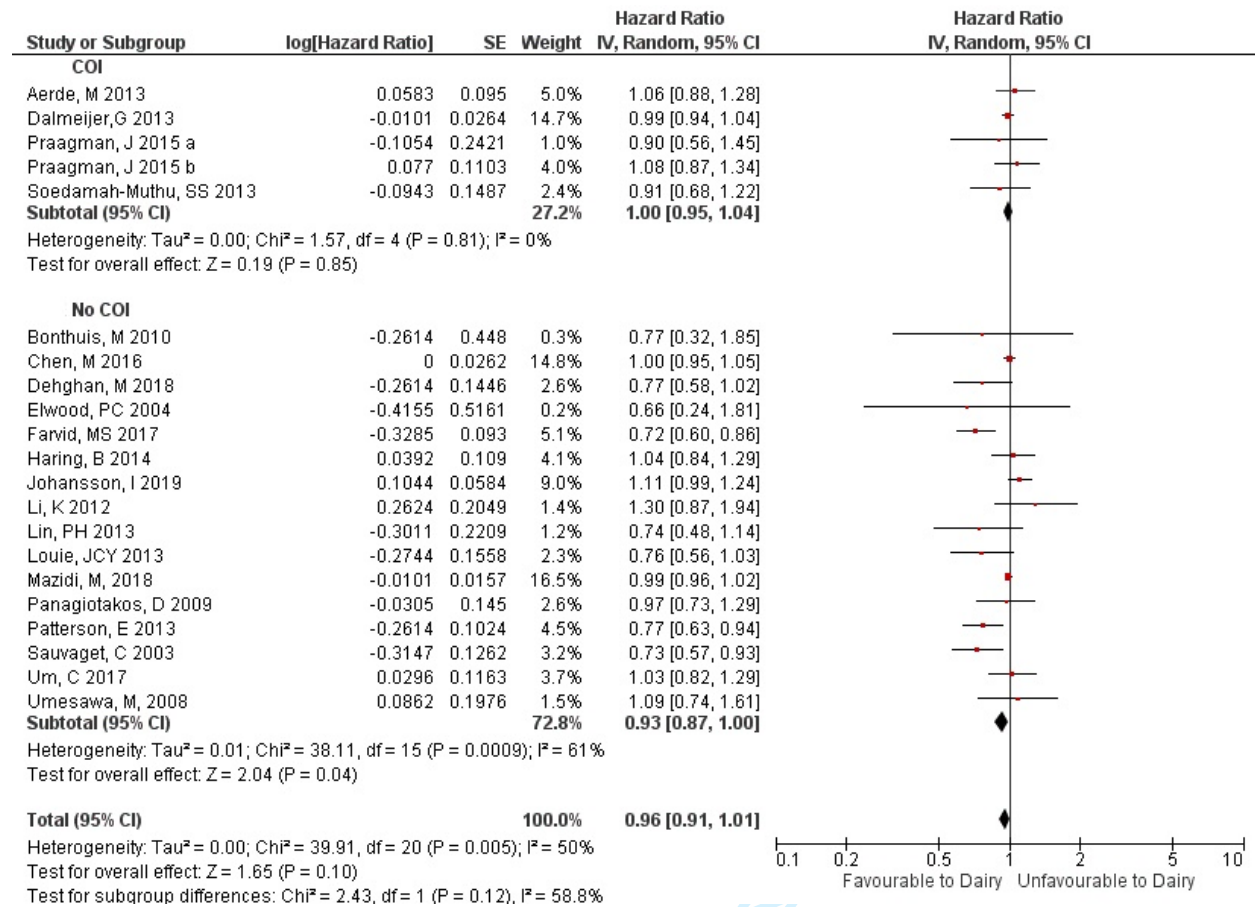
## Effect Size, Cardiovascular Disease: Industry sponsorship vs no industry sponsorship, Risk Ratio



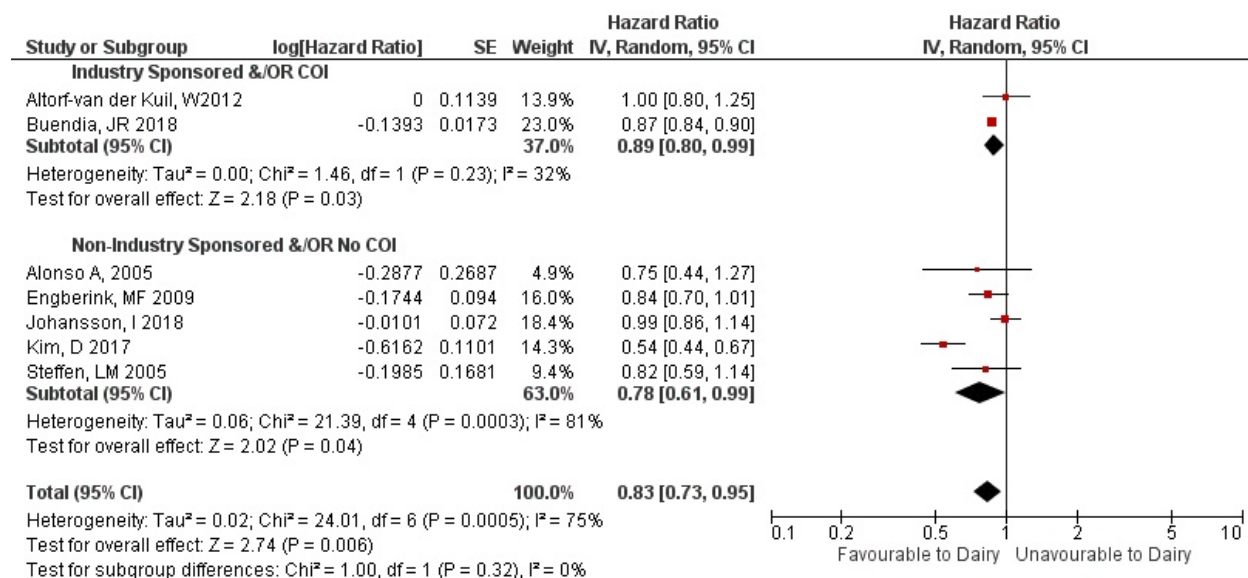
Effect Size, Cardiovascular Disease: COI vs No COI, Risk Ratio



## Effect Size, Cardiovascular Disease: COI vs no COI, Hazard Ratio



Effect Size, Elevated Blood Pressure / Hypertension: Industry ties v no industry ties





# PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3&5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Supp file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7 & 11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6 & 10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ for each meta-analysis). <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	10 -11



# PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11, Figure 1, Supp file 4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supp file 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13, Supp File 6, Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-15, Supp file 7 & 8, Figure 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13, Supp file 6, Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16





# PRISMA 2009 Checklist

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Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3&20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

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# BMJ Open

## The association of food industry ties with findings of studies examining the effect of dairy foods intake on cardiovascular disease and mortality: Systematic review and Meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-039036.R2
Article Type:	Original research
Date Submitted by the Author:	13-Oct-2020
Complete List of Authors:	Chartres, Nicholas; The University of Sydney, Charles Perkins Centre Fabbri, Alice; University of Insubria, Centre for Research in Medical Pharmacology McDonald, Sally ; The University of Sydney, ; the University of Sydney Diong, Joanna; The University of Sydney Faculty of Medicine and Health McKenzie, Joanne; Monash University Bero, Lisa; University of Sydney Faculty of Health Sciences, Pharmacy
<b>Primary Subject Heading</b>:	Research methods
Secondary Subject Heading:	Public health, Epidemiology, Health policy, Nutrition and metabolism
Keywords:	STATISTICS & RESEARCH METHODS, NUTRITION & DIETETICS, PUBLIC HEALTH

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3 1 **The association of food industry ties with findings of studies examining the effect of**  
4 **dairy foods intake on cardiovascular disease and mortality: Systematic review and**  
5 **Meta-analysis**  
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## 20 Abstract

21 **Objective:** To determine if the association of dairy foods with cardiovascular disease  
22 outcomes differs between studies with food industry ties versus those without industry ties.  
23 To determine whether studies with or without industry ties differ in their risk of bias.

24 **Eligibility criteria:** We included cohort and case control studies that estimated the  
25 association of dairy foods with cardiovascular disease (CVD) outcomes in healthy adults.

26 **Information sources:** We searched eight databases on February 1, 2019 from 2000-2019 and  
27 hand searched reference lists

28 **Risk of bias:** We used the Risk of Bias in Non-Randomized Studies-of Exposure (ROBINS-  
29 E) tool.

30 **Included studies:** 43 studies (3 case controls, 40 cohorts).

31 **Synthesis of results:** There was no clear evidence of an association between studies with  
32 industry ties (1/14) vs. no industry ties (8/29) and the reporting of favourable results, RR=  
33 0.26 (95% CI 0.04, 1.87; n=43 studies) and studies with industry ties (4/14) vs. no industry  
34 ties (11/29) and favourable conclusions, RR= 0.75 (95% CI 0.29, 1.95; n=43).. Studies with  
35 industry sponsorship, (HR =0.78; n= 3 studies) showed a decreased magnitude of risk of  
36 CVD outcomes compared to studies with no industry sponsorship (HR=0.97; n=18) (ratio of  
37 HRs 0.80 (95% CI 0.66, 0.97)) P=0.03.

38 **Strengths and Limitations of evidence:** Every study had an overall high risk of bias rating;  
39 this was primarily due to confounding.

40 **Interpretation:** There was no clear evidence of an association between studies with food  
41 industry ties and the reporting of favourable results and conclusions compared with studies  
42 without industry ties. The statistically significant difference in the magnitude of effects  
43 identified in industry sponsored studies compared to non-industry sponsored studies,  
44 however, is important in quantifying industry influence on studies included in dietary  
45 guidelines.

46 **Funding:** This work was supported by Australian Health and Medical Research Council  
47 Project Grant APP 1139997.

48 **Registration:** Prospero ID CRD42019129659

51 **Keywords:** Industry Sponsorship, Conflicts of Interest, Bias, Dietary Guidelines

53 **Strengths and limitations of this study**

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4 54 • This is the first systematic review and meta-analysis to evaluate the association of  
5 55 food industry ties (industry sponsorship and / or author conflicts of interest (COI))  
6 56 with the results, conclusions and risk of bias of primary nutrition studies examining  
7 57 the association of dairy foods with cardiovascular disease outcomes and mortality.  
8  
9 58 • We conducted a comprehensive search and followed explicit and well-defined  
10 59 inclusion and exclusion criteria for the included studies.  
11  
12 60 • For studies missing a funding or author COI disclosure, we did not contact the  
13 61 authors; thus we may be underestimating the number of studies with industry ties.  
14  
15 62 • The tool that we used to assess the risk of bias is still under modification, however it  
16 63 is unlikely any future changes to the tool will affect the risk of bias ratings.  
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18 64 • We did not analyse studies of low and full fat dairy separately. Industry ties may have  
19 65 different effects on studies of low or full fat dairy foods.  
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## 67 INTRODUCTION

68 The effect of dairy foods on cardiovascular disease (CVD) is unclear. Recent systematic  
69 reviews and meta-analyses of observational studies have reported conflicting results between  
70 the association of total dairy consumption and risk of CVD, with some showing decreased  
71 risk and some showing no clear evidence.<sup>1-4</sup> The beneficial effects of decreasing blood  
72 pressure, however, appear more consistent.<sup>4,5</sup> Further, dairy intake recommendations made in  
73 dietary guidelines around the world vary. Although the Australian Dietary Guidelines  
74 concluded that there is a probable association between dairy food consumption and a reduced  
75 risk of cardiovascular events,<sup>6</sup> recent amendments to the Eatwell guidelines by Public Health  
76 England recommend a significant reduction in the daily intake of dairy foods.<sup>7</sup>

77

78 Food industry sponsors and authors with a conflict of interest (COI) with the food industry  
79 may gain financially from finding that dairy foods have health benefits, since such a finding  
80 can be used to market dairy products. Such a driver may lead industry sponsors to magnify  
81 (or bias) the health benefits of dairy foods by influencing the research agenda, design and  
82 conduct of the study, or reporting of the results.<sup>8-11</sup> Prior examinations of pharmaceutical and  
83 tobacco research have identified that even when controlling for methodological biases,  
84 studies sponsored by industry were more likely to have results that favoured the sponsor than  
85 studies with other sources of sponsorship.<sup>12-14</sup>

86

87 The effects of food industry sponsorship or author COI with the food industry on study  
88 results needs further examination.<sup>15</sup> A systematic review assessing the association of  
89 wholegrain foods with CVD and mortality found that studies with food industry ties more  
90 often have favourable results and conclusions compared to those with no industry ties, but the  
91 association was uncertain.<sup>16</sup> One study has demonstrated an association of food industry  
92 sponsorship with the magnitude of effect estimates.<sup>17</sup> In this examination, studies of soft  
93 drink consumption sponsored by the food industry reported significantly smaller harm effect  
94 estimates than those with no food industry sponsorship. A recent dairy industry funded meta-  
95 analysis of observational studies found that studies without food industry sponsorship showed  
96 that dairy consumption was associated with a statistically significant decreased risk of  
97 developing CVD and Type 2 diabetes, while studies with food industry sponsorship did not.<sup>18</sup>

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3 98 The primary objective of this systematic review and meta-analysis is to determine whether:  
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5 99 • Studies of observational design examining the associations of dairy foods with CVD  
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7 100 with food industry ties (industry sponsorship and / or authors with a COI) are more  
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9 101 likely to have results and / or conclusions that are favourable to industry than those  
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11 102 with no industry ties.  
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14 104 The secondary objectives of this review are to determine whether observational studies with  
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16 105 food industry ties compared with no industry ties:

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18 106 I. differ in their risk of bias;  
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20 107 II. have a higher level of discordance between study results and conclusions, with the  
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22 108 conclusions more likely to be favourable compared to the results.  
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## 26 27 110 **METHODS**

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29 111 We conducted a systematic review of observational studies examining the effect of dairy  
30  
31 112 consumption on CVD. Our study is registered with Prospero ID CRD42019129659 (see  
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33 113 Supplementary file 1).<sup>19</sup>  
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### 36 115 **Search Strategy**

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38 116 The search included terms to locate observational studies and randomised control trials, the  
39  
40 117 latter of which are for a separate systematic review. The search used was based on the  
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42 118 Process Manual used to develop the 2013 Australian Dietary Guidelines and the guidance of  
43  
44 119 an information specialist.<sup>20</sup> The search dates used were to ensure that we identified the  
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46 120 studies used to inform the recommendations in these guidelines. We therefore searched the  
47  
48 121 following databases from January 2000-February 2019: MEDLINE; CINAHL; PubMed;  
49  
50 122 PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy  
51  
52 123 used for Ovid MEDLINE on February 1, 2019 is shown in Supplementary file 2. We adapted  
53  
54 124 this strategy for the other databases. We hand searched references lists of the identified  
55  
56 125 studies and reviews.  
57  
58  
59  
60



## 129 **Eligibility Criteria**

130 We included studies of cohort or case control designs that estimated the effects of dairy  
131 consumption on CVD outcomes in healthy adults. We focused on these study designs as they  
132 are often used to assess the association of diet with long term health outcomes.

133  
134 We included studies with no restriction on the authors' definition of dairy. For example, some  
135 authors' defined dairy as milk, yogurt and cheese, while others defined dairy as 'whole fat'  
136 milk, yogurt and cheese. We included studies that compared dairy foods to other foods or  
137 compared various levels of dairy consumption.

138  
139 We included studies that measured any clinical outcome of CVD, defined as either mortality  
140 related to specific CVD events, and / or CVD events, (e.g., first myocardial infarction, total  
141 stroke etc.) or incidence of elevated blood pressure / hypertension.

142  
143 We excluded conferences presentations, opinion pieces and letters to the editor. We had no  
144 language restrictions.

145

## 146 **Types of Outcome Measures**

### 147 **Primary Outcomes**

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

151 1. Statistical significance of results favourable to dairy

152 Favourable results were defined as those that were in the direction of showing a health  
153 benefit of dairy product(s), and were statistically significant at the 0.05 level (two tailed),  
154 such as a statistically significant decreased risk of CVD compared to the comparator (i.e.  
155 another food or lower dairy consumption). Otherwise, results were classified as unfavourable.  
156 In the circumstance where a study reported multiple results (e.g. first myocardial infarction  
157 and total stroke), only one result needed to be 'favourable' for the study as a whole to be  
158 classified as 'favourable'.

159

160 2. Effect size of results

161 Effect size was defined as the risk ratio (RR), hazard ratio (HR) or odds ratio (OR) between  
162 dairy foods tested versus comparator on the CVD outcome.

163

### 3. Conclusions

Conclusions that suggested that the dairy consumption was beneficial to health by decreasing CVD were considered favourable. Otherwise, the conclusions were considered unfavourable. In the circumstance where a study reported multiple results (e.g. first myocardial infarction and total stroke), only one conclusion needed to be 'favourable' for the study as a whole to be classified as 'favourable'.

170

#### **Secondary Outcomes**

We assessed two secondary outcomes:

##### 1. The risk of bias of the included studies

To evaluate the risk of bias of included observational studies, we used an adapted version of the Cochrane Collaboration's 'Risk of Bias in Non-Randomized Studies-of Interventions' (ROBINS-I) tool,<sup>21</sup> the ROBINS-E<sup>22</sup>. Bias is assessed across seven domains ('Bias due to confounding', 'Bias in selection of participants', 'Bias in classification of exposures', 'Bias due to deviations from exposures', 'Bias due to missing data', 'Bias in measurement of outcomes', 'Bias in selection of reported results'), with each domain classified low, moderate, serious, critical risk of bias, or no information. The first step in using the ROBINS-E tool is to identify all possible confounders that a study should control. We developed this list of confounders by searching the literature for the most recent systematic reviews on possible confounders and having this list reviewed by expert Professors in nutrition at The University of Sydney (see Supplementary file 3 for list of confounder). An overall risk of bias rating for the study is given based on the domain with the highest risk of bias rating. For example, if a study is rated as being at a 'critical' risk of bias in one domain, the overall risk of bias rating is 'critical.' In the circumstance where a study reported multiple results (e.g. stroke and myocardial infarction), the risk of bias was only assessed for one randomly selected outcome.

190

##### 2. Concordance between study results and conclusions

Results unfavourable to the sponsor with conclusions favourable to the sponsor, were considered discordant. Otherwise, the results and conclusions were considered concordant.

194

#### **Selection of studies**

195

1  
2  
3 196 Three investigators (NC, SMC & AF), working independently in pairs, screened the titles and  
4  
5 197 abstracts of all records for obvious exclusions. If both investigators agreed on excluding the  
6  
7 198 study, the full text was not retrieved. Three investigators (NC, SMC & AF) working  
8  
9 199 independently in pairs, assessed the full text of potentially eligible studies against the  
10  
11 200 inclusion criteria. If agreement could not be reached, a fourth investigator (LB) resolved the  
12  
13 201 conflict.  
14

202

### 203 **Selection of results for meta-analysis**

17 204 If total dairy consumption had been assessed in the study, we included this as our only  
18  
19 205 exposure. If total dairy consumption had not been assessed, we included any type of dairy  
20  
21 206 consumption (e.g. milk, yogurt, and cheese; or low fat, high fat) other than fermented milk as  
22  
23 207 our exposure. We included the results comparing the highest level of dairy consumption to  
24  
25 208 the lowest level of dairy consumption (e.g., 'yes' to dairy consumption vs. 'no' to dairy  
26  
27 209 consumption, tertile 3 vs. tertile 1, quartile 4 vs. quartile 1, quintile 5 vs. quintile 1). For the  
28  
29 210 meta-analyses if our pre-specified rules for selecting results did not allow us to uniquely  
30  
31 211 identify one exposure for inclusion, we randomly selected one result.

212

32  
33 213 If 'cardiovascular disease mortality/death/s' (verbatim) had been assessed, we included this  
34  
35 214 as our only outcome. If not, we included any type of CVD mortality (e.g., coronary heart  
36  
37 215 disease mortality, stroke mortality etc.) as our outcome. If there were no mortality outcomes  
38  
39 216 assessed in the study, we included any CVD event or incidence of elevated blood pressure /  
40  
41 217 hypertension as our outcome. If a study used a composite outcome, which was a combination  
42  
43 218 of multiple outcomes, the result pertaining to the composite outcome was selected. For the  
44  
45 219 meta-analyses if our pre-specified rules for selecting results did not allow us to uniquely  
46  
47 220 identify one outcome for inclusion, we randomly selected one result.

221

### 222 **Data Collection**

223 From each study we extracted:

- 51 224 • Year of publication
- 53 225 • Study design (cohort or case control)
- 55 226 • Sample size of study
- 57 227 • Age of participants (combined or if reported, separately)
- 59 228 • Exposure duration or observation period

60

- 1  
2  
3 229 • How the study defined dairy (verbatim)  
4  
5 230 • Disclosure of funding source (no disclosure, yes and there is a sponsor, the authors  
6 state they received no funding for their work)  
7 231  
8 232 • Name of the funders of the study (verbatim)  
9  
10 233 • Role of the funders (role of the sponsor not mentioned, sponsor not involved in study  
11 design and analyses, sponsor involved, N/A)  
12 234  
13 235 • Disclosure of author COI (no disclosure, yes (if at least 1 author had a COI), the authors  
14 state they had no conflicts of interest to declare)  
15 236  
16 237 • Authors COI statement (verbatim)  
17  
18 238 • Outcomes assessed in the study (any CVD death and/or event or blood  
19 pressure/hypertension)  
20 239  
21 240 • The numerical results of the study (e.g., OR, HR, RR)  
22  
23 241

24  
25 242 All extracted data from the included studies was stored in REDcap, a secure web-based  
26 application for the collection and management of data.<sup>23</sup> Five investigators (NC, SMc, AF,  
27 AL & JD) working independently in pairs extracted data from the included studies.  
28 243  
29 244 Discrepancies in data extraction were resolved by consensus. If agreement could not be  
30 reached, a sixth investigator (LB) resolved the discrepancy.  
31 245  
32 246  
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34 247

### 248 **Classification of industry sponsorship and author conflicts of interest**

249 Sponsorship was categorized as 1) industry or 2) non-industry. Industry sponsored studies  
250 were defined as those that declared any sponsorship from the food industry, including 'Big  
251 Food' (i.e. Danone, Kraft, Unilever etc), trade associations (i.e. dairy associations and  
252 organisations) and dairy industry (i.e. primary producers). Studies with food industry  
253 sponsorship plus any other sponsorship were classified as industry. Any study that did not  
254 contain a funding disclosure statement was classified as 'non-industry'.  
255

256 Studies with at least one author with any disclosed financial tie with the food industry were  
257 classified as having a conflict of interest (COI). Author COI were categorised as 1) COI or 2)  
258 no COI. Studies with no authors with disclosed financial ties with the food industry were  
259 classified as 'no conflict of interest'.  
260

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2  
3 261 Since the number of studies with industry sponsorship or author COI was small, we also  
4 262 categorized studies as having “industry ties” for analysis. Studies classified as having an  
5 263 industry tie were industry sponsored and / or had an author COI. Otherwise, they were  
6 264 classified as having no industry ties.  
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10 265

## 11 266 **Analysis**

12 267 We report the frequencies and percentages of the study characteristics across all studies, and  
13 268 separately, by sponsorship, COI and industry ties. We visually present the risk of bias rating  
14 269 for each domain and overall across each study.  
15  
16  
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19 270

20 271 To quantify the association between industry ties, food industry sponsorship, or authors with  
21 272 a conflict of interest with the food industry and (i) favourable results, (ii) favourable  
22 273 conclusions, (iii) overall risk of bias across each study, and (iv) level of concordance, we  
23 274 calculated RR (and 95% confidence intervals). To analyse the risk of bias rating for each  
24 275 study, we dichotomised the overall risk of bias ratings as low (low or moderate) or high  
25 276 (serious or critical).  
26  
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31 277

32 278 We conducted meta-analysis to examine whether studies with food industry ties, food  
33 279 industry sponsorship, or authors with a conflict of interest with the food industry modified the  
34 280 magnitude of effect of dairy on CVD outcomes.. For each outcome, we combined effect  
35 281 estimates using a random effects meta-analysis model using the inverse variance method.  
36 282 DerSimonian and Laird’s method of moments estimator was used to estimate between study  
37 283 heterogeneity. We fitted separate meta-analyses for studies that had measured the association  
38 284 using HRs and those that had used either RRs or ORs. It is not recommended to combine HRs  
39 285 with RRs and ORs in a meta-analysis, as HRs represent instantaneous risk over the study time  
40 286 period, whereas RRs and ORs estimate risk/odds at a fixed time point.<sup>24</sup> We considered that  
41 287 the ORs approximated RRs given CVD events were rare.  
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51 289 We undertook a fixed-effects test for subgroup differences (defined by industry sponsorship /  
52 290 authors conflict of interest) using the Chi<sup>2</sup> test and calculated the ratio of RRs (ORs) or HRs  
53 291 along with 95% confidence intervals. Analyses were undertaken in Review Manager 5.3.<sup>25</sup>  
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2  
3 293 We planned to use sensitivity analysis to assess the influence of risk of bias by restricting the  
4 294 analysis to studies at ‘low risk of bias’ overall (i.e. an overall risk of bias rating of low or  
5 295 moderate). However, as the overall risk of bias was high across all studies, this was not  
6 296 undertaken.  
7  
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10 297

## 11 298 **Patient and Public Involvement**

12 299 No patient involved  
13  
14  
15

16 300

## 17 301 **RESULTS**

18 302 As shown in Figure 1, there were 1, 858 studies screened for inclusion and 43 studies were  
19 303 included (3 case controls, 40 cohorts). See Supplementary file 4 for ‘List of excluded studies  
20 304 and reasons for exclusion’.  
21  
22  
23

24 305

### 25 306 **Characteristics of included Studies**

26 307 All studies were published between 2001 and 2019. All but one contained a funding  
27 308 disclosure. Eight studies disclosed food industry sponsorship, but only two of these studies  
28 309 described the role of the sponsor. Six studies did not contain an author COI disclosure  
29 310 statement. Ten studies contained an author with a COI with the food industry. Fourteen  
30 311 studies were classified as having industry ties, disclosing food industry sponsorship and / or  
31 312 an author with a COI.  
32  
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38 313

39 314 As shown in Table 1, most characteristics were similarly distributed across studies with  
40 315 industry ties or no industry ties. Studies with industry ties (64%) were more likely to have  
41 316 sample sizes <5000 than non-industry sponsored studies (34%). A greater proportion of  
42 317 industry sponsored studies (100%) than non-industry sponsored studies (83%) focused on  
43 318 total dairy intake rather than a specific food. Details of the individual studies are in  
44 319 Supplementary file 5.  
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325 **Table 1. Characteristics of the included studies by sponsorship, author conflict of**  
 326 **interest and industry ties**

327 Funding Source, n (%<sup>a</sup>)

Characteristic	Category	Total N = 43	Sponsorship		COI		Industry Ties	
			Industr y N= 8	Non- Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non- Industry/ No COI N = 29
<b>Sex</b>	Male	5 (12)	0 (0)	5 (14)	0 (0)	5 (15)	0 (0)	5 (17)
	Female	2 (5)	0 (0)	2 (6)	0 (0)	2 (6)	0 (0)	2 (7)
	Both	36 (84)	8 (100)	28 (80)	10 (100)	26 (79)	14 (100)	22 (76)
<b>Sample Size</b>	<5000	19 (44)	6 (75)	13 (37)	7 (70)	12 (36)	9 (64)	10 (34)
	5000-50,000	18 (42)	0 (0)	18 (51)	2 (20)	16 (48)	2 (14)	16 (55)
	>50,000	6 (14)	2 (25)	4 (11)	1 (10)	5 (15)	3 (21)	3 (10)
<b>Length of Follow up</b>	N/A*	3 (7)	2 (25)	1 (3)	1 (10)	2 (6)	2 (14)	1 (3)
	<10 years	11 (26)	3 (38)	8 (23)	2 (20)	9 (27)	3 (21)	8 (28)
	10-15 years	21 (49)	2 (25)	19 (54)**	6 (60)	15 (45)**	7 (50)	14 (48)
	>15 years	8 (19)	1 (13)	7 (20)	1 (10)	7 (21)	2 (14)	6 (21)
<b>Type of Dairy</b>	Total Dairy Intake***	37 (86)	8 (100)	29 (83)	9 (90)	28 (85)	13 (93)	24 (83)
	Individual Dairy Foods****	6 (14)	0 (0)	6 (17)	1 (10)	5 (15)	1 (7)	5 (17)

328 <sup>a</sup> Percentages may not add to 100 due to rounding

329 \* Follow up is not applicable for case control studies

330 \*\* Follow up for Johansson, I 2018 described the follow up as '8-12 years', we took the median of 10 years

331 \*\*\* This includes studies that looked at nutrients e.g calcium, fat & protein by measuring total dairy intake

332 \*\*\*\*Individual foods included milk, cheese & yogurt

### 333 **Risk of bias in included studies**

334 Every study was classified as having an overall high risk of bias, with 10 assessed as having a  
335 serious risk of bias and 33 as having a critical risk of bias (Figure 2). Most studies were  
336 assessed as having a critical risk of bias rating for the domain 'Bias due to confounding'. An  
337 example of one of the several confounders we identified that studies needed to control for was  
338 fruit and vegetable intake. If these confounders were not controlled for appropriately when  
339 measuring the effect of dairy intake on a CVD outcome, the study was classified as having a  
340 risk of bias for the confounding domain.

341  
342 Studies without industry ties or without an author with a COI were more likely to have a  
343 serious or critical risk of bias rating for 'Bias in classification of exposures'. For example, if a  
344 study did not use a validated food frequency questionnaire to measure the dietary intake of  
345 dairy, the study was classified as having a risk of bias for the domain of classification of  
346 exposures. For all other domains, the risk of bias classifications were similarly distributed  
347 across studies with industry ties, industry sponsorship or COI vs no industry ties, industry  
348 sponsorship or COI, respectively (see Supplementary file 6).

### 350 **Favourable results - Statistical significance: Industry ties vs no industry ties; industry** 351 **sponsorship vs no sponsorship; COI v no COI**

352 There was no clear evidence of an association between the reporting of favourable results and  
353 studies with industry ties (1/14) compared to those with no industry ties (8/29), RR= 0.26  
354 (95% CI 0.04, 1.87; n=43 studies) (Supplementary file 7). When comparing studies with  
355 industry sponsorship (1/8) with those with no industry sponsorship (8/35), there was no clear  
356 evidence of an association, RR = 0.55 (95% CI 0.08, 3.77; n=43 studies). There was again no  
357 clear evidence of an association between the reporting of favourable results and studies with  
358 an author with a COI (0/10) than those with no COI (9/33), RR= 0.16 (95% CI 0.01, 2.57;  
359 n=43 studies).

### 361 **Effect Size, Cardiovascular Disease: Industry ties v no industry ties; industry** 362 **sponsorship vs no industry sponsorship; COI v no COI**

363 For studies that quantified the association between dairy consumption and CVD outcomes  
364 using a RR, we found no important difference in the magnitude of the effect in studies with  
365 industry ties (RR = 0.89; n=3 studies) compared with those studies with no industry ties, (RR



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3 366 = 0.99; n=7 studies) (ratio of RRs 0.90 (95% CI 0.74, 1.09)); P=0.27 (Supplementary file 8).  
4  
5 367 For studies that had quantified the association using HRs, we similarly did not find an  
6  
7 368 important difference in the magnitude of HRs between studies with industry ties, (HR=0.96;  
8  
9 369 n=7 studies) and those studies with no industry ties, (HR=0.95; n=14 studies) (ratio of HRs  
10 370 1.01 (95% CI 0.90, 1.13)); P=0.86.  
11

371

12  
13 372 In our analysis comparing studies with industry sponsorship, (RR 0.83; n=2 studies) and  
14 373 those with no industry sponsorship, (RR 0.97; n=8 studies) we again did not find an  
15 374 important difference in the magnitude of RRs (ratio of RRs 0.86 (95% CI 0.44, 1.66));  
16  
17 375 P=0.65 (Supplementary file 8). However, when we compared industry sponsored studies,  
18  
19 376 (HR =0.78; n=3 studies) and non-industry sponsored studies, (HR=0.97; n=18 studies) that  
20 377 measured the association using HRs, we found a statistically significant difference in the  
21  
22 378 magnitude of the HRs (ratio of HRs 0.80 (95%CI 0.66, 0.97)); P=0.03 (Figure 3).  
23  
24  
25

379

26  
27 380 In our analysis comparing studies with an author with a COI (RR 0.89; n=2 studies) and those  
28 381 with no COI, (RR 0.99; n= 8 studies) we found no important difference in the magnitude of  
29 382 RRs (ratio of RRs 0.90 (95% CI 0.76-1.07)); P=0.22 (Supplementary file 8). When we  
30 383 compared studies with a COI, (HR =1.00; n= 5 studies) and studies with no COI, (HR=0.93;  
31 384 n=16 studies) that measured the association using HRs, we again found no difference in the  
32 385 magnitude of the HRs (ratio of HRs 1.08 (95% CI 0.99, 1.17)); P=0.12.  
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387 **Effect Size, Elevated Blood Pressure / Hypertension: Industry ties v no industry ties,**  
388 **and industry sponsorship vs no sponsorship**

389 We found no important difference in the magnitude of the HRs for elevated blood pressure /  
390 hypertension in studies with industry ties, (HR = 0.89; n =2) and those studies with no  
391 industry ties, (HR = 0.78; n= 5) (ratio of HRs 1.14 (95% CI 0.88, 1.49); P=0.32  
392 (Supplementary file 8).  
393

394

395 All of these studies with industry ties also had industry sponsorship, so the ratio of HRs was  
396 the same.  
397

398

399 **Favourable conclusions: Industry ties vs no industry ties; industry sponsorship vs no**  
400 **sponsorship; COI v no COI**

399 There was no clear evidence of an association between the reporting of favourable  
400 conclusions and studies with industry ties (4/14) compared to those with no industry ties  
401 (11/29), RR= 0.75 (95% CI 0.29, 1.95; n=43) (Supplementary file 7). When we compared  
402 studies only by industry sponsorship, there was no clear evidence of an association between  
403 industry sponsored studies (3/8), compared to studies with no sponsorship (12/35), RR = 1.09  
404 (95% CI 0.40, 2.99; n=43). There was again no clear evidence of an association between the  
405 reporting of favourable conclusions and studies with an author with a COI (2/10) than those  
406 without a COI (13/33), RR= 0.51 (95% CI 0.14, 1.88; n=43 studies).

407

### 408 **Risk of Bias Assessment by Industry Ties**

409 As every study had an overall high (serious or critical) risk of bias rating, there was no  
410 difference in the proportion of studies at a high risk of bias between those with industry ties,  
411 industry sponsorship or COI and those without industry ties, sponsorship or COI.

412

### 413 **Concordance between study results and conclusions**

414 Six (of 43) studies, all with unfavorable results, overemphasized the benefits of the dairy  
415 exposure in their conclusions and thus were coded as 'favourable' conclusions.

416 There was no clear evidence of an association between discordant results and conclusions and  
417 studies with industry ties (3/14) than those with no industry ties (3/29), RR = 2.07 (95% CI  
418 0.48, 8.99; n=43) (Supplementary file 7). There was no clear evidence of an association when  
419 comparing studies with industry sponsorship (2/8) to those with no industry sponsorship  
420 (4/35), RR = 2.19 (95% CI 0.48-9.94). There was again no clear evidence of an association  
421 between studies with an author with a COI (2/10) than those with no COI (4/33), RR = 1.65  
422 (95% CI 0.35, 7.72; n=43).

423

## 424 **DISCUSSION**

425 There was no clear evidence of an association between studies with food industry ties and the  
426 reporting of favourable results and conclusions of observational studies measuring the  
427 associations of dairy foods with cardiovascular disease outcomes. The 'mixed' group of  
428 funders we identified in the industry sponsored studies may influence these results, as the  
429 funding effect may be diluted by this heterogeneous group of sponsors. Unlike in drug

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3 430 studies,<sup>12</sup> the funders in the studies included in this review were extremely diverse, with Big  
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5 431 Food and trade association jointly sponsoring several studies. Thus, dairy foods are not their  
6  
7 432 sole interest.

8  
9 433 The meta-analysis of hazard ratios of CVD outcomes found that studies with industry  
10  
11 434 sponsorship showed a greater benefit from dairy than studies without industry sponsorship,  
12  
13 435 and this difference was statistically significant. The meta-analysis of risk ratios of CVD  
14  
15 436 outcomes found a similar estimate; however, this was not statistically significant. The likely  
16  
17 437 reason for this was that the meta-analysis of RRs had fewer studies, and so the ratio of RRs  
18  
19 438 could not be as precisely estimated. We found no evidence of a clinically important  
20  
21 439 difference in the magnitude of effect between studies with industry ties or authors with a COI  
22  
23 440 compared to those with no industry ties or no COI for other outcomes.

24  
25 441  
26 442 For every study, the overall risk of bias was classified as high (meaning either serious or  
27  
28 443 critical). Therefore, differences in the risk of bias across studies with and without industry  
29  
30 444 ties would not seem to provide an explanation for our findings. However, the version of the  
31  
32 445 ROBINS-E tool that we used may not have been able to adequately discriminate across the  
33  
34 446 studies, as perhaps is indicated by the uniformity in risk of bias classification.<sup>26</sup> Therefore, we  
35  
36 447 cannot rule out the possibility that differences in bias across studies with and without industry  
37  
38 448 ties may partly explain our findings.

#### 40 450 **Strengths and limitations of this review**

41  
42 451 Our review was prospectively registered in Prospero.<sup>19</sup> We followed explicit inclusion and  
43  
44 452 exclusion criteria, conducted a comprehensive search across multiple databases and hand  
45  
46 453 searched reference lists for the included studies.

47 454  
48  
49 455 For those studies missing a funding or author COI disclosure, we did not contact the authors  
50  
51 456 and we therefore may be underestimating the number of studies with industry ties. The tool  
52  
53 457 that we used to assess the risk of bias is still under development, however it is unlikely any  
54  
55 458 future changes to the tool will affect the risk of bias ratings.<sup>22</sup> We did not analyse studies of  
56  
57 459 low and full fat dairy or other types of dairy products separately. Industry ties may have  
58  
59 460 different effects on studies of low or full fat dairy foods or other foods and drinks. A final  
60  
61 461 limitation of our study is that we relied on definitions of exposures and outcomes that were

1  
2  
3 462 used in the original studies included in our analyses. Using finer categorizations of exposures  
4  
5 463 and outcomes would not provide a sufficient sample size to do our analyses. However, future  
6  
7 464 studies, using additional data and finer categorizations, may have different results.  
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9 465

### 10 466 **Agreements and disagreements with other studies or reviews**

11  
12 467 The observed greater benefit of dairy on CVD outcomes in industry sponsored studies  
13  
14 468 compared to non-industry sponsored studies corroborates previous research that has  
15  
16 469 demonstrated studies sponsored by the food industry reported smaller harmful effect sizes for  
17  
18 470 soft drink consumption, compared with non-industry sponsored studies.<sup>17</sup> It is not consistent,  
19  
20 471 however, with a recent meta-analysis funded by the Israel Dairy Board that found non  
21  
22 472 statistically significant differences in the estimated associations between industry and non-  
23  
24 473 industry funded studies.<sup>18</sup> The differences in the results of our current review and this  
25  
26 474 previous study can be attributed to a number of important factors in how the studies were  
27  
28 475 conducted, including how the exposures were classified, the outcomes selected for the meta-  
29  
30 476 analyses and the analysis method used. For the exposures, our review included yogurt and  
31  
32 477 cheese, as well as ‘total dairy’ and milk, whereas the Dairy Board study included only ‘total  
33  
34 478 dairy’ and milk as exposures. We included all outcomes related to CVD, and the Dairy Board  
35  
36 479 study included only CVD and stroke, as well as Type 2 diabetes. For the analysis method, we  
37  
38 480 fitted separate meta-analyses for studies that had measured the association using HRs and  
39  
40 481 those that had used either RRs or ORs, while the Dairy Board study only measured the  
41  
42 482 associations using RRs.

43  
44 483  
45 484 The lack of difference in the risks of bias between studies with industry ties and those with no  
46  
47 485 industry ties, is consistent with a previous review that examined the association of industry  
48  
49 486 ties with outcomes of studies examining the effect of wholegrain foods on CVD and mortality  
50  
51 487 that used the same tool to assess risk of bias.<sup>16</sup> These findings have also been shown in  
52  
53 488 pharmaceutical and tobacco research that have demonstrated industry sponsored studies are  
54  
55 489 of equal or better internal validity than studies with no sponsorship.<sup>12, 13, 15, 27, 28</sup>

### 56 490 57 491 **Implications for clinicians, policy makers and future research**

58 492 As dietary guidelines depend on an evidence base that should be as free as possible of bias,  
59  
60 493 the difference in the magnitude of effects between industry sponsored studies compared to  
494 494 non-industry sponsored studies is concerning. Therefore, the dairy intake recommendations

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3 495 made in dietary guidelines should account for the potential influence of industry sponsorship  
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5 496 on evidence of health effects. Nutrition studies included in systematic reviews used in the  
6  
7 497 development of dietary guidelines should be assessed using empirical methods to identify  
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9 498 factors associated with study results. Current risk of bias tools should therefore be amended  
10  
11 499 or supplemented to include industry sponsorship and author COI as a separate risk of bias  
12  
13 500 domain. The University of California, San Francisco's Navigation Guide assesses both author  
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15 501 conflicts of interest and funding sources as a risk of bias in human and animal studies.<sup>29</sup> As  
16  
17 502 the study designs used in nutrition are the same as those used to evaluate the harms of an  
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19 503 exposure in environmental health, dietary guideline committees could consider adopting this  
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21 504 tool to evaluate the risk of bias of the studies included in the systematic reviews used to  
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23 505 develop dietary guidelines.

506

24 507 Industry sponsors may bias research via different mechanisms, including the design and  
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26 508 conduct of a study, the selective reporting of results, how they code events, analyse data, by  
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28 509 spinning conclusions,<sup>11</sup> as well as framing how the questions are asked.<sup>30-32</sup> It has been  
29  
30 510 suggested that the dairy industry may preferentially fund research on topics which will  
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32 511 provide them with more favourable outcomes.<sup>33</sup> The influence of the food industry on the  
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34 512 research agenda has been demonstrated in an examination of research topics covered by  
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36 513 samples of randomised controlled trials included in systematic reviews of nutrition studies  
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38 514 and obesity.<sup>34</sup> It was shown that most food industry studies focused on the manipulations of  
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40 515 specific nutrients, and not on dietary behaviours, therefore limiting the public health  
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42 516 relevance of rigorous evidence available for use in both systematic reviews and dietary  
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44 517 guidelines.<sup>34</sup> The topics examined in cohort studies on the relationship of nutrition and  
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46 518 obesity, which tend to focus on more complex exposures than trials, did not demonstrate a  
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48 519 similar influence of funding source. However, the disclosure of food industry sponsorship  
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50 520 was low, making a comparison difficult.<sup>35</sup>

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51 522 This present study has also demonstrated that there is significant funding for nutrition  
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53 523 research that comes from non-industry sources, including academia and government. In this  
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55 524 study, only eight studies had food industry sponsorship, while 34 had a non-food industry  
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57 525 sponsorship. A similar rate was seen in a study that assessed the association of industry ties  
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59 526 with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease  
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60 527 and mortality, with only five industry sponsored studies and 17 non-industry sponsored

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3 528 studies.<sup>16</sup> To eliminate this risk of bias from nutrition research, investigators should use only  
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5 529 non-industry sources to fund their research.  
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10 532 **Conclusion**

11  
12 533 There was no clear evidence of an association between studies with food industry ties and the  
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14 534 reporting of favourable results and conclusions compared with studies without industry ties.

15 535 However, the statistically significant difference in the magnitude of effects identified in

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17 536 industry sponsored studies compared to non-industry sponsored studies is important in

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19 537 quantifying industry influence on studies included in dietary guidelines.  
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4  
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8  
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10  
11 542 strategy and undertook the literature search. NC, AF and SMc, conducted the title and  
12  
13 543 abstract screening and full article screening for final study inclusion. NC, AF, JD, AL and  
14  
15 544 SMc conducted data collection and cleaning, LB supervised. NC and JMc undertook all data  
16  
17 545 analysis. LB advised on methods, statistical analyses, and interpretation of findings. All  
18  
19 546 authors contributed to the final manuscript. NC and LB are guarantors.  
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22  
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26  
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31 552 **Competing interests:** None declared.  
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35 554 **Data sharing statement:** Available from The University of Sydney data repository. DOI to  
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37 555 be determined.  
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42 557 **Patient consent for publication:** Not required.  
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3 653 **Figures**  
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6 654 **Figure 1. Study Flow Diagram**  
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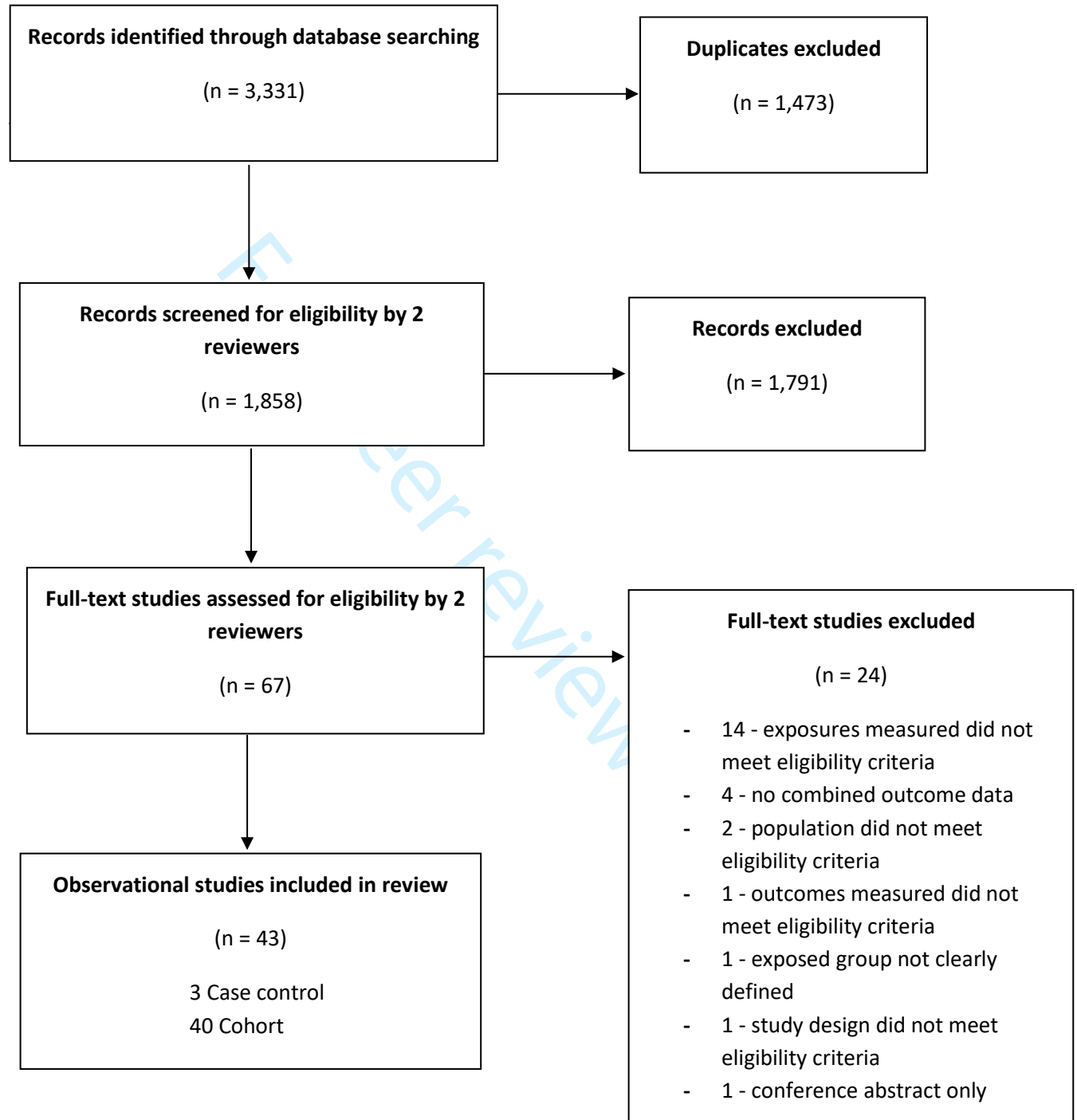
8 655 **Figure 2. Risk of Bias in Included Studies**  
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10 656 **Figure 3. Effect Size, Cardiovascular Disease: Industry sponsorship vs no industry**  
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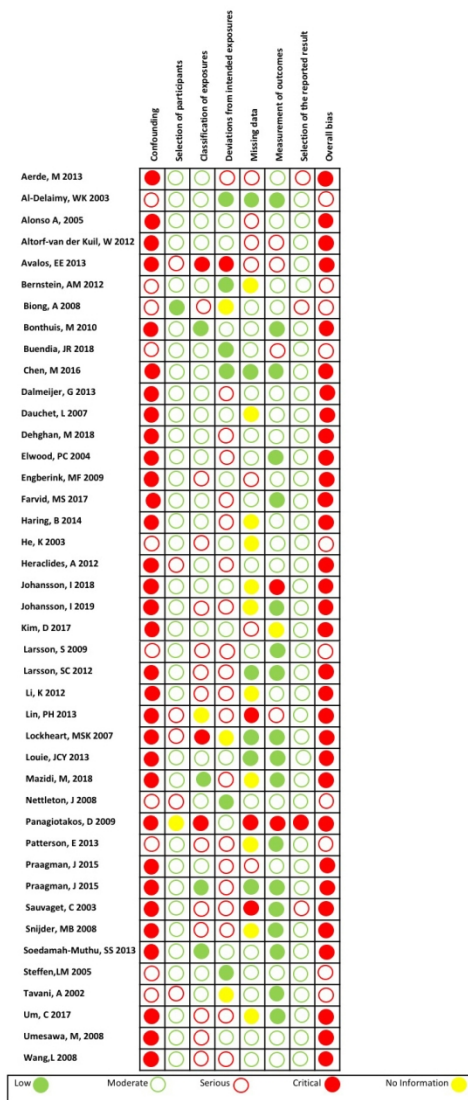
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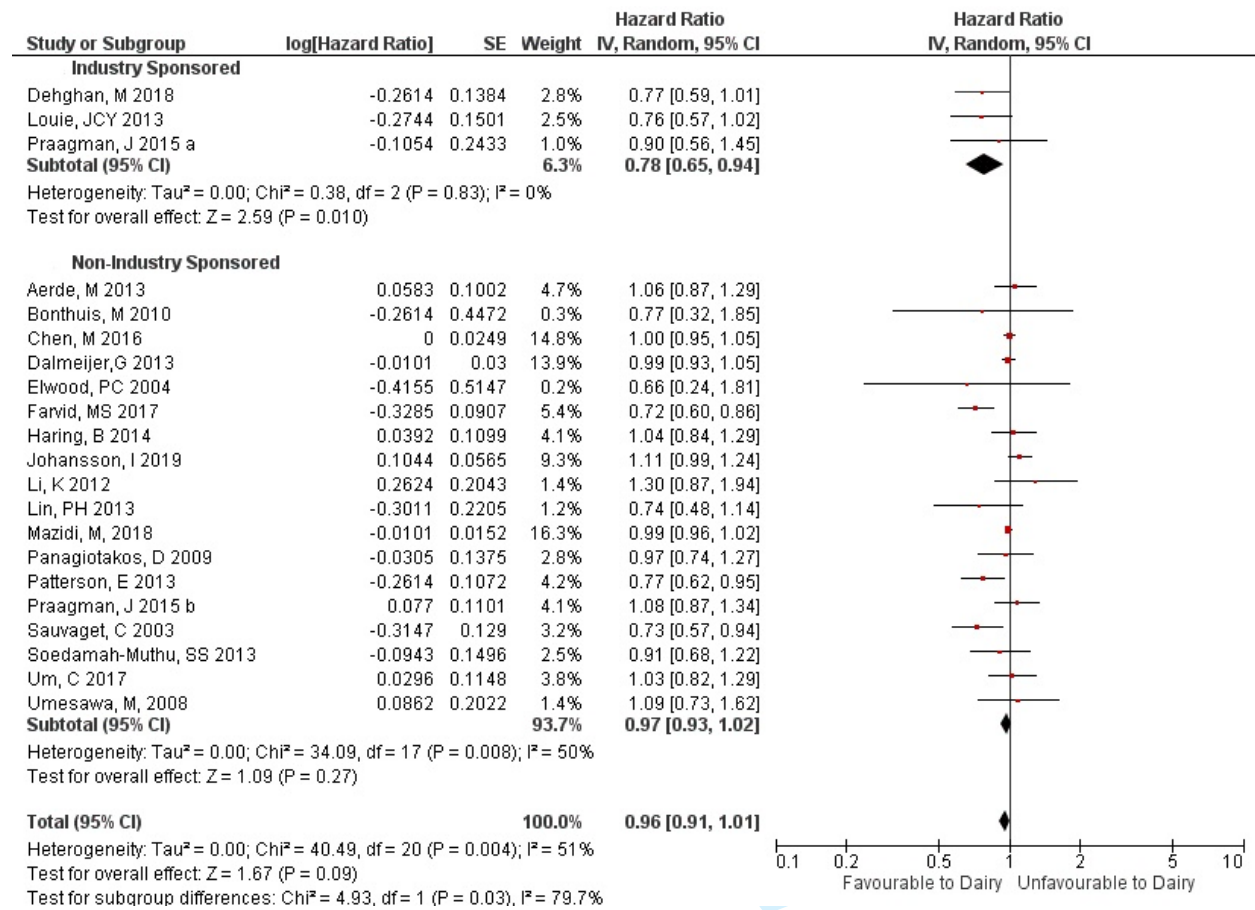
**Figure 1. Study Flow Diagram**

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Figure 3. Effect Size, Cardiovascular Disease, Industry sponsorship vs no Industry sponsorship, Hazard Ratio



## PROSPERO

### International prospective register of systematic reviews

UNIVERSITY *of* York  
Centre for Reviews and Dissemination

## Systematic review

Please complete all mandatory fields below (marked with an asterisk \*) and as many of the non-mandatory fields as you can then click *Submit* to submit your registration. You don't need to complete everything in one go, this record will appear in your *My PROSPERO* section of the web site and you can continue to edit it until you are ready to submit. Click *Show help* below or click on the icon to see guidance on completing each section.

This record cannot be edited because it has been rejected

### 1. \* Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

The association of food industry ties with findings of studies examining the effect of dairy foods intake with cardiovascular disease and mortality: Systematic review and Meta-analysis: protocol registration:

### 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.

01/09/2016

### 4. \* Anticipated completion date.

Give the date by which the review is expected to be completed.

01/06/2019

### 5. \* Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.

Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.

This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

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Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
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 (e.g. Funded proposal, protocol not yet finalised).

#### 6. \* Named contact.

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

Nicholas Chartres

#### Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr Chartres

#### 7. \* Named contact email.

Give the electronic mail address of the named contact.

ngar0960@uni.sydney.edu.au

#### 8. Named contact address

Give 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.

Give the telephone number for the named contact, including international dialling 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.

University of Sydney

#### Organisation web address:

#### 11. \* Review team members and their organisational affiliations.

## PROSPERO

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Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country are now mandatory fields for each person.**

Mr Nicholas Chartres. University of Sydney

Dr Alice Fabbri. The University of Sydney

Agnes Lau. University of California

Dr Joanna Diong. The University of Sydney

Assistant/Associate Professor Joanne Mckenzie. Monash University

Professor Lisa Bero. 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. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

Nicholas Chartres is a scholarship recipient (James Milner PhD scholarship in Pharmacy) from the University of Sydney.

#### Grant number(s)

#### 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.

None

#### 14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country are now mandatory fields for each person.**

#### 15. \* Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

The objective of this study is to determine if the presence of food industry sponsorship in primary nutrition studies examining the association of dairy 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 primary nutrition studies assessing the association of dairy foods with cardiovascular outcomes with industry sponsorship differ in their risk of bias compared with studies with no or other sources of sponsorship.

#### 16. \* Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

We will search the following databases from 2000-March 2019: Ovid MEDLINE; CINAHL; PubMed;

Cochrane Library; and ScienceDirect. No language restrictions will be applied



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#### 17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy. Do NOT provide links to your search results.

[https://www.crd.york.ac.uk/PROSPEROFILES/129659\\_STRATEGY\\_20190322.pdf](https://www.crd.york.ac.uk/PROSPEROFILES/129659_STRATEGY_20190322.pdf)

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

#### 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.

To determine whether industry sponsorship and/or study methods are associated with the results and/or conclusions of primary nutrition studies assessing the association of dairy foods and cardiovascular outcomes.

#### 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.

We will include primary research studies of any design that quantitatively examine the association of dairy foods with cardiovascular outcomes in healthy adults.

#### 20. \* Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

- The study quantitatively measures the effects of dairy consumption in humans.
- The study evaluates the effectiveness, efficacy or harms of dairy consumption.
- The study compares dairy food to control OR dairy food to other foods OR different levels of dairy consumption
- The study evaluates cow, goat or sheep milk, yogurt, cheese or custard. We will include and use the studies definition of dairy it is broader than milk, yogurt, cheese or custard.
- The study evaluates skim, low or full fat dairy products
- The study evaluates the effect of nutrients, e.g calcium and vitamin D when consumed within a dairy product

#### 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). The preferred format includes details of both inclusion and exclusion criteria.

Dairy vs Dairy (different doses) Dairy vs Dairy (different fat content) Dairy vs No dairy Dairy vs Other food

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Other (mixed intervention)

#### 22. \* Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

RCTs, Controlled Trials, Cohort, Case-control, Pre/Post, Other/Various

#### 23. Context.

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

- 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)

#### 24. \* Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

a. Primary Outcome 1 and 2

- o Statistical significance of results
- o Effect size of outcomes

For each study, the result reported for each primary outcome will be categorized as:

(1) Favourable if the result are statistically significant ( $p < 0.05$  or 95% confidence interval [CI] excluding no difference) and in the direction of dairy being more efficacious, less harmful or no more harmful than the comparator;

(2) Unfavourable if the result was statistically significant (e.g.  $P < 0.05$  or 95% confidence interval including the possibility of no difference) in the direction of the comparator being more efficacious or less harmful.

We will also extract the effect estimates for primary outcomes.

We will classify the results of the study as favourable if the stated primary outcome is reported as favourable.

If the study has multiple primary outcomes we will report the study as favourable if at least one of the outcomes is reported as favourable.

b. Primary Outcome 3 (Conclusions)

The conclusions reported in the published papers will be categorized as:

(1) Favourable if the dairy intervention was preferred to comparator

(2) Unfavourable if the comparator intervention was preferred to the test one OR if the test intervention

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showed a risk increase.

#### \* Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

As this is not relevant to our study, we have nothing to include.

#### 25. \* Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

We used the Cochrane Risk of Bias tool for randomised studies (15) 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-I tool for non-randomized studies (ROBINS-I)(16), which also measures bias across 7 domains.

#### d. Secondary Outcome 2 (Concordance between results and conclusions)

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'

#### \* Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

As this is not relevant to our study, we have nothing to include.

#### 26. \* Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

##### Selection Process

Two investigators (NC & AF) will independently screen the titles and abstracts of all retrieved records for obvious exclusions. Two investigators (NC & AF) will then assess the remaining papers based on full text, applying the aforementioned inclusion criteria for included studies. Agreement will be reached on any discrepancies by consensus between the two assessors. If agreement cannot be reached, a third assessor (LB) will make a decision. The reasons for the eligible papers being excluded will be described in

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'Characteristics of excluded papers' table.

Data collection process

- a) Title of the paper
- b) Year of publication
- c) Study design
- d) Comparisons:
- e) Sample size of study
- f) Mean age of participants
- g) Intervention or observation period
- h) Definition of intervention and exposure
- i) Risk of Bias
- j) Primary Hypothesis of the study (Verbatim)
- k) Primary outcomes measures
- l) Conclusion
- m) Concordance between conclusions and results
- n) Industry Sponsorship
- o) Role of the Funder: Information about the role of the sponsor as stated in the study
- p) The institutional affiliation of the corresponding author will be obtained from the article and classified into the following categories
- q) Country of origin (verbatim)
- r) Author COI

#### 27. \* Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

We will use the Cochrane Risk of Bias tool for randomised studies (15) 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-I tool for non-randomized studies (ROBINS-I)(16), which also measures bias across 7 domains.

#### 28. \* Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

To test our hypothesis that studies with dairy industry sponsorship will be more likely to have favourable

## PROSPERO

### International prospective register of systematic reviews

1 results, we will compare the risk of dairy industry sponsored studies having a favourable result with the risk  
2 of non-dairy industry funded studies having a favorable result. Using Rev Manager we will calculate the  
3 pooled risk ratio (RR) and its 95% confidence interval using the Mantel-Haenszel fixed-effect model.

4 However, when substantial heterogeneity is observed, we will use an inverse variance DerSimonian-Laird  
5 random-effects model. We will assess heterogeneity using  $I^2$  and use a random-effects model when  
6 statistical heterogeneity is substantial, defined as an  $I^2$  50%.

7 To test our hypothesis that effect estimates will differ between studies with dairy industry sponsorship and  
8 those without sponsorship, we will compare the pooled effect estimates from dairy vs. non-dairy sponsored  
9 studies. We will pool the effect estimates of homogenous studies measuring dichotomous outcomes, (e.g.  
10 RR, HR, OR for all-cause mortality, CVD mortality, cardiovascular events, etc) calculating pooled risk ratios  
11 as described above. Blood pressure is a continuous outcome, so we will attempt to pool homogeneous  
12 studies and measure the mean difference from baseline measures.

13 To test our hypothesis that studies with dairy industry sponsorship would be more likely to have favourable  
14 conclusions we will compare the risk of dairy industry sponsored studies having favourable conclusions with  
15 the risk of non-dairy industry funded studies having a favorable conclusion. We will calculate the pooled risk  
16 ratio (RR) and its 95% confidence interval using the Mantel-Haenszel fixed-effect model. However, when  
17 substantial heterogeneity is observed, we will use an inverse variance DerSimonian-Laird random-effects  
18 model. We will assess heterogeneity using  $I^2$  and use a random-effects model when statistical heterogeneity  
19 is substantial, defined as an  $I^2$  50%.

#### 29. \* Analysis of subgroups or subsets.

20 State any planned investigation of 'subgroups'. Be clear and specific about which type of study or  
21 participant will be included in each group or covariate investigated. State the planned analytic approach.

22 We will conduct an a priori subgroup analysis on low fat and full fat dairy products to determine if studies  
23 measuring the effects of low fat products have different results from studies that measure full fat dairy  
24 products.

25 We will conduct an a priori subgroup analysis by the risks of bias of the included studies to determine if  
26 studies that have a high risk of bias have different results from studies that have a low risk of bias. We  
27 hypothesize that industry sponsored studies will have the same level of risk of bias as non-industry  
28 sponsored studies.

#### 30. \* Type and method of review.

29 Select the type of review and the review method from the lists below. Select the health area(s) of interest for  
30 your review.

##### 31 Type of review

32 Cost effectiveness

**PROSPERO**
**International prospective register of systematic reviews**

1  
 2  
 3  
 4 No  
 5 Diagnostic  
 6 No  
 7 Epidemiologic  
 8 No  
 9 Individual patient data (IPD) meta-analysis  
 10 No  
 11 Intervention  
 12 No  
 13  
 14 Meta-analysis  
 15 Yes  
 16 Methodology  
 17 No  
 18 Narrative synthesis  
 19 No  
 20  
 21 Network meta-analysis  
 22 No  
 23 Pre-clinical  
 24 No  
 25 Prevention  
 26 No  
 27 Prognostic  
 28 No  
 29  
 30 Prospective meta-analysis (PMA)  
 31 No  
 32 Review of reviews  
 33 No  
 34 Service delivery  
 35 No  
 36  
 37 Synthesis of qualitative studies  
 38 No  
 39 Systematic review  
 40 Yes  
 41 Other  
 42 No  
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 44  
 45 **Health area of the review**  
 46 Alcohol/substance misuse/abuse  
 47 No  
 48  
 49 Blood and immune system  
 50 No  
 51 Cancer  
 52 No  
 53 Cardiovascular  
 54 Yes  
 55  
 56 Care of the elderly  
 57 No  
 58 Child health  
 59 No  
 60 Complementary therapies

**PROSPERO****International prospective register of systematic reviews**

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4 No  
5 Crime and justice  
6 No  
7 Dental  
8 No  
9 Digestive system  
10 No  
11 Ear, nose and throat  
12 No  
13 Education  
14 No  
15 Endocrine and metabolic disorders  
16 No  
17 Eye disorders  
18 No  
19 General interest  
20 No  
21 Genetics  
22 No  
23 Health inequalities/health equity  
24 No  
25 Infections and infestations  
26 No  
27 International development  
28 No  
29 Mental health and behavioural conditions  
30 No  
31 Musculoskeletal  
32 No  
33 Neurological  
34 No  
35 Nursing  
36 No  
37 Obstetrics and gynaecology  
38 No  
39 Oral health  
40 No  
41 Palliative care  
42 No  
43 Perioperative care  
44 No  
45 Physiotherapy  
46 No  
47 Pregnancy and childbirth  
48 No  
49 Public health (including social determinants of health)  
50 Yes  
51 Rehabilitation  
52 No  
53 Respiratory disorders  
54 No  
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## PROSPERO

### International prospective register of systematic reviews

Service delivery  
No

Skin disorders  
No

Social care  
No

Surgery  
No

Tropical Medicine  
No

Urological  
No

Wounds, injuries and accidents  
No

Violence and abuse  
No

### 31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.  
English

There is not an English language summary

### 32. \* Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Australia

### 33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

### 34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

**No I do not make this file publicly available until the review is complete**

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

### 35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.



1 **PROSPERO**  
2 **International prospective register of systematic reviews**  
3  
4

5 **Do you intend to publish the review on completion?**

6 Yes  
7

8 **36. Keywords.**  
9

10 Give words or phrases that best describe the review. Separate keywords with a semicolon or new line.  
11 Keywords will help users find the review in the Register (the words do not appear in the public record but are  
12 included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless  
13 these are in wide use.  
14

15 Nutrition, Industry Sponsorship, Conflict of Interest, Bias, Food Industry  
16

17 **37. Details of any existing review of the same topic by the same authors.**  
18

19 Give details of earlier versions of the systematic review if an update of an existing review is being registered,  
20 including full bibliographic reference if possible.  
21

22 CRD42017055841 The association of industry sponsorship with outcomes of studies examining the effect of  
23 intake of wholegrain foods with cardiovascular disease and mortality: protocol  
24

25 **38. \* Current review status.**  
26

27 Review status should be updated when the review is completed and when it is published. For  
28 new registrations the review must be Ongoing.

29 Please provide anticipated publication date  
30

31 Review\_Ongoing  
32

33 **39. Any additional information.**  
34

35 Provide any other information the review team feel is relevant to the registration of the review.  
36

37 **40. Details of final report/publication(s).**  
38

39 This field should be left empty until details of the completed review are available.  
40

41 Give the link to the published review.  
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**Supplementary file 2.** Search Strategy OVID Medline: Dairy, CVD, Adults

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1. Randomized controlled trial\*.tw.

2. experimental design.tw.

3. intervention\*.tw.

4. (RCT\* or rct\*).tw.

5. random\* control\* trial\*.tw.

6. clinical trial\*.tw.

7. field trial\*.tw.

8. community trial\*.tw.

9. controlled clinical trial\*.tw.

10. pragmatic trial\*.tw.

11. observational stud\*.tw.

12. cohort stud\*.tw.

13. prospective cohort\*.tw.

14. retrospective cohort\*.tw.

15. case control\*.tw.

16. ecological stud\*.tw.

17. time series analys?s\*.tw.

18. before-after stud\*.tw.

19. pre-post stud\*.tw.

20. follow up stud\*.tw.

21. comparative stud\*.tw.

22. evaluation stud\*.tw.

23. dairy.mp.

24. dairy intake\*.mp.

- 1
- 2
- 3 25. dairy consumption.mp.
- 4
- 5 26. dairy food\*.mp.
- 6
- 7 27. Dairy Products/ or dairy product\*.mp.
- 8
- 9 28. dairy serv\*.mp.
- 10
- 11 29. dairy type\*.mp.
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- 13 30. dairy source\*.mp.
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- 16 31. (calcium adj15 food sourc\*).mp. [mp=title, abstract, original title, name of substance word,
- 17 subject heading word, keyword heading word, protocol supplementary concept word, rare
- 18 disease supplementary concept word, unique identifier]
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- 20
- 21 32. (vitamin D adj15 food sourc\*).mp. [mp=title, abstract, original title, name of substance word,
- 22 subject heading word, keyword heading word, protocol supplementary concept word, rare
- 23 disease supplementary concept word, unique identifier]
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- 25
- 26 33. (milk and (cow or goat or sheep)).mp. [mp=title, abstract, original title, name of substance
- 27 word, subject heading word, keyword heading word, protocol supplementary concept word, rare
- 28 disease supplementary concept word, unique identifier]
- 29
- 30
- 31 34. yogurt.mp. or Yogurt/
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- 33 35. cheese.mp. or Cheese/
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- 35 36. custard.mp.
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- 37 37. (milk and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of
- 38 substance word, subject heading word, keyword heading word, protocol supplementary concept
- 39 word, rare disease supplementary concept word, unique identifier]
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- 42 38. (yogurt and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of
- 43 substance word, subject heading word, keyword heading word, protocol supplementary concept
- 44 word, rare disease supplementary concept word, unique identifier]
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- 47 39. Milk/
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- 49 40. 23 or 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
- 50 39
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- 52 41. cardiovascular disease.mp. or exp Cardiovascular Diseases/
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- 54 42. coronary\*.tw.
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- 3 43. heart\*.tw.
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- 5 44. cardia\*.tw.
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- 7 45. cardio\*.tw.
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- 9 46. myocard\*.tw.
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- 11 47. isch?em\*.tw.
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- 13 48. angina\*.tw.
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- 15 49. ventric\*.tw.
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- 17 50. tachycardi\*.tw.
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- 19 51. pericard\*.tw.
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- 21 52. endocardi\*.tw.
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- 23 53. atrial fibrillat\*.tw.
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- 25 54. arrhythmi\*.tw.
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- 27 55. athero\*.tw.
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- 29 56. arterio\*.tw.
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- 31 57. exp Atherosclerosis/
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- 33 58. exp Arteriosclerosis/
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- 35 59. HDL.tw.
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- 39 61. VLDL.tw.
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- 41 62. lipid\*.tw.
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- 43 63. lipoprotein\*.tw.
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- 45 64. triacylglycerol\*.tw.
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- 47 65. exp Hyperlipidemias/
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- 49 66. hyperlipid\*.tw.
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- 51 67. hypercholesterol\*.tw.
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3 68. hypercholester?emia\*.tw.  
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5 69. hypertriglycerid?emia\*.tw.  
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7 70. exp Cholesterol/  
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9 71. cholesterol\*.tw.  
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11 72. exp Stroke/  
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13 73. stroke\*.tw.  
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15 74. CVA.tw.  
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17 75. cerebrovasc\*.tw.  
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19 76. "vascular accident".tw.  
20  
21 77. TIA.tw.  
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23 78. cerebral vascular.tw.  
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25 79. thrombo\*.tw.  
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27 80. emboli\*.tw.  
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29 81. apoplexy.tw.  
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31 82. (brain adj2 accident\*).tw.  
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33 83. ((brain\* or cerebral or lacunar) adj2 infarct\*).tw.  
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35 84. Hypertension/  
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37 85. exp Blood Pressure/  
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39 86. hypertensi\*.tw.  
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41 87. blood pressure\*.tw.  
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43 88. systolic blood pressure.tw.  
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45 89. diastolic blood pressure.tw.  
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47 90. peripheral arter\* disease\*.tw.  
48  
49 91. (coronar\$ adj5 (bypas\$ or graft\$ or disease\$ or event\$)).tw.  
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51 92. (cerebrovasc\$ or cardiovasc\$ or mortal\$ or angina\$ or stroke or strokes).tw.  
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3 93. (myocardi\$ adj5 (infarct\$ or revascular\$ or ischaemi\$ or ischemi\$)).tw.  
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5 94. (morbid\$ adj5 (heart\$ or coronar\$ or ischaem\$ or ischem\$ or myocard\$)).tw.  
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7 95. (vascular\$ adj5 (peripheral\$ or disease\$ or complication\$)).tw.  
8

9 96. (heart\$ adj5 (disease\$ or attack\$ or bypass\$)).tw.  
10

11 97. 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or  
12 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73  
13 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or  
14 90 or 91 or 92 or 93 or 94 or 95 or 96  
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16 98. 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  
17 19 or 20 or 21 or 22  
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19 99. 40 and 97 and 98  
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21 100. limit 99 to yr="2000 - 2019"  
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23 101. limit 100 to humans  
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25 102. limit 101 to "all adult (19 plus years)"  
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## Supplementary File 3. List of confounders

Outcome	Confounders	Confounders (all outcomes)
1. CVD mortality	Fibre supplement (p) Red Meat (h) Sodium (Na+) (h)	Age Sex BMI
2. CVD events	Fibre supplement (p) Magnesium supplement (p)	Smoking Alcohol intake
3. CHD mortality (incident CVD)	Fibre supplement (p) Trans Fat (h) Polyunsaturated fat (n-6) (p) Sodium (+Na) (h)	History of co-morbidities Parenteral/Fhx MI < 60 yrs PA levels SES
4. CHD events (incident CHD)	Fibre supplement (p) Trans fat (h) Magnesium supplement (p) Polyunsaturated fat (n-6) (p)	Total energy intake Fruit & Vegetable intake  <i>Specialised Confounders</i>
5. Total MI	Aspirin (p) Vitamin E supplement (p)	Hormone therapy
6. Fatal MI	Vitamin E supplement (p)	
7. Non-fatal MI	Aspirin (p)	
8. Total stroke	Potassium supplement (p) Red Meat (h) Sodium (+Na) (h)	
9. Ischemic stroke	Aspirin (p) Polyunsaturated fat (LC n-3) (p) Red meat (h)	
10. Haemorrhagic stroke	Aspirin (h)	
11. Systolic BP	Magnesium supplement (p) Sodium (-Na) (p) Polyunsaturated fat (supplement) (LC n-3) (p) Potassium supplement (p)	
12. Diastolic BP	Magnesium supplement (p) Sodium (-Na) (p) Polyunsaturated fat (supplement) (LC n-3) (p) Potassium supplement (p)	

p = protective, h = harmful

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### a) Not Confounders (inconclusive evidence)

Outcome	Not a confounder (inconclusive)
1. CVD mortality	Aspirin Dietary Saturated Fat Folate supplement Monounsaturated Fat Multivitamin Polyunsaturated Fat Total Dietary Fat Vitamin E supplement
2. CVD events	Folate supplement Monounsaturated Fat Multivitamin Polyunsaturated Fat Sodium Total Dietary Fat Vitamin E supplement
3. CHD mortality	Dietary Saturated Fat Magnesium supplement
4. CHD events	Dietary Saturated Fat Sodium Red Meat
5. Total MI	Dietary Saturated Fat Folate supplement Magnesium supplement Multivitamin Polyunsaturated Fat Total Dietary Fat
6. Fatal MI	Folate supplement Multivitamin
7. Non-fatal MI	Dietary Saturated Fat Folate supplement Multivitamin Polyunsaturated Fat Total Dietary Fat Vitamin E supplement



8. Total stroke	Aspirin Dietary Saturated Fat Folate supplement Monounsaturated Fat Multivitamin Polyunsaturated Fat Total Dietary Fat Vitamin E supplement
9. Ischemic stroke	Dietary Saturated Fat Trans Fat
10. Haemorrhagic stroke	Polyunsaturated Fat Red Meat
11. Systolic BP	Polyunsaturated Fat (dietary)
12. Diastolic BP	Polyunsaturated Fat (dietary)

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## Supplementary file 4: List of excluded studies and reasons for exclusion

Author	Title	Reason for Exclusion
Akbaraly, T 2013 <sup>1</sup>	Does overall diet in midlife predict future aging phenotypes? A cohort study	Dietary patterns only were assessed, not dairy foods
Anderson, LA 2011 <sup>2</sup>	Dietary Patterns and Survival of Older Adults	No relevant outcomes were measured
Baylin, A 2003 <sup>3</sup>	High 18:2 trans-fatty acids in adipose tissue are associated with increased risk of nonfatal acute myocardial infarction in Costa Rican adults	Effects of dairy foods not measured
Beydoun, MA 2018 <sup>4</sup>	Dairy product consumption and its association with metabolic disturbance in a prospective study of urban adults	Groups exposed to dairy not clearly defined
Biong, AS 2006 <sup>5</sup>	Intake of milk fat, reflected in adipose tissue fatty acids and risk of myocardial infarction: a case-control study	Effects of dairy foods not measured
Chen, y 2013 <sup>6</sup>	Prospective investigation of major dietary patterns and risk of cardiovascular mortality in Bangladesh	Dietary patterns only were assessed, not dairy foods
Ding, M 2017 <sup>7</sup>	Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study	Not an observational design study
Eguchi, E 2012 <sup>8</sup>	Healthy lifestyle behaviours and cardiovascular mortality among Japanese men and women: the Japan collaborative cohort study	Dietary patterns only were assessed, not dairy foods
Geleijnse, JM 2017 <sup>9</sup>	Dietary Patterns in Relation to Cardiovascular Disease Incidence and Risk Markers in a Middle-Aged British Male Population: Data from the Caerphilly Prospective Study	Dietary patterns only were assessed, not dairy foods
Goldbohm, RA 2011 <sup>10</sup>	Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands	No combined outcome data
Julián-Almárcegui, C 2016 <sup>11</sup>	Association of heart rate and blood pressure among European adolescents with usual food consumption: The HELENA study	Participants were adolescents, not adults
Larsson, SC 2018 <sup>12</sup>	Dietary patterns, food groups, and incidence of aortic valve stenosis: A prospective cohort study	Dietary patterns only were assessed, not dairy foods
Lupton, BS 2003 <sup>13</sup>	The Finnmark Intervention Study: is it possible to change CVD risk factors by community-based intervention in an Arctic village in crisis?	No combined outcome data
Meyer, J 2011 <sup>14</sup>	Dietary patterns, subclinical inflammation, incident coronary heart disease and mortality	Dietary patterns only were assessed, not dairy foods

	in middle-aged men from the MONICA/KORA Augsburg cohort study	
Michaelsson, K 2013 <sup>15</sup>	Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study	Dietary calcium only was assessed, not dairy foods
Oomen, CM 2000 <sup>16</sup>	Arginine intake and risk of coronary heart disease mortality in elderly men	Effects of dairy foods not measured
Paillard, F 2015 <sup>17</sup>	Cardiovascular risk and lifestyle habits of consumers of a phytosterol-enriched yogurt in a real-life setting	Yogurt was enriched with phytosterols
Praagman, J 2016 <sup>18</sup>	The association between dietary saturated fatty acids and ischemic heart disease depends on the type and source of fatty acid in the European Prospective Investigation into Cancer and Nutrition-Netherlands cohort	Effects of dairy foods not measured
Streppel, MT 2014 <sup>19</sup>	Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study	Dietary patterns only were assessed, not dairy foods
Umesawa, M 2006 <sup>20</sup>	Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study	No combined outcome data
van der Pols, J C 2009 <sup>21</sup>	Childhood dairy and calcium intake and cardiovascular mortality in adulthood: 65-year follow-up of the Boyd Orr cohort	Participants were children, not adults
Warensjo, E 2009 <sup>22</sup>	Stroke and plasma markers of milk fat intake – a prospective nested case-control study	Effects of dairy foods not measured
Warensjo, E 2009 <sup>23</sup>	Milk Fat Biomarkers and the Risk of a First Ever Acute Myocardial Infarction - A Prospective Nested Case-Control Study. <i>Journal of the American Dietetic Association.</i> 2009;1	Poster presentation only, full study not available
Warensjo, E 2010 <sup>24</sup>	Biomarkers of milk fat and the risk of myocardial infarction in men and women: a prospective, matched case-control study	No combined outcome data

1. Akbaraly T, Sabia S, Hagger-Johnson G, et al. Does overall diet in midlife predict future aging phenotypes? A cohort study. *The American journal of medicine.* 2013;126(5):411-419.e413.
2. Anderson AL, Harris TB, Tylavsky FA, et al. Dietary Patterns and Survival of Older Adults. *Journal of the American Dietetic Association.* 2011;111(1):84-91.
3. Baylin A, Kabagambe EK, Ascherio A, et al. 18:2 trans-fatty acids in adipose tissue are associated with increased risk of nonfatal acute myocardial infarction in costa rican adults. *Journal of Nutrition.* 2003;133(4):1186-1191.
4. Beydoun MA, Fanelli-Kuczmarski MT, Beydoun HA, et al. Dairy product consumption and its association with metabolic disturbance in a prospective study of urban adults. *British Journal of Nutrition.* 2018;119(6):706-719.

5. Biong AS, Veierod MB, Ringstad J, et al. Intake of milk fat, reflected in adipose tissue fatty acids and risk of myocardial infarction: a case-control study. *European Journal of Clinical Nutrition*. 2006;60(2):236-244.
6. Chen Y, McClintock TR, Segers S, et al. Prospective investigation of major dietary patterns and risk of cardiovascular mortality in Bangladesh. *International Journal of Cardiology*. 2013;167(4):1495-1501.
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## Supplementary file 5: 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 dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Aerde, M 2013 <sup>(1)</sup>	Cohort	12.4 years	1,956 men & women	61.6 years	Total Dairy, 271 g/day per SD of the mean intake for Total dairy (all dairy products except butter)		Fatal CVD	Non-Industry <sup>1</sup>	Yes <sup>a</sup>
Al-Delaimy, WK 2003 <sup>(2)</sup>	Cohort	12 years	39,800 men	40-75 years	Dairy Calcium Q5, 819 mg/day (median) (dairy calcium intake summed the calcium intake from whole milk, skim or low-fat milk, yogurt, ice cream, cottage cheese, and other cheese was summed)	Q1, 106 mg/day	Fatal Ischemic Heart Disease	Non Industry <sup>2</sup>	No <sup>b</sup>
Alonso A, 2005 <sup>(3)</sup>	Cohort	27 months	5,880 men & women	37 years	Dairy Q 5, 798.8 g/day (whole-fat milk, partially skim milk, skim milk, condensed milk, whipped cream, yogurt, skim yogurt, milk-shake, cottage cheese or junket, petit Suisse cheese, spreadable cheese wedges, soft unripened cheese, other cheese, custard, and ice cream)	Q 1, 155.6 g/day	Hypertension	Non-industry <sup>3</sup>	No <sup>c</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Altorf-van der Kuil, W2012 <sup>(4)</sup>	Cohort	Mean follow up 7.5 years	3,588 men & women	44 years	Dairy Protein T3, $\geq 27$ g/day (dairy protein was calculated as protein from milk, yogurt, coffee creamer, curd, pudding, porridge, custard, whipped cream and cheese)	T1, $\leq 19$ g/day	Hypertension	Industry <sup>4</sup>	Yes <sup>d</sup>
Avalos, EE 2013 <sup>(5)</sup>	Cohort	Mean follow up 16.2 years	1,759 men & women	70.6 years men, 70.1 women	Whole Milk, Non-Fat Milk, Yogurt & Cheese, Sometimes/often (included daily, 4–6 times/week, 1–3 times/week and 1–3 times/months)	Rarely/never (included never & 1–11 times/year)	Incident CHD	Non-industry <sup>5</sup>	No <sup>e</sup>
Bernstein, AM 2012 <sup>(6)</sup>	2 Cohorts	26 and 22 years of follow-up in women and men, respectively	127,160 (43 150 men 84 010 women)	Men 40 to 75 years, Woman 30 to 55 years	Whole Fat Q 5, Men 2.55 servings/day, Woman 2.81 servings/day (whole milk, ice cream, hard cheese, full fat cheese, cream, sour cream, cream cheese, butter)  Low Fat Q5, Men 2.64 servings/day, Women 2.20 servings/day (skim/low-fat milk, 1% and 2% milk, yogurt, cottage and ricotta cheeses, low-fat cheese, sherbet)	Q 1, Men 0.21 servings/day, Woman 0.34 servings/day.  Low Fat Q1, Men 0.11 servings/day, Women 0.07 servings/day	Total Stroke	Non-industry <sup>6</sup>	Yes <sup>f</sup>
Biong, A 2008 <sup>(7)</sup>	Case Control		218 men & women	62.4 years	Dairy Fat, $> 34.1$ g/day	$<14.6$ g/day	First Myocardial Infarction	Industry <sup>7</sup>	Yes <sup>g</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Bonthuis, M 2010 <sup>(8)</sup>	Cohort	Mean 14.4 years	1,529 men & women	25–78 years	Total Dairy T3, 599 g/day (median) ('low-fat dairy products was computed by adding daily servings (in grams) of skim milk, low-fat milk, low-fat yoghurt, cottage or ricotta cheese, whereas the food group 'high-fat/unmodified dairy' included whole milk, cream, ice cream, yoghurt, full-fat cheese and custard. Total dairy intake was the sum of intake of all these dairy foods)	T1, 174 g/day	Cardiovascular Disease Mortality	Non-Industry <sup>8</sup>	No <sup>h</sup>
Buendia, JR 2018 <sup>(9)</sup>	3 Cohorts	30 years of follow-up in NHS, 20 years in NHS II, 24 years in the HPFS	NHS (N=69298), NHS II (N=84368), HPFS (N=30512)	Mean baseline ages in the 3 cohorts were 44.6, 35.8, and 50.7 years, respectively	Total Dairy Q4, 3 - <6 servings/day (total dairy intake included: milk (skim, low-fat, whole), ice cream, sherbet/ frozen yogurt, cheese (cottage, ricotta, hard, sliced), and yogurt (all types)	Q1, <0.5 servings/day	High Blood Pressure	Industry <sup>9</sup>	No <sup>i</sup>
Chen, M 2016 <sup>(10)</sup>	3 Cohorts	24 years in the HPFS, 32 years NHS, 20 years in NHS II	222,234 - 43,652 men HPFS, 87,907 women NHS, 90,675 women NHS II	40–75 years HPFS, 30–55 years NHS, 25–42 y NHS II	Dairy Fat, Q5	Q1	CVD	Non-Industry <sup>10</sup>	No <sup>j</sup>



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Study ID	Study Deign	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Dalmeijer,G 2013 <sup>(11)</sup>	Cohort	13 years	33,625 men & women	49.0 years	Total dairy and its subtypes were evaluated as continuous variables per standard deviation of the mean intake which is 265 g/d for total dairy (total dairy included all dairy food products except for butter and ice cream. Milk and milk products included all kinds of milk, yogurt, coffee creamers, curd, pudding, porridge, custard, and whipping cream)		Incident of Coronary Heart Disease & Incident Stroke	Non-Industry <sup>11</sup>	Yes <sup>k</sup>
Dauchet, L 2007 <sup>(12)</sup>	Cohort	5.4 years	2,341 men & women	Men 52.7 years, Women 46.9 years	Dairy Q4, 456 g/day (dairy products including milk, cheese, yogurt, and other dairy products)	Q1, 84 g/day	Systolic & Diastolic Blood Pressure	Non-Industry <sup>12</sup>	No <sup>l</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Dehghan, M 2018 <sup>(13)</sup>	Cohort	9.1 yrs	136,384 men & women	50-1 years	Dairy Q4, >2 servings/day (median) (dairy comprised milk, yoghurt, various types of cheese, yoghurt drink, and mixed dishes prepared with dairy. Mixed dishes prepared with dairy were dis- aggregated into their constituents and a proportional weight was assigned to each component. Then each component was included in the related dairy group.	Q1, 0 servings/day	Cardiovascular Mortality or Major Events	Industry <sup>13</sup>	No <sup>m</sup>
Elwood, PC 2004 <sup>(14)</sup>	Cohort	20-24 years	2,403 men	45-59 years	Milk Q4, >1 pint per day	Q1, None	Vascular Event	Non-Industry <sup>14</sup>	No disclosure

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Engberink, MF 2009 <sup>(15)</sup>	Cohort	6 years	2,245 men & women	>55 years	Dairy Q4, 691 g/day (i.e. 4.5 servings/day) (median intake) (calculated total dairy intake by summing the intake of individual dairy items, except butter and ice cream. The category "milk and milk products" included all kinds of milk, yogurt, coffee creamer, curd, pudding, porridge, custard, and whipped cream. The category "cheese" included all kinds of cheese products, ie, soft cheese, hard cheese, and cheese spreads)	Q1, 164 g/day (i.e. 1 serving/day) (median intake)	Hypertension	No disclosure	No <sup>a</sup>
Farvid, MS 2017 <sup>(16)</sup>	Cohort	8 years	42,403 men & women	51.6 years	Total Dairy Q5, 2.4 servings/day (median) (total dairy product items listed in the food frequency questionnaire included milk, cheese, yogurt, liquid yogurt (doogh), dried yogurt paste (kashk), and cream)	Q1, 0.4 servings/day (median)	Cardiovascular Disease Mortality	Non-Industry <sup>15</sup>	No <sup>a</sup>
Haring, B 2014 <sup>(17)</sup>	Cohort	22 years (median)	12,066 men & women	45-64 years	Dairy Protein Q5, 2.9 servings/day	Q1, 0.1 median servings/day	Coronary Heart Disease	Non-Industry <sup>16</sup>	No <sup>a</sup>
He, K 2003 <sup>(18)</sup>	Cohort	14 years	43,732 men	40-75 years	High Fat Dairy Q5, ≥1/day	Q1, <1/week	Ischaemic & Haemorrhagic Stroke	Non-Industry <sup>17</sup>	No <sup>a</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Heraclides, A 2012 <sup>(19)</sup>	Cohort	10 years	1,750 men & women	Men 43 years, Women 53 years	Total Dairy T3, 309.0 g/day (median) (full-fat milk; semi-skimmed milk; skimmed milk; milk-containing beverages (full fat, semi-skimmed and skimmed); full-fat cheese; low-fat cheese; full-fat yoghurt; low-fat yoghurt; fruit-flavoured yoghurt (full fat and low fat); and milk-based puddings)	T1, 224.1 g/day	Incident Hypertension	Non-Industry <sup>18</sup>	Yes <sup>r</sup>
Johansson, I 2018 <sup>(20)</sup>	Cohort	8-12 years	27,682 men & women	29-65 years	Dairy Q 5, 7.1 servings/day (median)	Q1, 1.6 servings/day (median)	Blood Pressure	Non-Industry <sup>19</sup>	No <sup>s</sup>
Johansson, I 2019 <sup>(21)</sup>	Cohort	14.2 years	108,065 men & women	calculated mean = 52.5 years *	High Fat & Low Fat Non-Fermented Milk & Cheese Q 4, high dose	Q1, low dose	Myocardial Infarction & Stroke	Non-Industry <sup>20</sup>	No <sup>t</sup>
Kim, D 2017 <sup>(22)</sup>	Cohort	67-4 months	4,335 men & women	40-69 years	Total Dairy Q 5, >7 servings/week	Q 1, <1 servings/week	Blood Pressure	Non-Industry <sup>21</sup>	No <sup>u</sup>
Larsson, S 2009 <sup>(23)</sup>	Cohort	13.6 years	26,556 men	50-69 years	Dairy Q5, 1295.6 g/day (median) (including low-fat milk, whole milk, sour milk, yogurt, cheese, cream, ice cream, and butter)	Q1 286.5 g/day	Cerebral Infarction, Intracerebral Haemorrhage, Subarachnoid Hemorrhage	Non-Industry <sup>22</sup>	No disclosure

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Larsson, SC 2012 <sup>(24)</sup>	Cohort	10.2 years	74,961 men & women	45-83 years	Dairy Q5, 9.3 servings/day (median) (dairy foods included low-fat milk (0.5% fat), medium-fat milk (1.5% fat), full-fat milk (3% fat), milk in pancakes, low-fat sour milk/yogurt (0.5% fat), full-fat sour milk/yogurt (3% fat), cottage cheese (4% fat), low-fat cheese (10%-17% fat), full-fat cheese (approximately 28% fat), ice cream, cream, and creme fraiche)	Q1, 2.3 servings/day	Total Stroke	Non-Industry <sup>23</sup>	No <sup>v</sup>
Li, K 2012 <sup>(25)</sup>	Cohort	11 years	23,980 men & women	35-64 years	Dairy Calcium Q4, 780 mg/day	Q1, 188 mg/day	CVD Mortality	Non-Industry <sup>24</sup>	No <sup>w</sup>
Lin, PH 2013 <sup>(26)</sup>	Cohort	12 years	2,061 men & women	45.8 years (no information for stroke group)	Dairy T3, (dairy milk of any kind, cheese, yogurt).	T1	Total Stroke	Non-Industry <sup>25</sup>	No <sup>x</sup>
Lockheart, MSK 2007 <sup>(27)</sup>	Case Control		211 men & women	62.5 years cases and 62.2 years controls	Low Fat Dairy T3, 618 g/day (Low-fat milk, skimmed milk, light sour cream)	T 1, 48 g/day	First Myocardial Infarction	Industry <sup>26</sup>	No disclosure
Louie, JCY 2013 <sup>(28)</sup>	Cohort	15 years	2,625 men & women	49-97 years	Total Dairy T3, 2.9 servings/day (median) (included all dairy foods)	T1, 0.6 servings/day	Total CVD	Industry <sup>27</sup>	No disclosure
Mazidi, M, 2018 <sup>(29)</sup>	Cohort	76.4 months	24,474 men & women	47.6 years	Total Dairy Q4, 3.08 cup equivalent servings/day (total dairy, milk, cheese, and yogurt)	Q1, 0.25 cup equivalent servings/day	CHD Mortality & Cerebrovascular Disease mortality	Non-Industry <sup>28</sup>	No <sup>y</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Ness, AR 2001 <sup>(30)</sup>	Cohort	25 years	5,765 men	35-64 years	Milk T3, > 1 pint (= 0.568 liters)	T1, None	Cardiovascular Disease Deaths	Non-Industry <sup>29</sup>	No <sup>z</sup>
Nettleton, J 2008 <sup>(31)</sup>	Cohort	13.3 years	14,153 men & women	45 to 64 years	High Fat Dairy, per 1 daily serving difference in food group intake		Incident Heart Failure	Non Industry <sup>30</sup>	No <sup>aa</sup>
Panagiotakos, D 2009 <sup>(32)</sup>	Cohort	5 years	3,042 men & women	18-89 years	Low Fat Dairy, 1-unit increase in components' scores (0%, 2% or total fat), like cheese, yogurt, milk)		CVD Events	Non-Industry <sup>31</sup>	No disclosure
Patterson, E 2013 <sup>(33)</sup>	Cohort	11.6 years	33,636 women	48-83 years	Total Dairy, Q5 8.4 servings/day (median) (total dairy intake was the sum of milk [full-fat ( $\geq 3.0\%$ fat), semi-skimmed ( $\leq 1.5\%$ fat), skimmed (0.5% fat), and pancakes], cultured milk/yogurt [full-fat ( $\geq 3.0\%$ fat) and low-fat ( $\leq 1.5\%$ fat)], cheese [full-fat ( $> 17\%$ fat), low-fat ( $\leq 17\%$ fat), and cottage cheese/ quark], cream and creme fariche (full fat and low fat) intakes)	Q1, 2.2 servings/day	Myocardial Infarction	Non Industry <sup>32</sup>	No <sup>bb</sup>
Praagman, J 2015 (a) <sup>(34)</sup>	Cohort	13.3 years (median)	4,235 men & women	66.9 years	Total Dairy, T3 >400g/day (total dairy included milk, buttermilk, yogurt, coffee creamer, curd, pudding, porridge, custard, whipped cream, ice cream, and cheese, but not butter)	Total Dairy, T 1 <200 g/day	Fatal Stroke & Fatal CHD	Industry <sup>33</sup>	Yes <sup>cc</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Praagman, J 2015 (b) <sup>(35)</sup>	Cohort	15 years	34,409 men & women	Men 51 years & women 43 years	Total Yogurt & Cheese Q4, (fermented dairy foods)	Q1	CVD Mortality	Non-Industry <sup>34</sup>	Yes <sup>dd</sup>
Sauvaget, C 2003 <sup>(36)</sup>	Cohort	16 years	37,130 men & women	56 years	Dairy Q4, Almost Daily (dairy products (butter and cheese, excluding margarine))	Q1, Never	Total Stroke	Non-Industry <sup>35</sup>	No disclosure
Snijder, MB 2008 <sup>(37)</sup>	Cohort	6.4 years	1,124 men & women	50-75 years	Dairy Q4, 5.75-17.24 servings/day (range) (total dairy consumption was categorized as low-fat dairy ( $\leq 2\%$ fat) or high-fat dairy ( $> 2\%$ fat). The variable dairy desserts included yoghurt, curds, and custard. The variable milk included low-fat, skim, and, whole milk. The variable yoghurt included all low-fat, skim, and whole yoghurts)	Q1 0-2.97 servings/day (range)	Systolic & Diastolic Blood Pressure	Industry <sup>36</sup>	Yes <sup>ee</sup>
Soedamah-Muthu, SS 2013 <sup>(38)</sup>	Cohort	10.8 years	4,255 men & women	56 years	Dairy, T3 575 g/day (median) (all dairy products, except butter and ice cream)	T1, 246 g/day (median)	Fatal & Non-Fatal CHD	Non-Industry <sup>37</sup>	Yes <sup>ff</sup>
Steffen, LM 2005 <sup>(39)</sup>	Cohort	15 years	4,304 men & women	18-30 years	Dairy Foods Q5, $> 3.4$ times/day (dairy foods, including milk, cheese, yogurt, and dairy desserts)	Q1, $< 1.1$ times/day	Blood Pressure	Non-Industry <sup>38</sup>	No <sup>gg</sup>

Study ID	Study Design	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or 'yes' to dairy foods)	Comparison (lowest tertile/quartile/quintile or 'no' to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Tavani, A 2002 <sup>(40)</sup>	Case Control		985 men & women	61 years (median)	Total milk >7 cups/week, Yogurt >= 7 portions/week, Cheese >=350g/week	Total milk 0 cups/week, Yogurt 0 portions/week, Cheese <200g/week	Acute Myocardial Infarction	Non-Industry <sup>39</sup>	No <sup>hh</sup>
Um, C 2017 <sup>(41)</sup>	Cohort	5.7 years of follow-up	21,427 men & women	calculated mean = 64.8 years**	Total Dairy Q5, 17.8 servings/day (dairy products (milk, cream, fermented dairy products, ice cream, butter, cheeses))	Q1, 0.9 servings/day	CVD Mortality	Non-Industry <sup>40</sup>	No <sup>ii</sup>
Umesawa, M, 2008 <sup>(42)</sup>	Cohort	12.9-year follow-up	41,526 men & women	40-59 years	Dairy Calcium, Q5, 116 mg/day (median) (to calculate dairy calcium intake, we specified 2 kinds of dairy products, ie, cheese and dairy products except cheese, for the baseline questionnaire, and 4 kinds, ie, whole milk, low fat milk, cheese, and yogurt, for the 5-year follow-up questionnaire)	Q1, 0 mg/day	Total Stroke & CHD	Non-Industry <sup>41</sup>	No <sup>jj</sup>



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Study ID	Study Deign	Length of Intervention /Follow up	Number of Participants	Age (mean years)	Exposure (highest tertile/quartile/quintile or ‘yes’ to dairy foods)	Comparison (lowest tertile/quartile/quintile or ‘no’ to dairy foods)	Outcomes Measured (verbatim)	Funding Source	Disclosed author conflicts of interest
Wang,L 2008 <sup>(43)</sup>	Cohort	10 years	28,886 women	53.8 years	Total Dairy Q5, 3.69 servings/day (median) (total dairy product intake was calculated by summing the intake of individual dairy items: low-fat dairy items include skim or low-fat milk, sherbet, yogurt, and cottage/ricotta cheese, high-fat dairy items include whole milk, cream, sour cream, ice cream, cream cheese, and other cheese)	Q1, 0.56 servings/day (median)	Hypertension	Non-Industry <sup>42</sup>	No <sup>kk</sup>

\* We calculated the mean age score of participants by summing Non-cases, T2D, MI and stroke cases at baseline and dividing them by 4

\*\*We calculated the mean age score of participants by summing all quintiles 1, 3, & 5 (they were the only ones available) at baseline and dividing them by 5

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8. This study was supported by the National Health and Medical Research Council of Australia.
9. Funding sources: The Nurses' Health Study and Health Professionals Follow-up Study cohorts are supported by grants UM1 CA186107, UM1 CA176726, and UM1 CA167552 from the National Institutes of Health. The current analyses were supported by small grants from the National Dairy Council, the General Mills Bell Institute for Health and Nutrition, and the Boston Nutrition and Obesity Research Center.
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- 6 b) None of the authors had any conflict of interest from a financial, personal, or professional aspect in relation to the findings of this study.
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- 8 c) None of the authors had any conflicts of interest.
- 9
- 10 d) Altorf-van der Kuil W, Engberink MF, Geleijnse JM - Top Institute Food and Nutrition, PO Box 557, 6700 AN, Wageningen, The
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- 26
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- 28
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- 30
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- 37
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- 39
- 40 n) There were no conflicts of interest.
- 41
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- 43
- 44 p) The authors have declared that no competing interests exist.
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21 jj) Disclosures: None.  
22 kk) Disclosures: None.  
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## Supplementary File 6. Risk of bias in included studies

Funding Source, n (%<sup>a</sup>)

Characteristic	Category	Total N = 43	Sponsorship		COI		Industry Ties	
			Industr y N= 8	Non- Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non- Industry/ No COI N = 29
<b>Risk of Bias Assessment</b>								
	Serious/Critical Bias due to confounding	43 (100)	8 (100)	35 (100)	10 (100)	33 (100)	14 (100)	29 (100)
	Serious/Critical Bias in selection of participants into the study	6 (14)	1 (13)	5 (14)	1 (10)	5 (15)	2 (14)	4 (14)
	Serious/Critical Bias in classification of exposures	16 (37)	3 (38)	13 (37)	2 (20)	14 (42)	3 (21)	13 (44)
	Serious/Critical Bias due to deviations from exposures	21 (49)	3 (38)	18 (51)	6 (60)	15 (45)	7 (50)	14 (48)
	Serious/Critical Bias due to missing data	10 (23)	2 (25)	8 (23)	3 (30)	7 (21)	3 (21)	7 (24)

	Serious/Critical Bias in measurement of outcomes	6 (14)	2 (25)	4 (11)	1 (10)	5 (15)	2 (14)	4 (14)
	Serious/Critical Bias in selection of reported results	4 (9)	1 (13)	3 (9)	2 (20)	2 (6)	2 (14)	2 (7)
	Serious/Critical overall risk of bias	43 (100)	8 (100)	35 (100)	10 (100)	33 (100)	14 (100)	29 (100)

<sup>a</sup> Percentages may not add to 100 due to rounding

Supplementary File 7: Favorable Outcomes by Industry Ties v No Industry Ties, Industry Sponsorship v No Industry Sponsorship and Conflicts of Interest v No Conflicts of Interest

Industry Ties: Industry Sponsorship and/or Author Conflicts of Interest					No Industry Ties: No Industry Sponsorship and No Author Conflicts of Interest				
Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable	Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable
Aerde, M 2013	Non-Industry	Yes	U	U	Al-Delaimy, WK 2003	Non Industry	No	U	U
Altorf-van der Kuil, W2012	Industry	Yes	U	U	Alonso A, 2005	Non-industry	No	U	U
Bernstein, AM 2012	Non-industry	Yes	U	U	Avalos, EE 2013	Non-industry	No	U	U
Biong, A 2008	Industry	Yes	U	F	Bonthuis, M 2010	Non-Industry	No	U	U
Buendia, JR 2018	Industry	No	F	F	Chen, M 2016	Non-Industry	No	U	F
Dalmeijer, G 2013	Non-Industry	Yes	U	F	Dauchet, L 2007	Non-Industry	No	U	U
Dehghan, M 2018	Industry	No	U	F	Elwood, PC 2004	Non-Industry	No disclosure	U	U
Heraclides, A 2012	Non-Industry	Yes	U	U	Engberink, MF 2009	No disclosure	No	U	F
Lockheart, MSK 2007	Industry	No disclosure	U	U	Farvid, MS 2017	Non-Industry	No	F	F
Louie, JCY 2013	Industry	No disclosure	U	U	Haring, B 2014	Non-Industry	No	U	U
Praagman, J 2015	Industry	Yes	U	U	He, K 2003	Non-Industry	No	U	U

Industry Ties: Industry Sponsorship and/or Author Conflicts of Interest					No Industry Ties: No Industry Sponsorship and No Author Conflicts of Interest				
Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable	Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable
Praagman J, 2015	Non-Industry	Yes	U	U	Johansson, I 2018	Non-Industry	No	U	U
Snijder, MB 2008	Industry	Yes	U	U	Johansson, I 2019	Non-Industry	No	U	U
Soedamah-Muthu, SS 2013	Non-Industry	Yes	U	U	Kim, D 2017	Non-Industry	No	F	F
					Larsson,S 2009	Non-Industry	No disclosure	U	U
					Larsson, SC 2012	Non-Industry	No	U	U
					Li, K 2012	Non-Industry	No	U	U
					Lin, PH 2013	Non-Industry	No	U	U
					Mazidi, M, 2018	Non-Industry	No	F	F
					Ness, AR 2001	Non-Industry	No	U	U
					Nettleton, J 2008	Non-Industry	No	U	U
					Panagiotakos, D 2009	Non-Industry	No disclosure	U	U
					Patterson, E 2013	Non-Industry	No	F	F
					Sauvaet, C 2003	Non-Industry	No disclosure	F	F
					Steffen, LM 2005	Non-Industry	No	U	U

Industry Ties: Industry Sponsorship and/or Author Conflicts of Interest					No Industry Ties: No Industry Sponsorship and No Author Conflicts of Interest				
Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable	Study ID	Funding Source	Disclosed author conflicts of interest	Results Favourable/ Unfavourable	Conclusions Favourable/ Unfavourable
					Tavani, A 2002	Non-Industry	No	F	F
					Um, C 2017	Non-Industry	No	U	F
					Umesawa, M, 2008	Non-Industry	No	F	F
					Wang,L 2008	Non-Industry	No	F	F

**Favourable results - Statistical significance: Industry ties vs no industry ties; industry sponsorship vs no sponsorship; COI v no COI**

#### Industry Ties

	Industry/COI	Non-Industry/No COI
Favourable	1	8
Unfavourable	13	21

RR= 0.26 (95% CI 0.04, 1.87)

#### Industry Sponsorship

	Industry	Non-Industry
Favourable	1	8
Unfavourable	7	27

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RR = 0.55 (95% CI 0.08, 3.77)

**Conflicts of Interest**

	COI	No/COI
Favourable	0	9
Unfavourable	10	24

RR= 0.16 (95% CI 0.01, 2.57)

**Favourable conclusions: Industry ties vs no industry ties; industry sponsorship vs no sponsorship; COI v no COI**

**Industry Ties**

	Industry/COI	Non-Industry/NO COI
Favourable	4	11
Unfavourable	10	18

RR = 0.75 (95% CI 0.29, 1.95)

**Industry Sponsorship**

	Industry	Non-Industry
Favourable	3	12
Unfavourable	5	23

For peer review only

RR= 1.09 (95% CI 0.40, 2.99)

### Conflicts of Interest

	COI	No COI
Favourable	2	13
Unfavourable	8	20

RR =0.51 (95% 0.14, 1.88)

**Concordance between study results and conclusions: Industry ties vs no industry ties; industry sponsorship vs no sponsorship; COI v no**

### COI Industry Ties

#### Industry Ties

	Industry/COI	Non-Industry/NO COI
Discord	3	3
Concord	11	26

RR = 2.07 (95% CI 0.48, 8.99)

### Industry Sponsorship

	Industry	Non-Industry
Discord	2	4
Concord	6	31

RR = 2.19 (95% CI 0.48, 9.94)



**Conflicts of Interest**

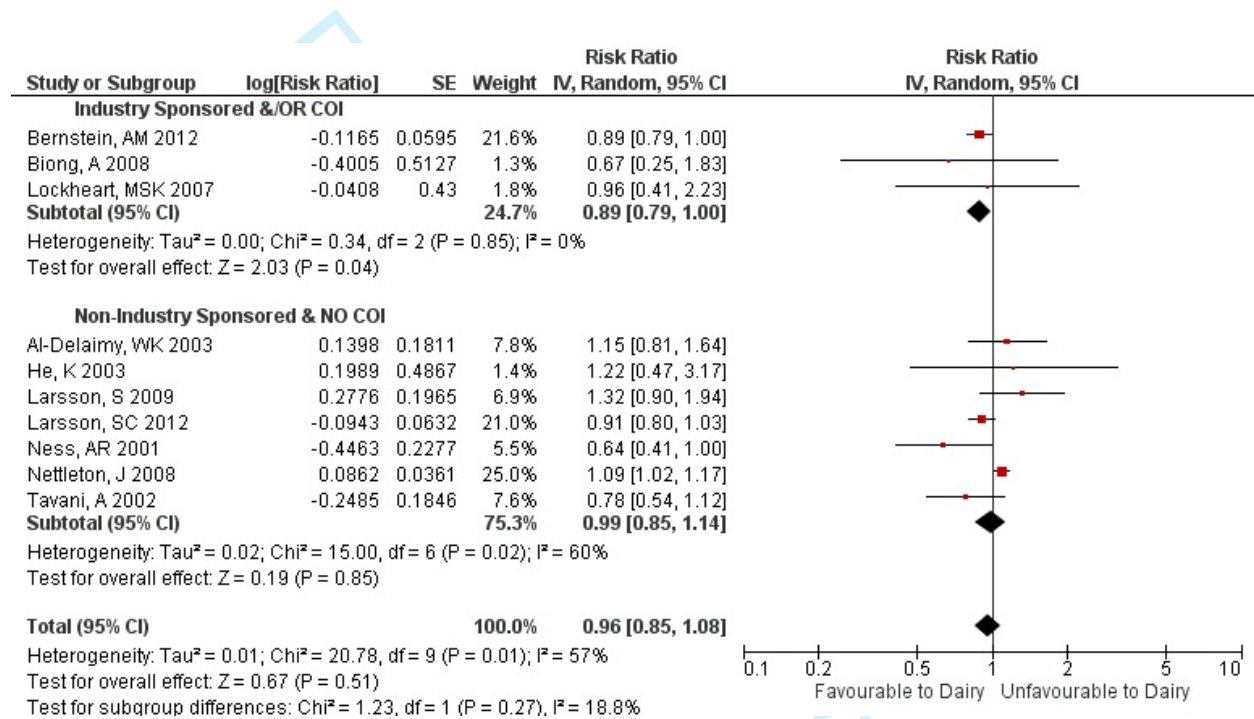
	COI	No/COI
Favourable	2	4
Unfavourable	8	29

RR = 1.65 (95% CI 0.35, 7.72)

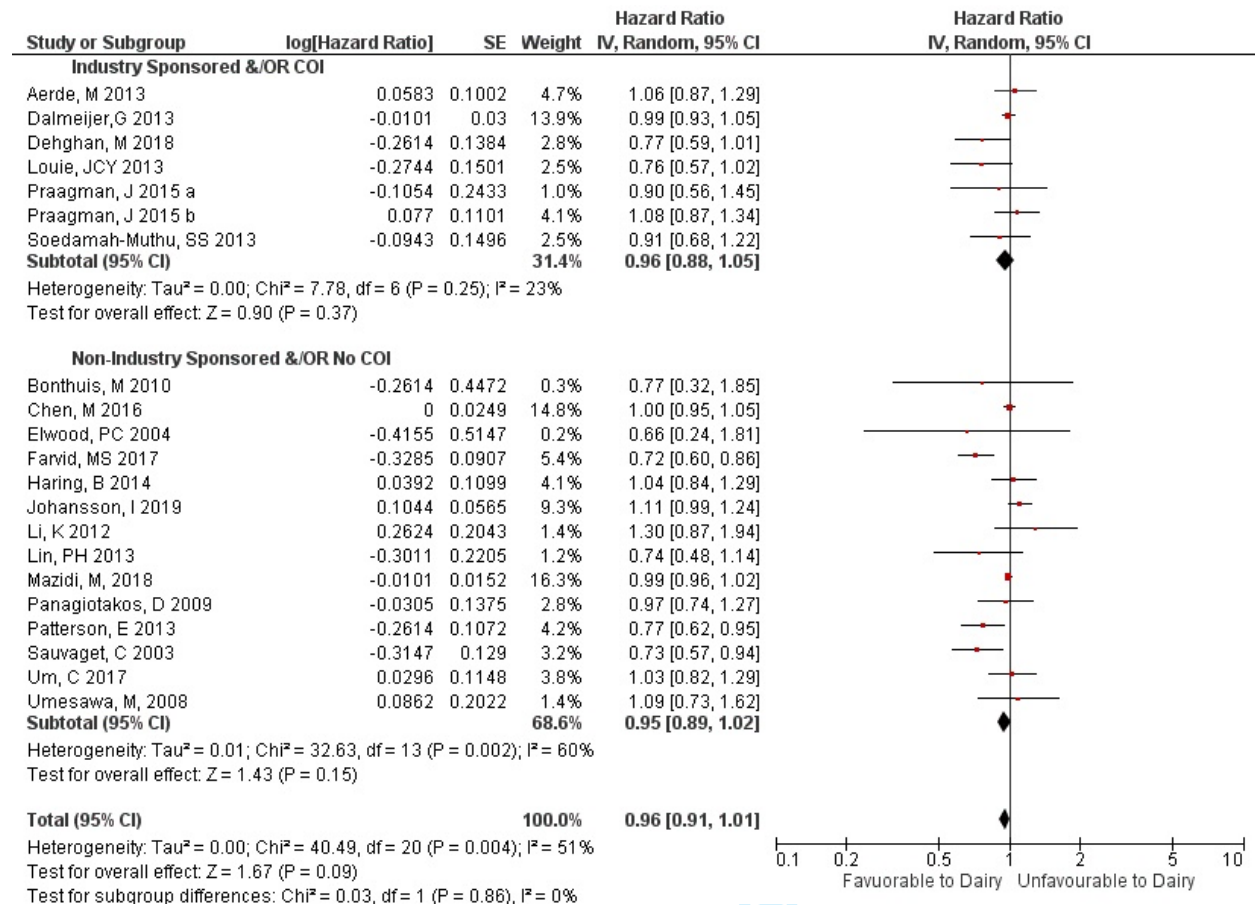
For peer review only

Supplementary File 8. Results for each of the meta-analyses conducted

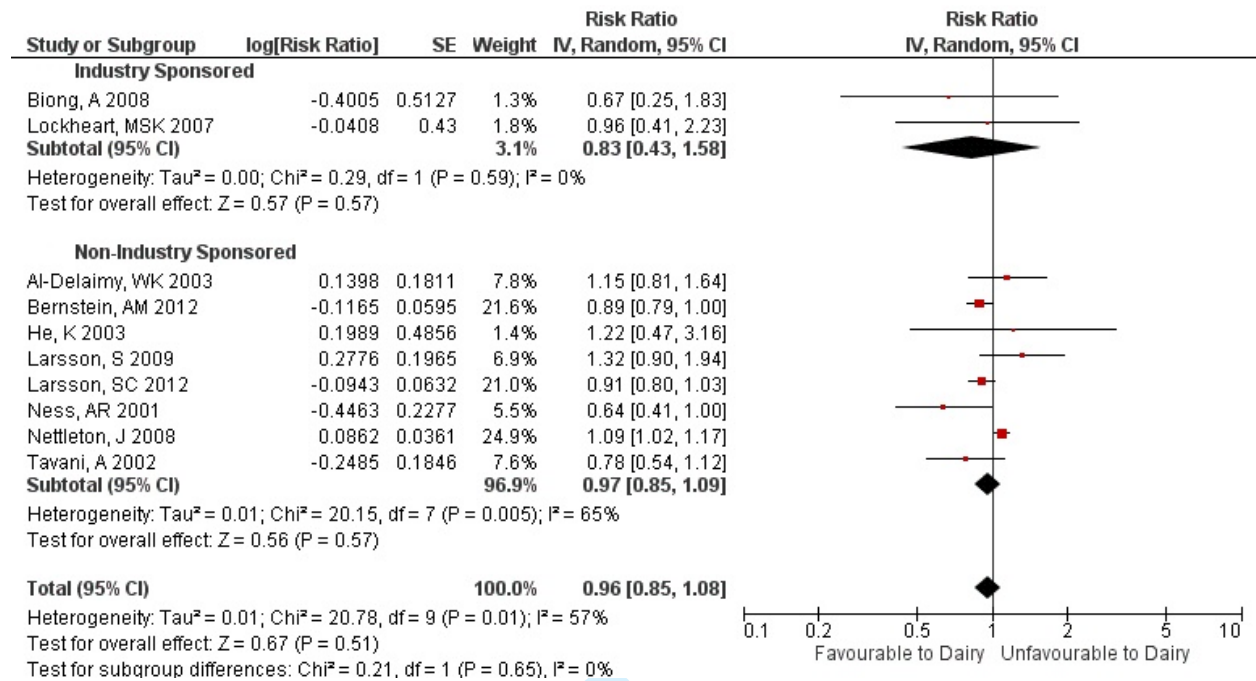
Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Risk Ratio



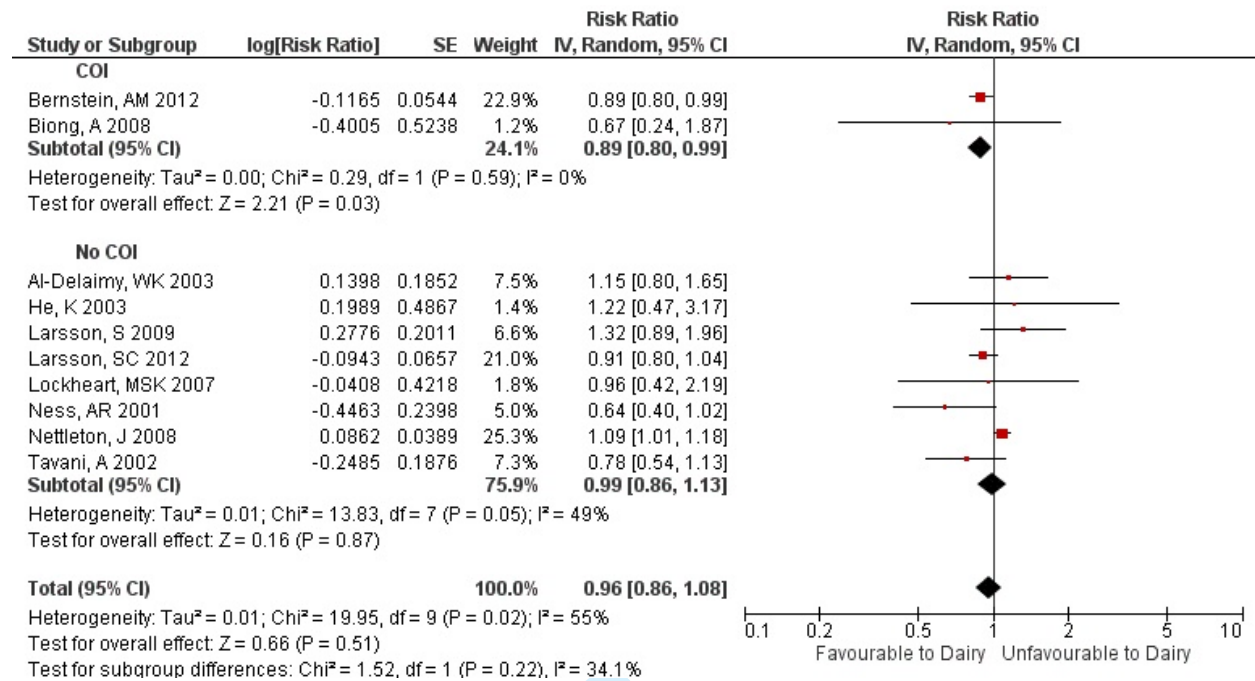
## Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Hazard Ratio



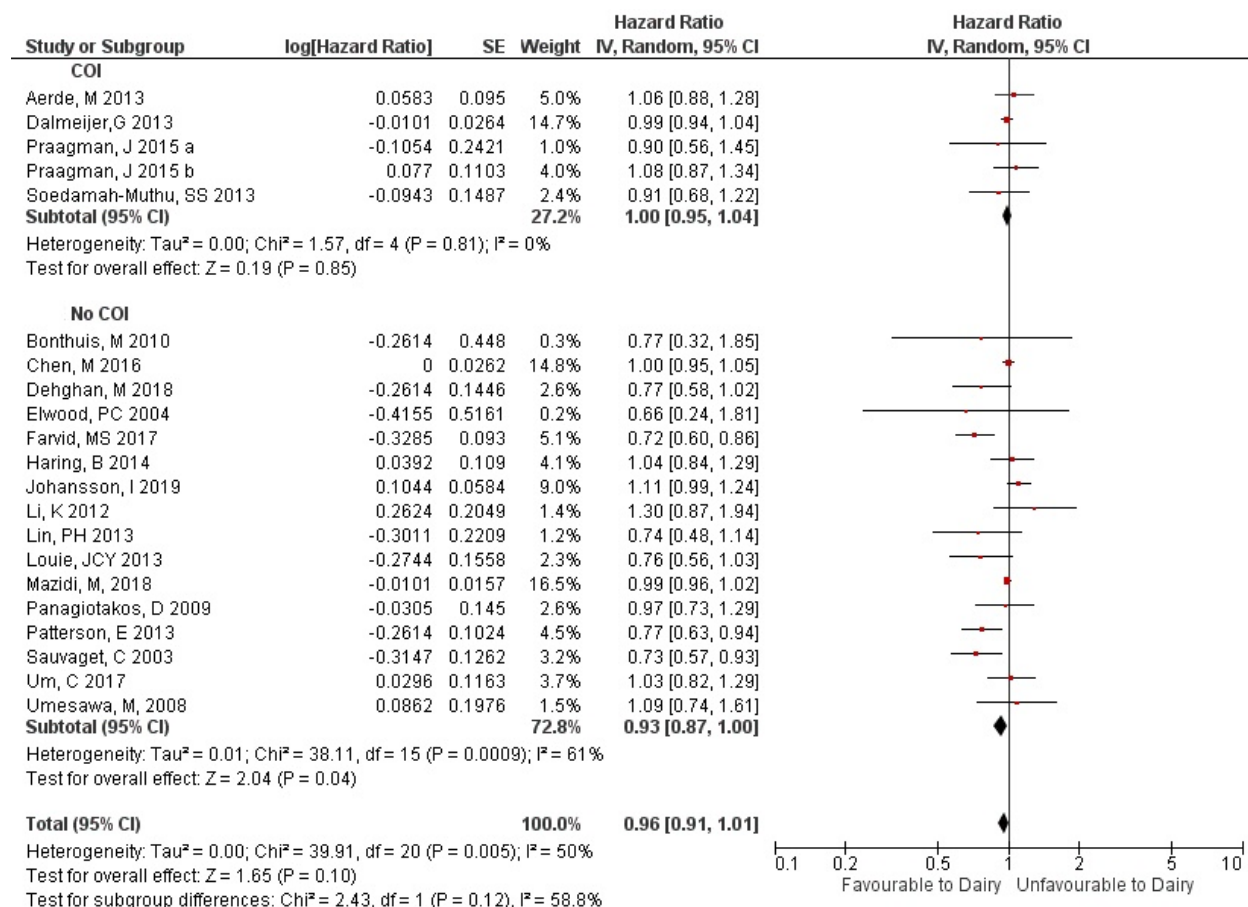
Effect Size, Cardiovascular Disease: Industry sponsorship vs no industry sponsorship, Risk Ratio



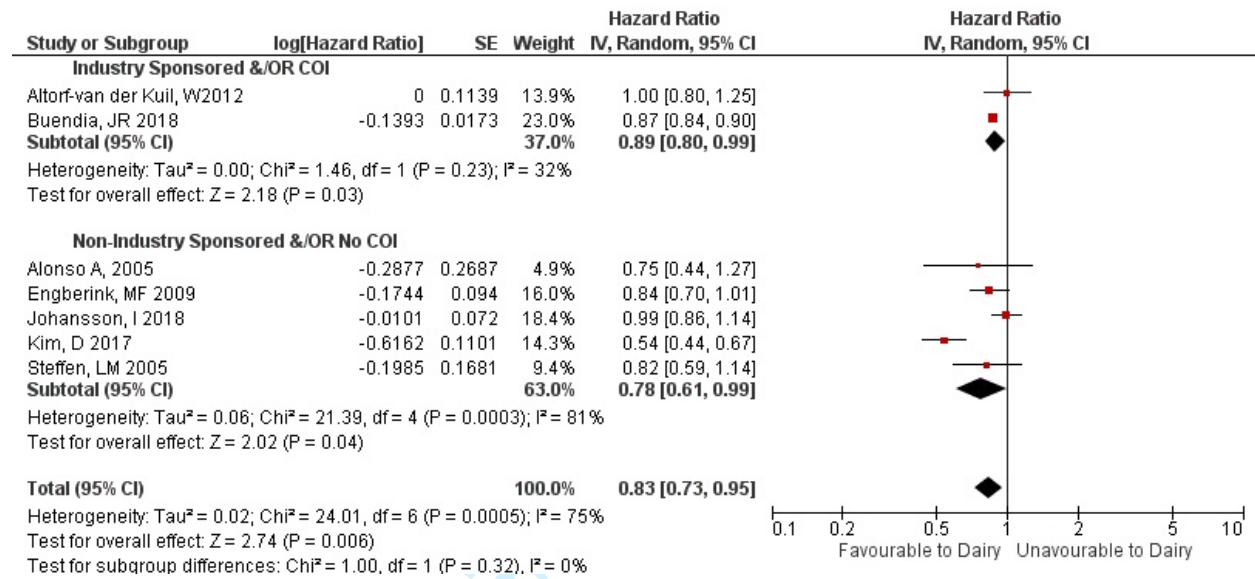
## Effect Size, Cardiovascular Disease: COI vs No COI, Risk Ratio



Effect Size, Cardiovascular Disease: COI vs no COI, Hazard Ratio



## Effect Size, Elevated Blood Pressure / Hypertension: Industry ties v no industry ties





# PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
<b>TITLE</b>			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
<b>ABSTRACT</b>			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
<b>METHODS</b>			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3&5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5, Supp file 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8-9
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8-9
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7 & 11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6 & 10
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$ for each meta-analysis). <a href="http://bmjopen.bmj.com/site/about/guidelines.xhtml">http://bmjopen.bmj.com/site/about/guidelines.xhtml</a>	10 -11





# PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10-11
<b>RESULTS</b>			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11, Figure 1, Supp file 4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Supp file 5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13, Supp File 6, Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-15
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-15, Supp file 7 & 8, Figure 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13, Supp file 6, Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
<b>DISCUSSION</b>			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15-18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16



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Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
<b>FUNDING</b>			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3&20

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: [www.prisma-statement.org](http://www.prisma-statement.org).

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