BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-039036
Article Type:	Original research
Date Submitted by the Author:	01-Apr-2020
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Keywords:	STATISTICS & RESEARCH METHODS, NUTRITION & DIETETICS, PUBLIC HEALTH

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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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Word Count: 4530

Abstract

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

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

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

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

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

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

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

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

Strengths and limitations of this study

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

with the results, conclusions and risk of bias of primary nutrition studies examining the effect of dairy foods on cardiovascular disease outcomes and mortality.

- We conducted a comprehensive search and followed explicit and well-defined inclusion and exclusion criteria for the included studies.
- For studies missing a funding or author COI disclosure, we did not contact the authors; thus we may be underestimating the number of studies with industry ties.
- The tool that we used to assess the risk of bias is still under modification, however it is unlikely any future changes to the tool will affect the risk of bias ratings.
- We did not analyse studies of low and full fat dairy separately. Industry ties may have different effects on studies of low or full fat dairy foods.

INTRODUCTION

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

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

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

The primary objective of this systematic review and meta-analysis is to determine whether:

- Studies of observational design examining the effects of dairy foods on CVD with food industry ties (industry sponsorship and / or authors with a COI) with the food industry are more likely to have results and / or conclusions that are favourable to industry than those with no industry ties.

The secondary objectives of this review are to determine whether observational studies with food industry ties compared with no industry ties:

I. differ in their risk of bias;
II. have a higher level of discordance between study results and conclusions, with the conclusions more likely to be favourable compared to the results.

METHODS

We conducted a systematic review of observational studies examining the effect of dairy consumption on CVD. Our study is registered with Prospero ID CRD42019129659 (see Supplementary file 1).[19]

Search Strategy

The search included terms to locate observational studies and randomised control trials, the latter of which are for a separate systematic review. The search used was based on the Process Manual used to develop the 2013 Australian Dietary Guidelines and the guidance of an information specialist.[20] The search dates used were to ensure that we identified the studies used to inform the recommendations in these guidelines. We therefore searched the following databases from January 2000-February 2019: MEDLINE; CINAHL; PubMed; PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy used for Ovid MEDLINE on February 1, 2019 is shown in Supplementary file 2. We adapted this strategy for the other databases. We hand searched references lists of the identified studies and reviews.

Eligibility Criteria

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

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

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

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

Types of Outcome Measures

Primary Outcomes

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

1. Statistical significance of results favourable to dairy

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

2. Effect size of results

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

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'.

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,[21] the ROBINS-E[22]. 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.

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.

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

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

Selection of results for meta-analysis

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

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

Data Collection

From each study we extracted:

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

- Role of the funders (role of the sponsor not mentioned, sponsor not involved in study design and analyses, sponsor involved, N/A)
- Disclosure of author COI (no disclosure, yes (if at least 1 author had a COI), the authors state they had no conflicts of interest to declare)
- Authors COI statement (verbatim)
- Outcomes assessed in the study (any CVD death and/or event or blood pressure/hypertension)
- The numerical results of the study (e.g., OR, HR, RR)

All extracted data from the included studies was stored in REDcap, a secure web-based application for the collection and management of data.[23] Five investigators (NC, SMc, AF, AL & JD) working independently in pairs extracted data from the included studies. Discrepancies in data extraction were resolved by consensus. If agreement could not be reached, a sixth investigator (LB) resolved the discrepancy.

Classification of industry sponsorship and author conflicts of interest

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

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

Since the number of studies with industry sponsorship or author COI was small, we also categorized studies as having "industry ties" for analysis. Studies classified as having an industry tie were industry sponsored and / or had an author COI. Otherwise, they were classified as having no industry ties.

Analysis

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

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

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

We undertook a fixed-effects test for subgroup differences (defined by industry sponsorship / authors conflict of interest) using the Chi2 test and calculated the ratio of RRs (ORs) or HRs along with 95% confidence intervals. Analyses were undertaken in Review Manager 5.3.[25]

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

RESULTS

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

Characteristics of included Studies

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

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

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

			Funding Source, n (%[a])					
			Sponsorship		COI		Industry Ties	
Characteristic	Category	Total N = 43	Industry N= 8	Non-Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non-Industry/ No COI N = 29
Sex	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)
Sample Size	<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)
Length of Follow up	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)
Type of Dairy	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)

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

* Follow up is not applicable for case control studies

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

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

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

Risk of bias in included studies

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

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

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

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

Effect Size, Cardiovascular Disease: Industry ties v no industry ties; industry sponsorship vs no industry sponsorship; COI v no COI

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

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

In our analysis comparing studies with industry sponsorship, (RR 0.83; n=2 studies) and those with no industry sponsorship, (RR 0.97; n=8 studies) we again did not find an important difference in the magnitude of RRs (ratio of RRs 0.86 (95% CI 0.44, 1.66)); P=0.65 (Supplementary file 7). However, when we compared industry sponsored studies, (HR =0.78; n=3 studies) and non-industry sponsored studies, (HR=0.97; n=18 studies) that measured the association using HRs, we found a statistically significant difference in the magnitude of the HRs (ratio of HRs 0.80 (95%CI 0.66, 0.97)); P=0.03 (Figure 3).

In our analysis comparing studies with an author with a COI (RR 0.89; n=2 studies) and those with no COI, (RR 0.99; n= 8 studies) we found no important difference in the magnitude of RRs (ratio of RRs 0.90 (95% CI 0.76-1.07)); P=0.22 (Supplementary file 7). When we compared studies with a COI, (HR =1.00; n= 5 studies) and studies with no COI, (HR=0.93; n=16 studies) that measured the association using HRs, we again found no difference in the magnitude of the HRs (ratio of HRs 1.08 (95% CI 0.99, 1.17)); P=0.12.

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

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

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

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

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

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

Risk of Bias Assessment by Industry Ties

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

Concordance between study results and conclusions

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

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

DISCUSSION

There was no clear evidence of an association between studies with food industry ties and the reporting of favourable results and conclusions of observational studies measuring the effects of dairy foods on cardiovascular disease outcomes. The 'mixed' group of funders we identified in the industry sponsored studies may influence these results, as the funding effect may be diluted by this heterogeneous group of sponsors. Unlike in drug studies, [12] the funders in the studies included in this review were extremely diverse, with Big Food and trade association jointly sponsoring several studies. Thus, dairy foods are not their sole interest.

The meta-analysis of hazard ratios of CVD outcomes found that studies with industry sponsorship showed a greater benefit from dairy than studies without industry sponsorship, and this difference was statistically significant. The meta-analysis of risk ratios of CVD outcomes found a similar estimate; however, this was not statistically significant. The likely reason for this was that the meta-analysis of RRs had fewer studies, and so the ratio of RRs could not be as precisely estimated. We found no evidence of a clinically important difference in the magnitude of effect between studies with industry ties or authors with a COI compared to those with no industry ties or no COI for other outcomes.

For every study, the overall risk of bias was classified as high (meaning either serious or critical). Therefore, differences in the risk of bias across studies with and without industry ties would not seem to provide an explanation for our findings. However, the version of the ROBINS-E tool that we used may not have been able to adequately discriminate across the studies, as perhaps is indicated by the uniformity in risk of bias classification.[26] Therefore, we cannot rule out the possibility that differences in bias across studies with and without industry ties may partly explain our findings.

Strengths and limitations of this review

Our review was prospectively registered in Prospero.[19] We followed explicit inclusion and exclusion criteria, conducted a comprehensive search across multiple databases and hand searched reference lists for the included studies.

For those studies missing a funding or author COI disclosure, we did not contact the authors and we therefore may be underestimating the number of studies with industry ties. The tool that we used to assess the risk of bias is still under development, however it is unlikely any future changes to the tool will affect the risk of bias ratings.[22] We did not analyse studies of low and full fat dairy separately. Industry ties may have different effects on studies of low or full fat dairy foods.

Agreements and disagreements with other studies or reviews

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

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

Implications for clinicians, policy makers and future research

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

Industry sponsors may bias research via different mechanisms, including the design and conduct of a study, the selective reporting of results and by spinning conclusions,[11] as well as how the questions are asked.[29] It has been suggested that the dairy industry may preferentially fund research on topics which will provide them with more favourable outcomes.[30] The influence of the food industry on the research agenda has been demonstrated in an examination of research topics covered by samples of randomised controlled trials included in systematic reviews of nutrition studies and obesity.[31] It was shown that most food industry studies focused on the manipulations of specific nutrients, and not on dietary behaviours, therefore limiting the public health relevance of rigorous evidence available for use in both systematic reviews and dietary guidelines.[31] The topics examined in cohort studies on the relationship of nutrition and obesity, which tend to focus on more complex exposures than trials, did not demonstrate a similar influence of funding source. However, the disclosure of food industry sponsorship was low, making a comparison difficult.[32]

Conclusion

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

Acknowledgements: We thank Agnes Lau, University of California, San Francisco, for her assistance with data collection.

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

Funding: This work was supported by Australian Health and Medical Research Council Project Grant APP 1139997. Nicholas Chartres is a recipient of the James Millner PhD Scholarship in Pharmacy from the University of Sydney.

Competing interests: None declared.

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

Patient consent for publication: Not required.

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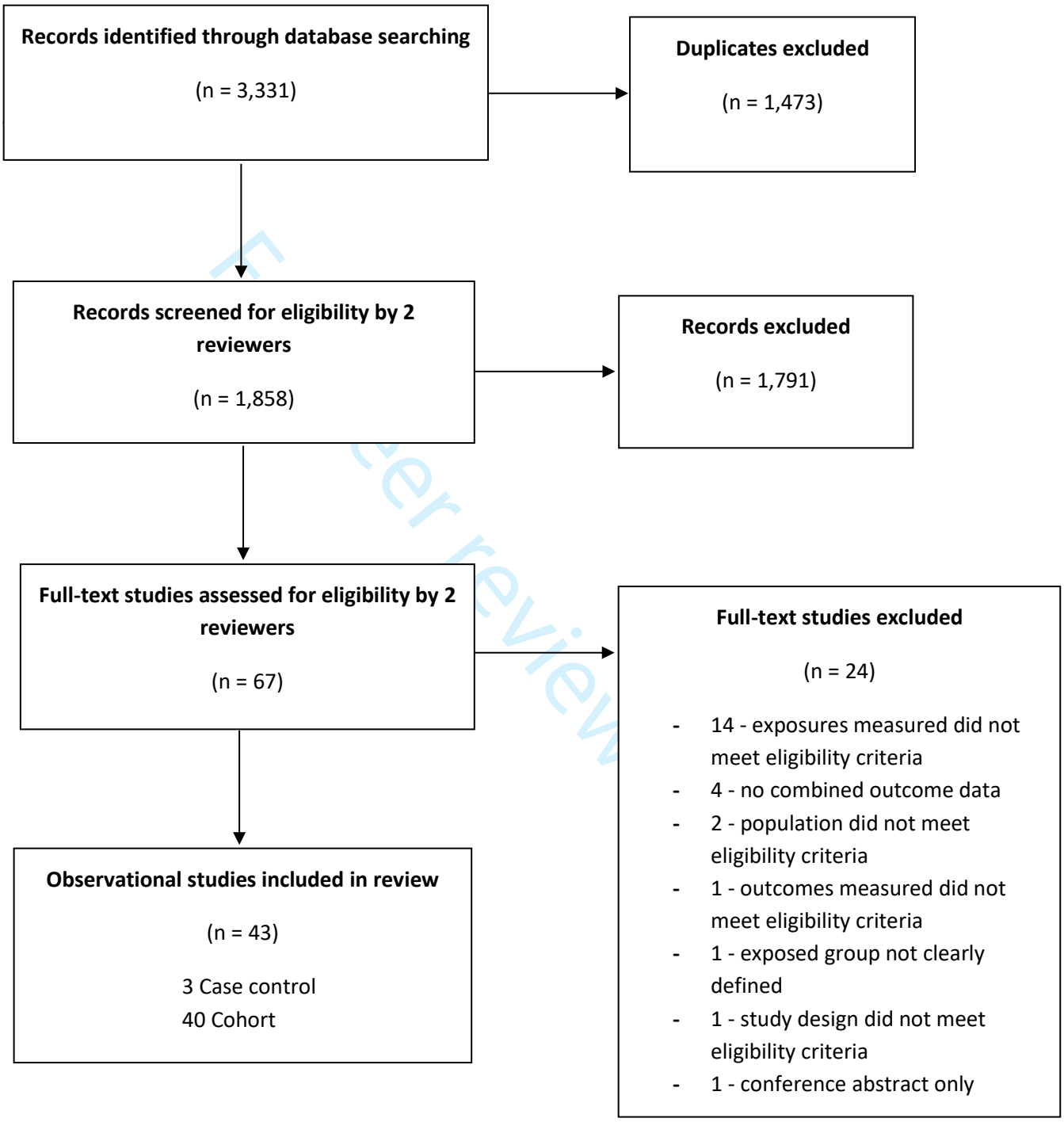
Figures

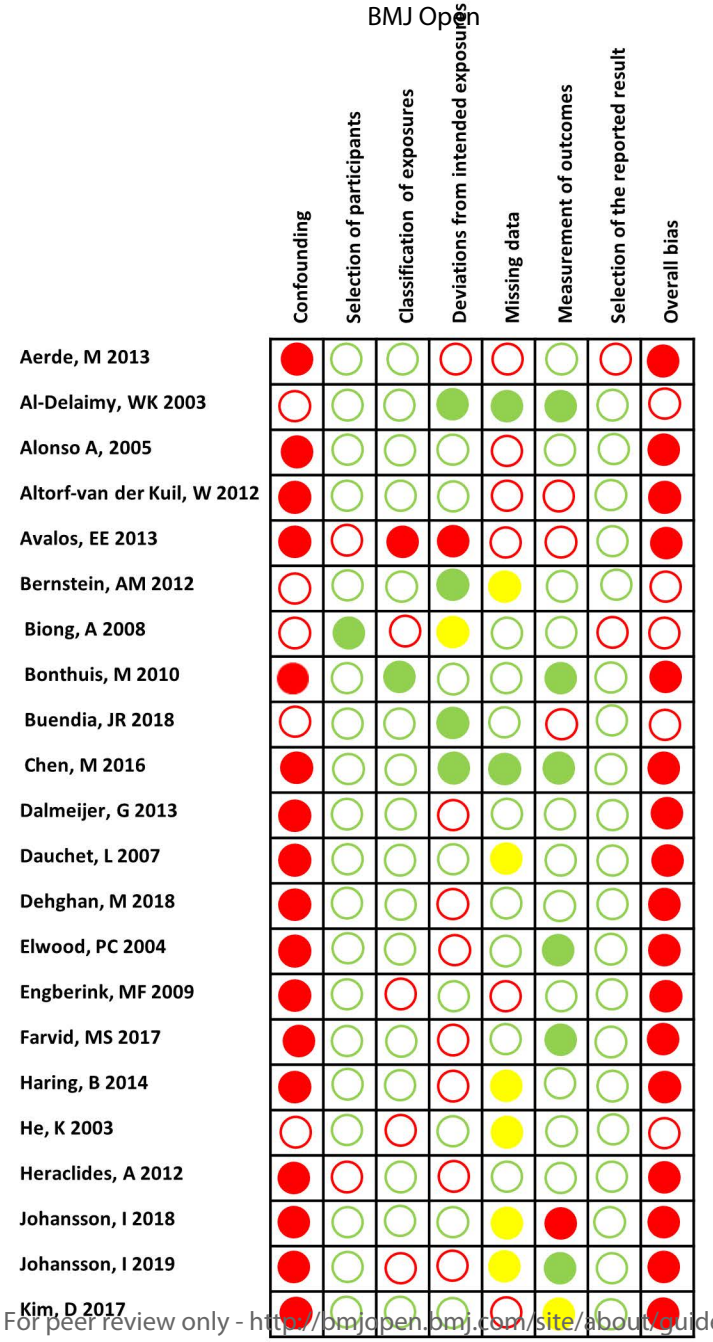
Figure 1. Study Flow Diagram

Figure 2. Risk of Bias in Included Studies

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

Figure 1. Study Flow Diagram





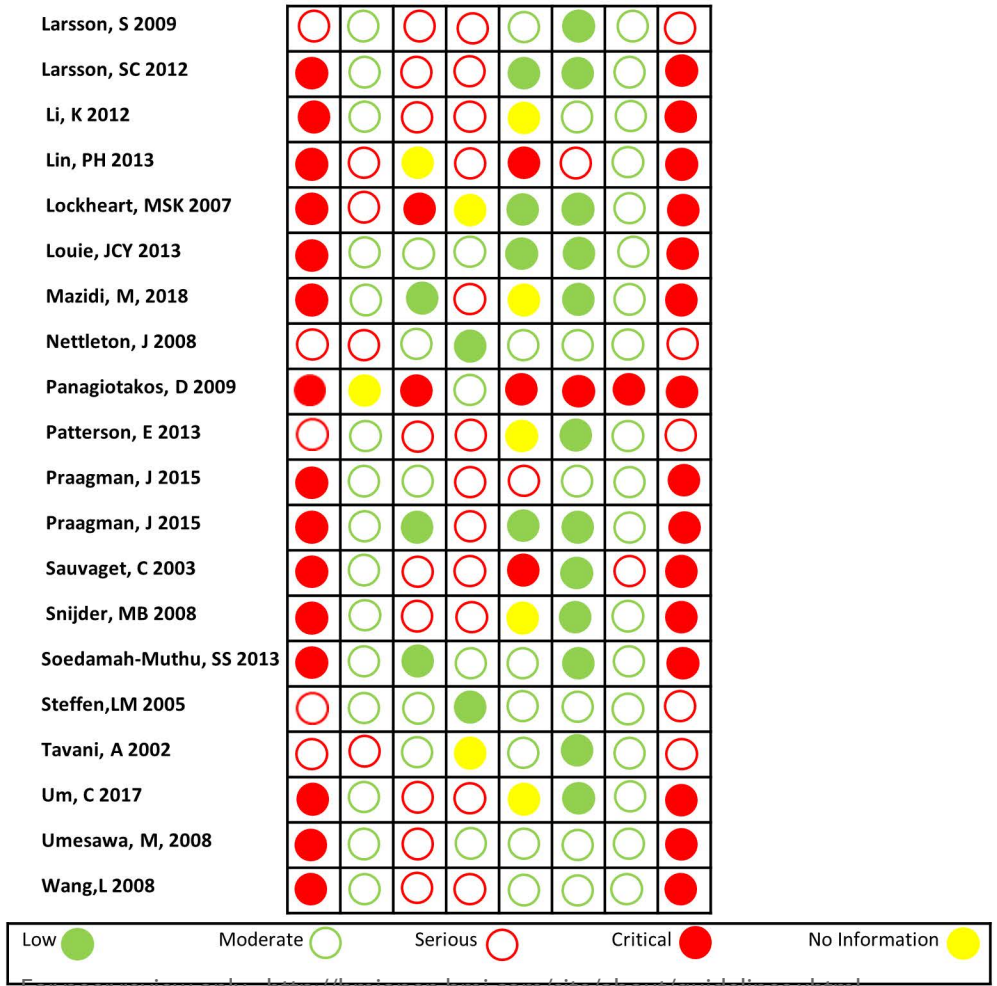
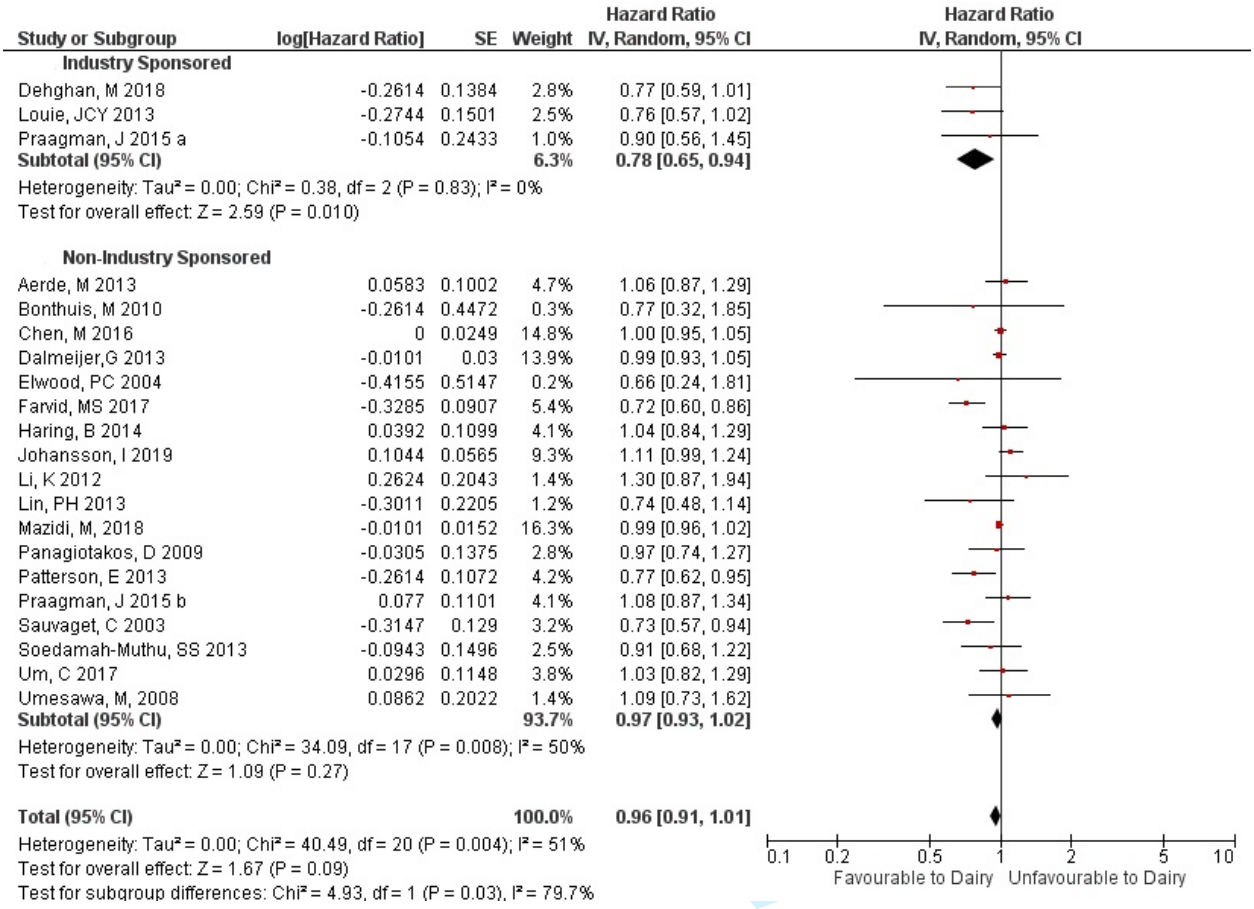


Figure 3. Effect Size, Cardiovascular Disease, Industry sponsorship vs no Industry sponsorship, Hazard Ratio



PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
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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

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National Institute for Health Research

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.

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

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

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

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

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

c. Secondary Outcome 1 (Risk of Bias tool for studies)

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.

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

‘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

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

No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
Yes

Care of the elderly
No

Child health
No

Complementary therapies

No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
Yes

Rehabilitation
No

Respiratory disorders
No

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.

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 newregistrations 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.

25. dairy consumption.mp.

26. dairy food*.mp.

27. Dairy Products/ or dairy product*.mp.

28. dairy serv*.mp.

29. dairy type*.mp.

30. dairy source*.mp.

31. (calcium adj15 food sourc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

32. (vitamin D adj15 food sourc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

33. (milk and (cow or goat or sheep)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

34. yogurt.mp. or Yogurt/

35. cheese.mp. or Cheese/

36. custard.mp.

37. (milk and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

38. (yogurt and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

39. Milk/

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 39

41. cardiovascular disease.mp. or exp Cardiovascular Diseases/

42. coronary*.tw.

43. heart*.tw.

44. cardia*.tw.

45. cardio*.tw.

46. myocard*.tw.

47. isch?em*.tw.

48. angina*.tw.

49. ventric*.tw.

50. tachycardi*.tw.

51. pericard*.tw.

52. endocardi*.tw.

53. atrial fibrillat*.tw.

54. arrhythmi*.tw.

55. athero*.tw.

56. arterio*.tw.

57. exp Atherosclerosis/

58. exp Arteriosclerosis/

59. HDL.tw.

60. LDL.tw.

61. VLDL.tw.

62. lipid*.tw.

63. lipoprotein*.tw.

64. triacylglycerol*.tw.

65. exp Hyperlipidemias/

66. hyperlipid*.tw.

67. hypercholesterol*.tw.

68. hypercholester?emia*.tw.

69. hypertriglycerid?emia*.tw.

70. exp Cholesterol/

71. cholesterol*.tw.

72. exp Stroke/

73. stroke*.tw.

74. CVA.tw.

75. cerebrovasc*.tw.

76. "vascular accident".tw.

77. TIA.tw.

78. cerebral vascular.tw.

79. thrombo*.tw.

80. emboli*.tw.

81. apoplexy.tw.

82. (brain adj2 accident*).tw.

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

84. Hypertension/

85. exp Blood Pressure/

86. hypertensi*.tw.

87. blood pressure*.tw.

88. systolic blood pressure.tw.

89. diastolic blood pressure.tw.

90. peripheral arter* disease*.tw.

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

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

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

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

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

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

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 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 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96

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 19 or 20 or 21 or 22

99. 40 and 97 and 98

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

101. limit 100 to humans

102. limit 101 to "all adult (19 plus years)"

Supplementary file 3: List of excluded studies and reasons for exclusion

Author	Title	Reason for Exclusion
Akbaraly, T 2013[1]	Does overall diet in midlife predict future aging phenotypes? A cohort study	Dietary patterns only were assessed, not dairy foods
Anderson, LA 2011[2]	Dietary Patterns and Survival of Older Adults	No relevant outcomes were measured
Baylin, A 2003[3]	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[4]	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[5]	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[6]	Prospective investigation of major dietary patterns and risk of cardiovascular mortality in Bangladesh	Dietary patterns only were assessed, not dairy foods
Ding, M 2017[7]	Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study	Not an observational design study
Eguchi, E 2012[8]	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[9]	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[10]	Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands	No combined outcome data
Julián-Almárcegui, C 2016[11]	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[12]	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[13]	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[14]	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[15]	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[16]	Arginine intake and risk of coronary heart disease mortality in elderly men	Effects of dairy foods not measured
Paillard, F 2015[17]	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[18]	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[19]	Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study	Dietary patterns only were assessed, not dairy foods
Umesawa, M 2006[20]	Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study	No combined outcome data
van der Pols, J C 2009[21]	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[22]	Stroke and plasma markers of milk fat intake – a prospective nested case-control study	Effects of dairy foods not measured
Warensjo, E 2009[23]	Milk Fat Biomarkers and the Risk of a First Ever Acute Myocardial Infarction - A Prospective Nested Case-Control Study. Journal of the American Dietetic Association. 2009;1	Poster presentation only, full study not available
Warensjo, E 2010[24]	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.
7. Ding M, Huang T, Bergholdt HK, et al. Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study. *Bmj.* 2017;356:j1000.
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10. Goldbohm RA, Chorus AMJ, Galindo Garre F, et al. Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands. *American Journal of Clinical Nutrition.* 2011;93(3):615-627 613p.
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12. Larsson SC, Wolk A, Bäck M. Dietary patterns, food groups, and incidence of aortic valve stenosis: A prospective cohort study. *International Journal of Cardiology.* 2018.
13. Lupton BS, Fonnebo V, Sogaard AJ, et al. The Finnmark Intervention Study: is it possible to change CVD risk factors by community-based intervention in an Arctic village in crisis? *Scandinavian Journal of Public Health.* 2003;31(3):178-186.
14. Meyer J, Doring A, Herder C, et al. Dietary patterns, subclinical inflammation, incident coronary heart disease and mortality in middle-aged men from the MONICA/KORA Augsburg cohort study. *European journal of clinical nutrition.* 2011;65(7):800-807.
15. Michaelsson K, Melhus H, Warensjo E, et al. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. *Bmj.* 2013;346:f228.
16. Oomen CM, van Erk MJ, Feskens EJ, et al. Arginine intake and risk of coronary heart disease mortality in elderly men. *Arteriosclerosis, thrombosis, and vascular biology.* 2000;20(9):2134-2139.
17. Paillard F, Bruckert E, Naelten G, et al. Cardiovascular risk and lifestyle habits of consumers of a phytosterol-enriched yogurt in a real-life setting. *Journal of Human Nutrition & Dietetics.* 2015;28(3):226-235 210p.
18. Praagman J, Beulens JW, Alssema M, et al. 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. *American Journal of Clinical Nutrition.* 2016;103(2):356-365.
19. Streppel MT, Sluik D, van Yperen JF, et al. Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study. *European journal of clinical nutrition.* 2014;68(6):741-747.
20. Umesawa M, Iso H, Date C, et al. Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study. *Stroke.* 2006;37(1):20-26.
21. van der Pols JC, Gunnell D, Williams GM, et al. Childhood dairy and calcium intake and cardiovascular mortality in adulthood: 65-year follow-up of the Boyd Orr cohort. *Heart.* 2009;95(19):1600-1606.
22. Warensjo E, Smedman A, Stegmayr B, et al. Stroke and plasma markers of milk fat intake--a prospective nested case-control study. *Nutrition Journal.* 2009;8:21.

23. Warensjo E, Sjogren P, Cederholm T, et al. Milk Fat Biomarkers and the Risk of a First Ever Acute Myocardial Infarction - A Prospective Nested Case-Control Study. *Journal of the American Dietetic Association.* 2009;109(9, Supplement):A51.

24. Warensjö E, Jansson JH, Cederholm T, et al. Biomarkers of milk fat and the risk of myocardial infarction in men and women: a prospective, matched case-control study. *American Journal of Clinical Nutrition.* 2010;92(1):194-202 199p.

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[(1)]	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[1]	Yes[a]
Al-Delaimy, WK 2003[(2)]	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[2]	No[b]
Alonso A, 2005[(3)]	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[3]	No[c]

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
Altorf-van der Kuil, W2012[4]	Cohort	Mean follow up 7·5 years	3,588 men & women	44 years	Dairy Protein T3, ≥ 27 g/day (dairy protein was calculated as protein from milk, yogurt, coffee creamer, curd, pudding, porridge, custard, whipped cream and cheese)	T1, ≤ 19 g/day	Hypertension	Industry[4]	Yes[d]
Avalos, EE 2013[5]	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[5]	No[e]
Bernstein, AM 2012[6]	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[6]	Yes[f]
Biong, A 2008[7]	Case Control		218 men & women	62.4 years	Dairy Fat, > 34.1 g/day	<14.6 g/day	First Myocardial Infarction	Industry[7]	Yes[g]

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[8]	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[8]	No[h]
Buendia, JR 2018[9]	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[9]	No[i]
Chen, M 2016[10]	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[10]	No[j]

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[11]	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[11]	Yes[k]
Dauchet, L 2007[12]	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[12]	No[l]

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[13]	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[13]	No[m]
Elwood, PC 2004[14]	Cohort	20-24 years	2,403 men	45-59 years	Milk Q4, >1 pint per day	Q1, None	Vascular Event	Non-Industry[14]	No disclosure

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
Engberink, MF 2009[15]	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[n]
Farvid, MS 2017[16]	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[15]	No[o]
Haring, B 2014[17]	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[16]	No[p]
He, K 2003[18]	Cohort	14 years	43,732 men	40-75 years	High Fat Dairy Q5, ≥1/day	Q1, <1/week	Ischaemic & Haemorrhagic Stroke	Non-Industry[17]	No[q]

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[19]	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 [18]	Yes[r]
Johansson, I 2018[20]	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[19]	No[S]
Johansson, I 2019[21]	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[20]	No[t]
Kim, D 2017[22]	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 [21]	No[u]
Larsson,S 2009[23]	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[22]	No disclosure

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
Larsson, SC 2012[24]	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[23]	No[v]
Li, K 2012[25]	Cohort	11 years	23,980 men & women	35-64 years	Dairy Calcium Q4, 780 mg/day	Q1, 188 mg/day	CVD Mortality	Non-Industry[24]	No[w]
Lin, PH 2013[26]	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[25]	No[x]
Lockheart, MSK 2007[27]	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 [26]	No disclosure
Louie, JCY 2013[28]	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[27]	No disclosure
Mazidi, M, 2018[29]	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[28]	No[y]

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[30]	Cohort	25 years	5,765 men	35-64 years	Milk T3, > 1 pint (= 0.568 liters)	T1, None	Cardiovascular Disease Deaths	Non-Industry[29]	No[z]
Nettleton, J 2008[31]	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[30]	No[aa]
Panagiotakos, D 2009[32]	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[31]	No disclosure
Patterson, E 2013[33]	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[32]	No[bb]
Praagman, J 2015 (a)[34]	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[33]	Yes[cc]

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
Praagman, J 2015 (b)[35]	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[34]	Yes[dd]
Sauvaget, C 2003[36]	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[35]	No disclosure
Snijder, MB 2008[37]	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 (≤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[36]	Yes[ee]
Soedamah-Muthu, SS 2013[38]	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 [37]	Yes[ff]
Steffen, LM 2005[39]	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[38]	No[gg]

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
Tavani, A 2002[40]	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[39]	No[hh]
Um, C 2017[41]	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-Indutry[40]	No[ii]
Umesawa, M, 2008[42]	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[41]	No[ij]

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[43]	Cohort	10 years	28,886 women	53.8 years	Total Diary 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[42]	No[kk]

* 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

Description of Funding Source (Verbatim)

1. The Hoorn Study has been made possible by the Vrije Universiteit Amsterdam and the VU University Medical Center, and by grants from the Dutch Diabetes Research Foundation, the Dutch Organization for Scientific Research, the Netherlands Heart Foundation, and the Health Research and Development Council of the Netherlands.
2. Supported by research grants HL24074, HL34594, DK36798, and CA87969 from the National Institutes of Health.
3. Supported by the Spanish Ministry of Health (grants PI040233 and G03-140), the Navarra Regional Government (PI41-2005), and the University of Navarra (línea especial Nutricio LE-97).AA was supported partially by a Fulbright fellowship and an MMA Foundation grant.
4. The Doetinchem Cohort Study was financially supported by the Ministry of Health, Welfare and Sport of the Netherlands and the National Institute for Public Health and the Environment. For the present analysis, Wageningen University was supported by the Top Institute Food and Nutrition, which is a public/private partnership that generates vision on scientific breakthroughs in food and nutrition, resulting in the development of innovative products and technologies. Partners are major Dutch Food companies and research organisations.
5. The study was supported by grants AG007181 and AG028507 from the National Institutes of Health/National Institute on Aging, and by grant DK31801 from the National Institute of Diabetes and Digestive and Kidney Diseases.
6. This study was supported by grant P01CA087969 from the National Institutes of Health, Department of Health and Human Services. A.M.B. was supported through the Harvard Human Nutrition Program.
7. The study was supported financially by the Research Council of Norway, Throne Holst's Foundation for Nutrition Research, The Norwegian Association of Margarine Producers, DeNoFa Fabrikker A/S and Tine BA. Tine BA is a dairy company.
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.
10. Supported by the NIH (grants R01 HL034594, UM1 CA176726, UM1 CA186107, R01 HL35464, R01 HL088521, R01 CA67262, HL60712, and UM1 CA167552).
11. This research was supported by a personal Dr. Dekker postdoctoral grant (2008T062) from The Netherlands Heart Foundation (JWJ Beulens).
12. The SU.VI.MAX study is supported by the Direction Générale de la Santé, the Ministère de la Santé, and the Institut Virtuel de Recherche en Santé Publique (groupe cohorte) INSERM.
13. The PURE Study is an investigator-initiated study that is funded by the Population Health Research Institute, the Canadian Institutes of Health Research (CIHR), Heart and Stroke Foundation of Ontario, support from CIHR's Strategy for Patient Oriented Research (SPOR) through the Ontario SPOR Support Unit, as well as the Ontario Ministry of Health and Long-Term Care and through unrestricted grants from several pharmaceutical companies, with major contributions from AstraZeneca (Canada), Sanofi-Aventis (France and Canada), Boehringer Ingelheim (Germany and Canada), Servier, and GlaxoSmithKline, and additional contributions from Novartis and King Pharma and from various

national or local organisations in participating countries. These include Brazil: Unilever Health Institute, Brazil; South Africa: The SA Sugar Association (SASA).

14. The Medical Research Council, the University of Wales College of Medicine and Bristol University, Food Standards Agency.
15. This work was supported by Tehran University of Medical Sciences (grant 82-603); Cancer Research UK (grant C20/A5860); the Intramural Research Program of the National Cancer Institute, US National Institutes of Health (grant Z01 CP000185-03); and various collaborative research agreements with the International Agency for Research on Cancer. M.F. was supported by a Takemi Fellowship from the Japan Pharmaceutical Manufacturers Association.
16. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).
17. This work was supported by the research grant HL35464 and CA55075 from the National Institutes of Health.
18. The study was funded by the Medical Research Council, and some aspects of the analysis were funded by The European Commission, Quality of Life and Management of Living Resources Programme, contract number QLG1-CT-2000–01643.
19. The present study was supported by the Swedish Research Council for Health, Working Life and Welfare (FORTE).
20. This research was funded by The Swedish Research Council for Health, Working Life and Welfare (FORTE), grant number 2016-00960. The Northern Sweden Diet Database has been supported by the Swedish Research Council for Health, Working Life and Welfare (FORTES) and The Swedish Research Council.
21. This research was supported by the Basic Science Research Program of the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology (NRF2016R1D1A1B03931307).
22. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was supported by Public Health Service contracts N01-CN-45165, N01-RC-45035 and N01-RC-37004 from the US National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Md. Dr. Larsson's research at the National Public Health Institute in Helsinki, Finland, was supported by a grant from the Swedish Council for Working Life and Social Research.
23. This study was supported by a research grant from the Swedish Council for Working Life and Social Research (FAS), the Swedish Research Council, and by a Research Fellow grant from Karolinska Institutet (to Dr Larsson).
24. This work was supported by supported by the Deutsche Krebshilfe (grant-No70-488-Ha I) and the Graduiertenkolleg 793: Epidemiology of communicable and chronic non-communicable disease and their inter-relationships.
25. Data collection was supported by the Department of Health in Taiwan.
26. The present study was supported by NIH NRSA T32HL007779, CVD Epidemiology and Prevention, American Heart Association – Greater Midwest Affiliate, Throne Holst's Foundation for Nutrition Research, The Norwegian Association of Margarine Producers, DeNoFa Fabriker A/S and Tine Norwegian Dairies.
27. This study was funded by Dairy Australia.

28. This manuscript was written independently; no company or institution supported it financially.
29. Funding: this study was provided with funding by a grant from the NHS Management Executive Cardiovascular Disease and Stroke Research and Development Initiative.
30. This research was supported by the National Institutes of Health grant HL73366, training grant T32 HL07779, and contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022 from the National Heart, Lung, and Blood Institute.
31. The ATTICA study was supported by research grants from the Hellenic Cardiological Society (HCS2002).
32. Supported by research grants from the Swedish Council for Working Life and Social Research and from the Swedish Research Council/Infrastructure Medicine.
33. This study was supported by an unrestricted grant from the Dutch Dairy Organization (NZO) for epidemiological analyses on dairy intake and cardiovascular diseases.
34. The present study was supported by a personal Dr Dekker postdoctoral grant (2008T062) from the Netherlands Heart Foundation (J. W. J. B.).
35. This publication is based on research performed at the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan. RERF is a private nonprofit foundation funded equally by the Japanese Ministry of Health, Labor and Welfare and the US Department of Energy through the National Academy of Sciences.
36. This particular study has been supported by a grant from the Dutch Dairy Association (NZO).
37. The Whitehall II study was supported by grants from the Medical Research Council (G0902037), the British Heart Foundation (RG/07/008/23674), the Stroke Association, the National Heart Lung and Blood Institute (5RO1 HL036310), the National Institute on Aging (5RO1AG13196) and the Agency for Health Care Policy Research (5RO1AG034454).
38. The CARDIA Study is supported by National Heart, Lung, and Blood Institute contracts N01-HC-48047, N01-HC-48048, N01-HC-48049, N01- HC-48050, and N01-HC-95095.
39. Funding: partly supported by the Italian Ministry of Health (Programmi Speciali).
40. The REGARDS research project is supported by a cooperative agreement U01 NS041588 from the National Institute of Neu- rological Disorders and Stroke, National Institutes of Health, Department of Health and Human Service. Additional support provided by the Franklin Foundation.
41. This study was supported by grants-in-aid for cancer research and by the Third Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan.
42. This work was supported by research grants CA-047988 and HL-080467 from the National Institutes of Health, Bethesda, Md.

Description of Author Disclosure Statement (Verbatim)

a) Sabita S. Soedamah-Muthu and Johanna M. Geleijnse obtained an unrestricted grant from the Dutch Dairy Association (NZO) to carry out meta-analyses on the association between dairy products and CVD.
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.
c) None of the authors had any conflicts of interest.
d) Altorf-van der Kuil W, Engberink MF, Geleijnse JM - Top Institute Food and Nutrition, PO Box 557, 6700 AN, Wageningen, The Netherlands.
e) The authors have no conflicts of interest.
f) D.M. received research grants for studying the effects of diet on cardiometabolic diseases from the National Institutes of Health; the Searle Scholar Award from the Searle Funds at The Chicago Community Trust; the Genes and Environment Initiative at the Harvard School of Public Health; and the Gates Foundation/World Health Organization Global Burden of Diseases, Injuries, and Risk Factors Study; and from GlaxoSmithKline, Sigma Tau, Pronova, and the National Institutes of Health for an investigator-initiated, not- for-profit clinical trial of fish oil and postsurgical complications. He also received ad hoc travel reimbursement and/or honoraria for research presentations from the Chicago Council, International Life Sciences Institute, Aramark, Unilever, SPRIM, Nutrition Impact, Norwegian Seafood Export Council, United Nations Food and Agricultural Organization, World Health Organization, US Food and Drug Administration, and several universities. He received ad hoc consulting fees from Foodminds and royalties from UpToDate for an online chapter on fish oil.
g) A. S. Biong is employed as a Ph.D. student in a research project funded jointly by TINE BA, a Norwegian dairy company, and the Norwegian Research Council.
h) The authors declare no conflict of interest.
i) There are no conflicts of interest.
j) None of the authors reported a conflict of interest related to the study.
k) SS-Mand MG obtained an unrestricted grant from the Dutch Dairy Association (NZO) to carry out meta-analyses on the association between dairy products and cardiovascular diseases.
l) None of the authors had any personal or financial conflicts of interest.
m) We declare no competing interests.
n) There were no conflicts of interest.
o) Conflict of interest: none declared
p) The authors have declared that no competing interests exist.
q) Competing interests: None declared.
r) SSM, JMG and AH and were supported by an unrestricted grant from the Dutch dairy industry (NZO).
s) The authors declare that they have no competing interests.
t) The authors declare no conflict of interest
u) The authors have no conflicts of interest to declare.

v) Disclosures: None.
w) Competing interests None.
x) AUTHOR DISCLOSURES None.
y) All authors have nothing to declare in relation to the subject of this paper.
z) Conflicts of interest: none.
aa) The authors have no conflicts of interest to report.
bb) Author disclosures: E. Patterson, S. C. Larsson, A. Wolk, and A. A kesson, no conflicts of interest.
cc) J.M.G and S.S.S.M received an unrestricted grant from the Dutch Dairy Organization (NZO) for epidemiological analyses on dairy intake and cardiovascular diseases.
dd) S. S. S. M. received an unrestricted research grant from the Global Dairy Platform, Dairy Research Institute and Dairy Australia for a meta-analysis project on the effect of cheese on lipids.
ee) Gerrit J. Hiddink - Dutch Dairy Association (NZO), Zoetermeer, The Netherlands.
ff) S. S. S.-M., L. V. and J. M. G. obtained an unrestricted grant from the Dutch Dairy Association (NZO) to carry out meta-analyses on the association between dairy products.
gg) None of the authors had any conflicts of interest.
hh) Conflicts of interest: none.
ii) Conflict of Interests: None.
jj) Disclosures: None.
kk) Disclosures: None.

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Supplementary File 5. Risk of bias in included studies

			Funding Source, n (%[a])					
			Sponsorship		COI		Industry Ties	
Characteristic	Category	Total N = 43	Industry N= 8	Non-Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non-Industry/ No COI N = 29
Risk of Bias Assessment								
	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)

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

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**

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-Indutry	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

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)

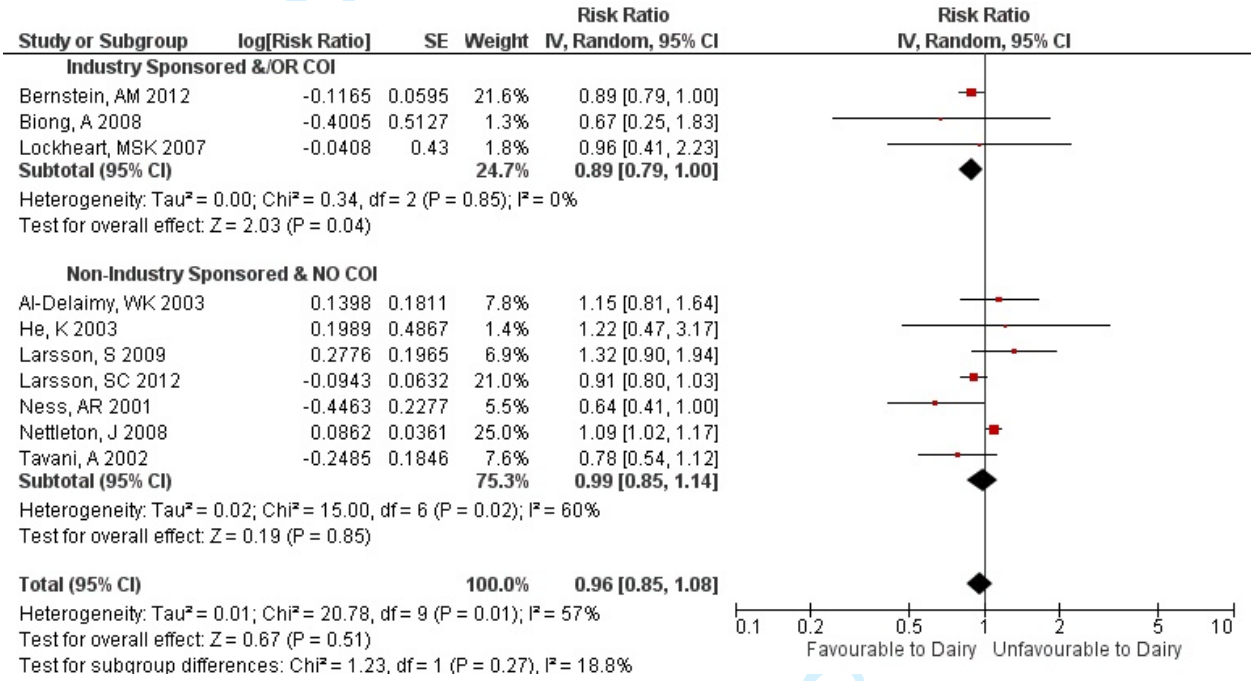
Conflicts of Interest

	COI	No/COI
Favourable	2	4
Unfavourable	8	29

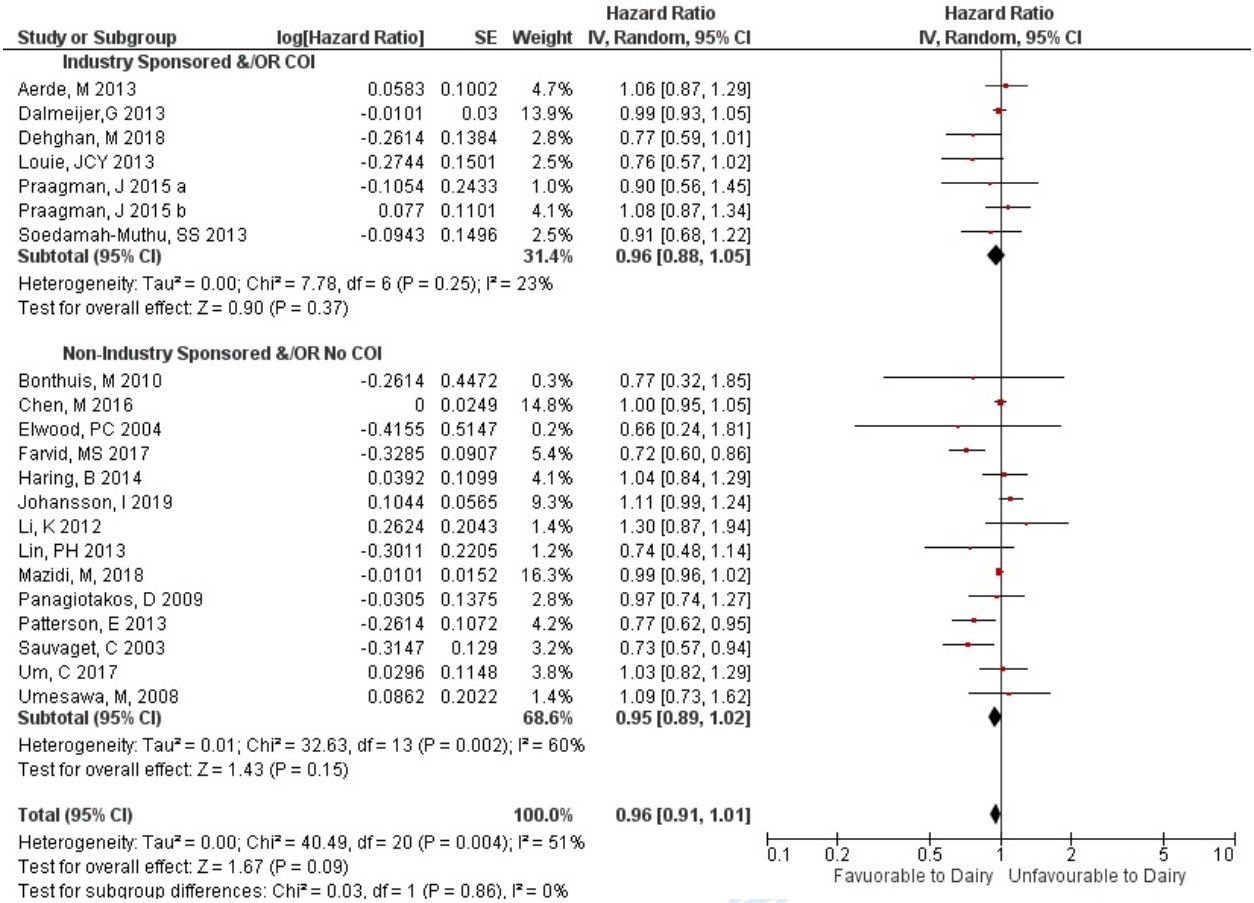
RR = 1.65 (95% CI 0.35, 7.72)

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

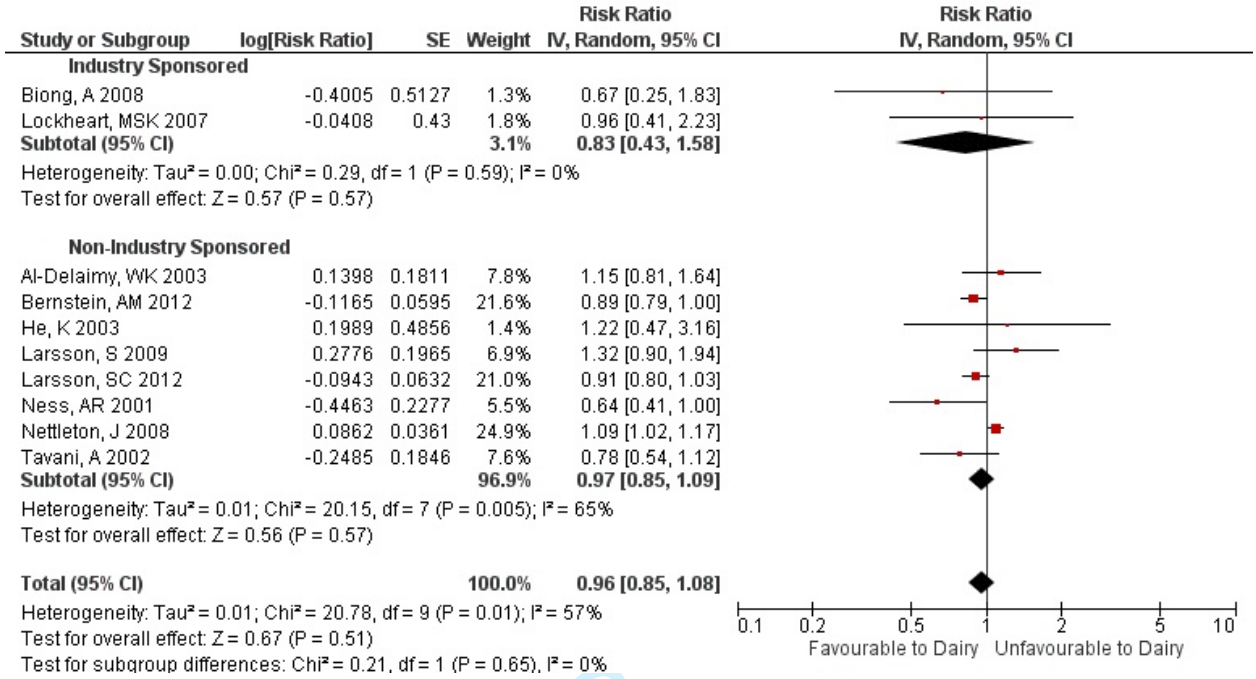
Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Risk Ratio



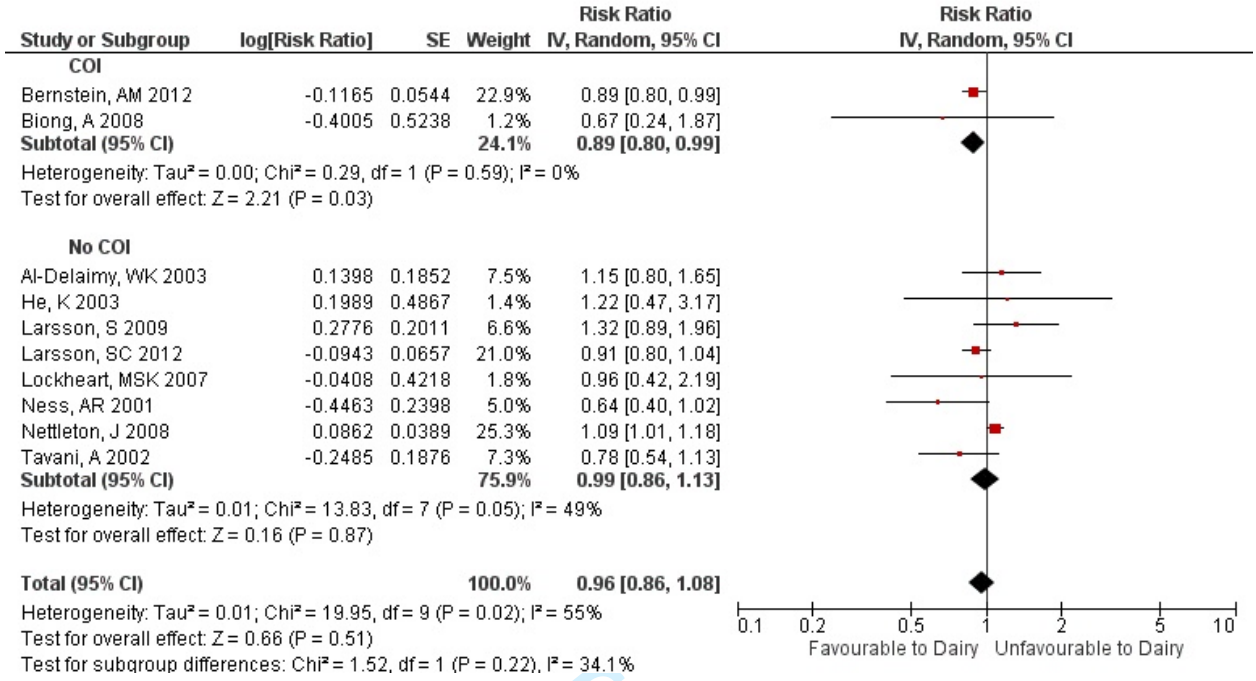
Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Hazard Ratio



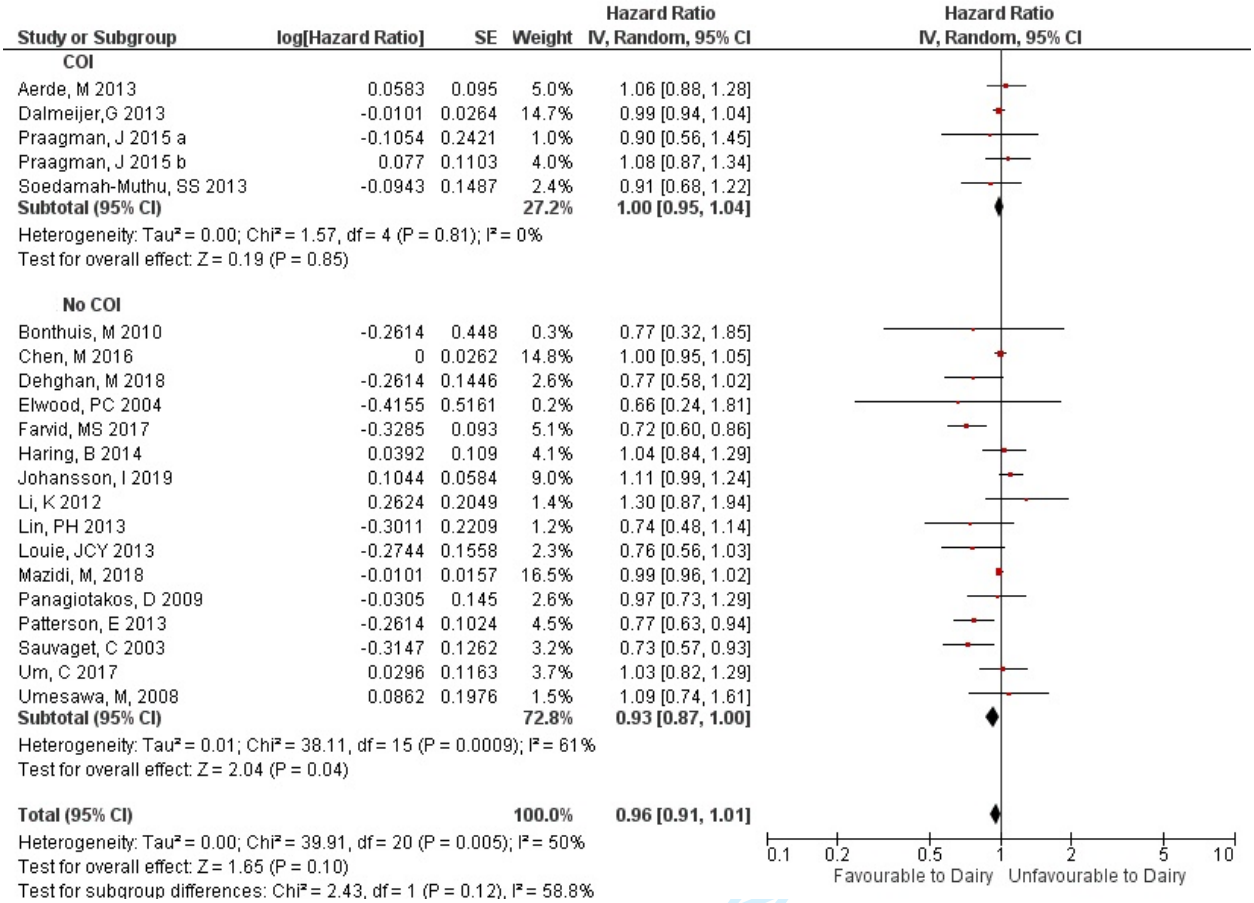
Effect Size, Cardiovascular Disease: Industry sponsorship vs no industry sponsorship, Risk Ratio



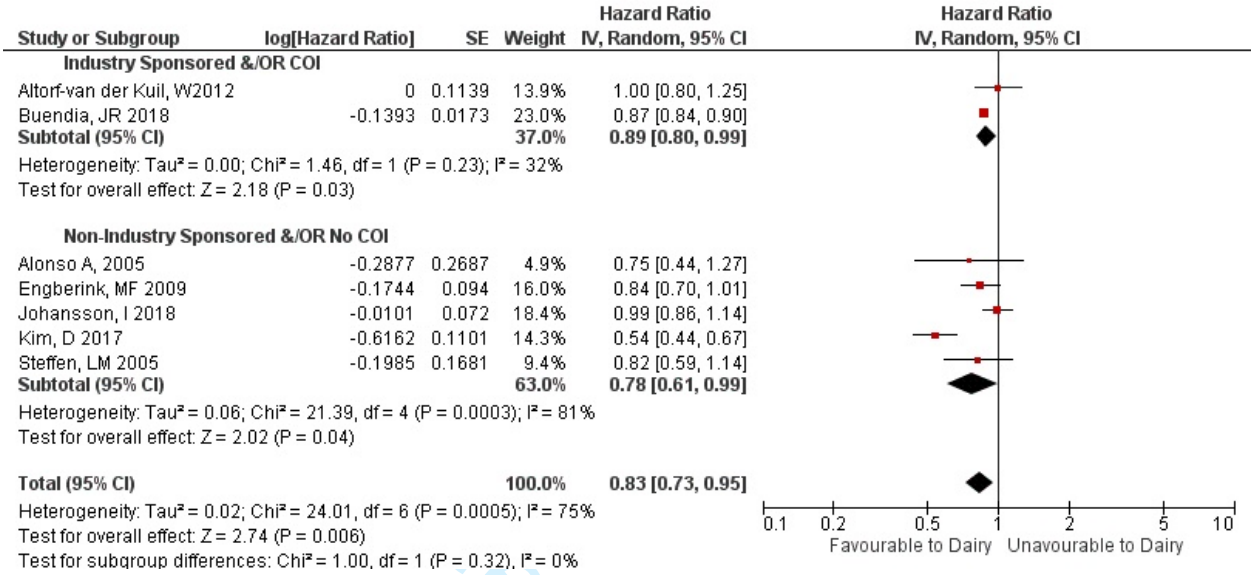
Effect Size, Cardiovascular Disease: COI vs No COI, Risk Ratio



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 #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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

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
RESULTS			
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
DISCUSSION			
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

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
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

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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:	*BMJ Open*
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
Primary Subject Heading:	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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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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Word Count: 5006

Abstract

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

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

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

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

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

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

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

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

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

Registration: Prospero ID CRD42019129659

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

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to evaluate the association of food industry ties (industry sponsorship and / or author conflicts of interest (COI)) with the results, conclusions and risk of bias of primary nutrition studies examining the association of dairy foods with cardiovascular disease outcomes and mortality.
- We conducted a comprehensive search and followed explicit and well-defined inclusion and exclusion criteria for the included studies.
- For studies missing a funding or author COI disclosure, we did not contact the authors; thus we may be underestimating the number of studies with industry ties.
- The tool that we used to assess the risk of bias is still under modification, however it is unlikely any future changes to the tool will affect the risk of bias ratings.
- We did not analyse studies of low and full fat dairy separately. Industry ties may have different effects on studies of low or full fat dairy foods.

INTRODUCTION

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

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

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

The primary objective of this systematic review and meta-analysis is to determine whether:

- Studies of observational design examining the associations of dairy foods with CVD with food industry ties (industry sponsorship and / or authors with a COI) are more likely to have results and / or conclusions that are favourable to industry than those with no industry ties.

The secondary objectives of this review are to determine whether observational studies with food industry ties compared with no industry ties:

I. differ in their risk of bias;
II. have a higher level of discordance between study results and conclusions, with the conclusions more likely to be favourable compared to the results.

METHODS

We conducted a systematic review of observational studies examining the effect of dairy consumption on CVD. Our study is registered with Prospero ID CRD42019129659 (see Supplementary file 1).[19]

Search Strategy

The search included terms to locate observational studies and randomised control trials, the latter of which are for a separate systematic review. The search used was based on the Process Manual used to develop the 2013 Australian Dietary Guidelines and the guidance of an information specialist.[20] The search dates used were to ensure that we identified the studies used to inform the recommendations in these guidelines. We therefore searched the following databases from January 2000-February 2019: MEDLINE; CINAHL; PubMed; PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy used for Ovid MEDLINE on February 1, 2019 is shown in Supplementary file 2. We adapted this strategy for the other databases. We hand searched references lists of the identified studies and reviews.

Eligibility Criteria

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

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

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

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

Types of Outcome Measures

Primary Outcomes

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

1. Statistical significance of results favourable to dairy

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

2. Effect size of results

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

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'.

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,[21] the ROBINS-E[22]. 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.

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.

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

Selection of results for meta-analysis

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

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

Data Collection

From each study we extracted:

- Year of publication
- Study design (cohort or case control)
- Sample size of study
- Age of participants (combined or if reported, separately)
- Exposure duration or observation period

- How the study defined dairy (verbatim)
- Disclosure of funding source (no disclosure, yes and there is a sponsor, the authors state they received no funding for their work)
- Name of the funders of the study (verbatim)
- Role of the funders (role of the sponsor not mentioned, sponsor not involved in study design and analyses, sponsor involved, N/A)
- Disclosure of author COI (no disclosure, yes (if at least 1 author had a COI), the authors state they had no conflicts of interest to declare)
- Authors COI statement (verbatim)
- Outcomes assessed in the study (any CVD death and/or event or blood pressure/hypertension)
- The numerical results of the study (e.g., OR, HR, RR)

All extracted data from the included studies was stored in REDcap, a secure web-based application for the collection and management of data.[23] Five investigators (NC, SMc, AF, AL & JD) working independently in pairs extracted data from the included studies. Discrepancies in data extraction were resolved by consensus. If agreement could not be reached, a sixth investigator (LB) resolved the discrepancy.

Classification of industry sponsorship and author conflicts of interest

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

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

Since the number of studies with industry sponsorship or author COI was small, we also categorized studies as having "industry ties" for analysis. Studies classified as having an industry tie were industry sponsored and / or had an author COI. Otherwise, they were classified as having no industry ties.

Analysis

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

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

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

We undertook a fixed-effects test for subgroup differences (defined by industry sponsorship / authors conflict of interest) using the Chi2 test and calculated the ratio of RRs (ORs) or HRs along with 95% confidence intervals. Analyses were undertaken in Review Manager 5.3.[25]

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

Patient and Public Involvement

No patient involved

RESULTS

As shown in Figure 1, there were 1, 858 studies screened for inclusion and 43 studies were included (3 case controls, 40 cohorts). See Supplementary file 4 for 'List of excluded studies and reasons for exclusion'.

Characteristics of included Studies

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

As shown in Table 1, most characteristics were similarly distributed across studies with industry ties or no industry ties. Studies with industry ties (64%) were more likely to have sample sizes <5000 than non-industry sponsored studies (34%). A greater proportion of industry sponsored studies (100%) than non-industry sponsored studies (83%) focused on total dairy intake rather than a specific food. Details of the individual studies are in Supplementary file 5.

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

			Funding Source, n (%[a])					
			Sponsorship		COI		Industry Ties	
Characteristic	Category	Total N = 43	Industry N= 8	Non-Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non-Industry/ No COI N = 29
Sex	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)
Sample Size	<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)
Length of Follow up	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)
Type of Dairy	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)

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

* Follow up is not applicable for case control studies

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

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

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

Risk of bias in included studies

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

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

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

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

Effect Size, Cardiovascular Disease: Industry ties v no industry ties; industry sponsorship vs no industry sponsorship; COI v no COI

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

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

In our analysis comparing studies with industry sponsorship, (RR 0.83; n=2 studies) and those with no industry sponsorship, (RR 0.97; n=8 studies) we again did not find an important difference in the magnitude of RRs (ratio of RRs 0.86 (95% CI 0.44, 1.66)); P=0.65 (Supplementary file 8). However, when we compared industry sponsored studies, (HR =0.78; n=3 studies) and non-industry sponsored studies, (HR=0.97; n=18 studies) that measured the association using HRs, we found a statistically significant difference in the magnitude of the HRs (ratio of HRs 0.80 (95%CI 0.66, 0.97)); P=0.03 (Figure 3).

In our analysis comparing studies with an author with a COI (RR 0.89; n=2 studies) and those with no COI, (RR 0.99; n= 8 studies) we found no important difference in the magnitude of RRs (ratio of RRs 0.90 (95% CI 0.76-1.07)); P=0.22 (Supplementary file 8). When we compared studies with a COI, (HR =1.00; n= 5 studies) and studies with no COI, (HR=0.93; n=16 studies) that measured the association using HRs, we again found no difference in the magnitude of the HRs (ratio of HRs 1.08 (95% CI 0.99, 1.17)); P=0.12.

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

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

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

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

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

Risk of Bias Assessment by Industry Ties

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

Concordance between study results and conclusions

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

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

DISCUSSION

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

studies, [12] the funders in the studies included in this review were extremely diverse, with Big Food and trade association jointly sponsoring several studies. Thus, dairy foods are not their sole interest.

The meta-analysis of hazard ratios of CVD outcomes found that studies with industry sponsorship showed a greater benefit from dairy than studies without industry sponsorship, and this difference was statistically significant. The meta-analysis of risk ratios of CVD outcomes found a similar estimate; however, this was not statistically significant. The likely reason for this was that the meta-analysis of RRs had fewer studies, and so the ratio of RRs could not be as precisely estimated. We found no evidence of a clinically important difference in the magnitude of effect between studies with industry ties or authors with a COI compared to those with no industry ties or no COI for other outcomes.

For every study, the overall risk of bias was classified as high (meaning either serious or critical). Therefore, differences in the risk of bias across studies with and without industry ties would not seem to provide an explanation for our findings. However, the version of the ROBINS-E tool that we used may not have been able to adequately discriminate across the studies, as perhaps is indicated by the uniformity in risk of bias classification.[26] Therefore, we cannot rule out the possibility that differences in bias across studies with and without industry ties may partly explain our findings.

Strengths and limitations of this review

Our review was prospectively registered in Prospero.[19] We followed explicit inclusion and exclusion criteria, conducted a comprehensive search across multiple databases and hand searched reference lists for the included studies.

For those studies missing a funding or author COI disclosure, we did not contact the authors and we therefore may be underestimating the number of studies with industry ties. The tool that we used to assess the risk of bias is still under development, however it is unlikely any future changes to the tool will affect the risk of bias ratings.[22] We did not analyse studies of low and full fat dairy or other types of dairy products separately. Industry ties may have different effects on studies of low or full fat dairy foods or other foods and drinks.

Agreements and disagreements with other studies or reviews

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

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

Implications for clinicians, policy makers and future research

As dietary guidelines depend on an evidence base that should be as free as possible of bias, the difference in the magnitude of effects between industry sponsored studies compared to non-industry sponsored studies is concerning. Therefore, the dairy intake recommendations made in dietary guidelines should account for the potential influence of industry sponsorship on evidence of health effects. Nutrition studies included in systematic reviews used in the development of dietary guidelines should be assessed using empirical methods to identify 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

domain. The University of California, San Francisco's Navigation Guide assesses both author conflicts of interest and funding sources as a risk of bias in human and animal studies. [29] As the study designs used in nutrition are the same as those used to evaluate the harms of an exposure in environmental health, dietary guideline committees could consider adopting this tool to evaluate the risk of bias of the studies included in the systematic reviews used to develop dietary guidelines.

Industry sponsors may bias research via different mechanisms, including the design and conduct of a study, the selective reporting of results, how they code events, analyse data, by spinning conclusions,[11] as well as framing how the questions are asked.[30–32] It has been suggested that the dairy industry may preferentially fund research on topics which will provide them with more favourable outcomes.[33] The influence of the food industry on the research agenda has been demonstrated in an examination of research topics covered by samples of randomised controlled trials included in systematic reviews of nutrition studies and obesity.[34] It was shown that most food industry studies focused on the manipulations of specific nutrients, and not on dietary behaviours, therefore limiting the public health relevance of rigorous evidence available for use in both systematic reviews and dietary guidelines.[34] The topics examined in cohort studies on the relationship of nutrition and obesity, which tend to focus on more complex exposures than trials, did not demonstrate a similar influence of funding source. However, the disclosure of food industry sponsorship was low, making a comparison difficult.[35]

This present study has also demonstrated that there is significant funding for nutrition research that comes from non-industry sources, including academia and government. In this study, only eight studies had food industry sponsorship, while 34 had a non-food industry sponsorship. A similar rate was seen in a study that assessed the association of industry ties with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality, with only five industry sponsored studies and 17 non-industry sponsored studies.[16] To eliminate this risk of bias from nutrition research, investigators should use only non-industry sources to fund their research.

Conclusion

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

Acknowledgements: We thank Agnes Lau, University of California, San Francisco, for her assistance with data collection.

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

Funding: This work was supported by Australian Health and Medical Research Council Project Grant APP 1139997. Nicholas Chartres is a recipient of the James Millner PhD Scholarship in Pharmacy from the University of Sydney.

Competing interests: None declared.

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

Patient consent for publication: Not required.

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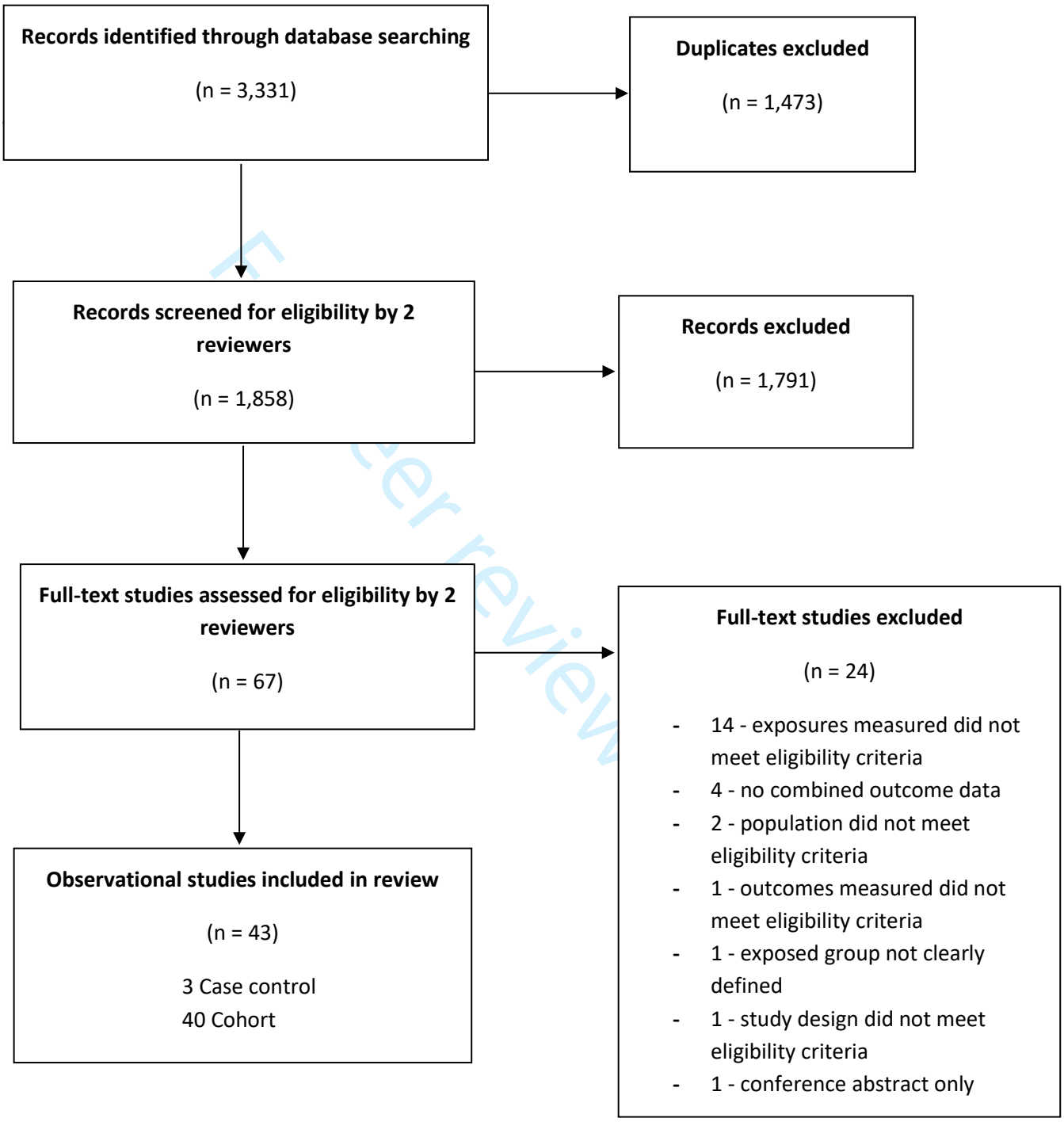
Figures

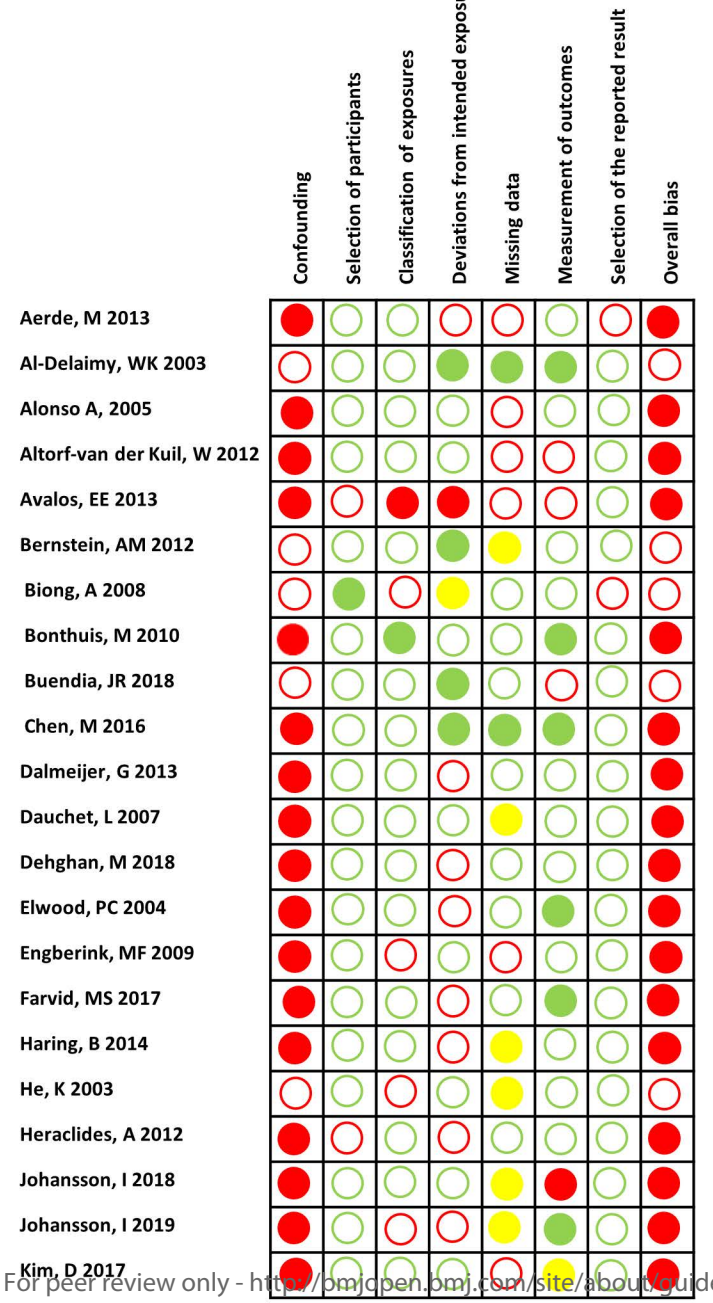
Figure 1. Study Flow Diagram

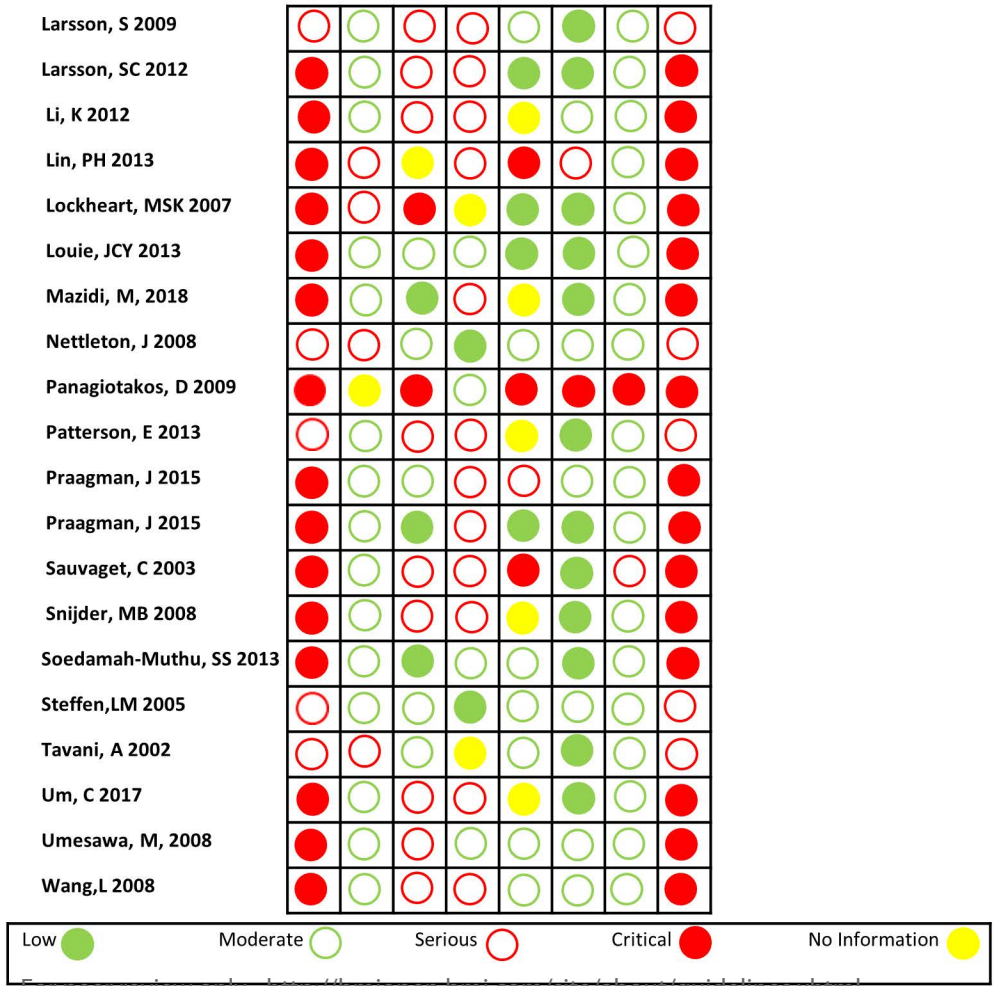
Figure 2. Risk of Bias in Included Studies

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

Figure 1. Study Flow Diagram



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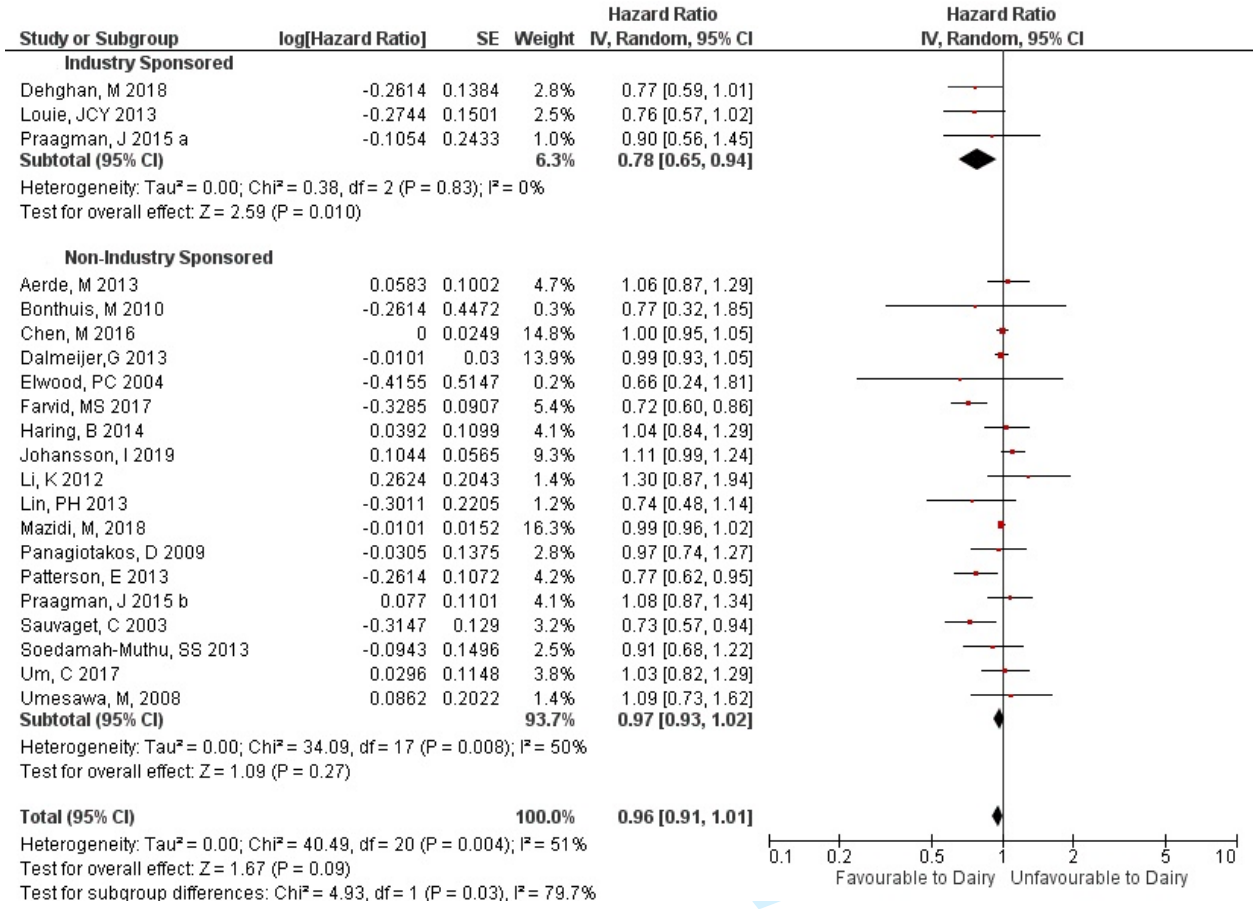
Critical
No Information

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



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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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NHS National Institute for Health Research

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.

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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

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

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

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 outcome measures (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

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 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.

c. Secondary Outcome 1 (Risk of Bias tool for studies)

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

‘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

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

No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
Yes

Care of the elderly
No

Child health
No

Complementary therapies

No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
Yes

Rehabilitation
No

Respiratory disorders
No

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.

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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 newregistrations 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.

25. dairy consumption.mp.

26. dairy food*.mp.

27. Dairy Products/ or dairy product*.mp.

28. dairy serv*.mp.

29. dairy type*.mp.

30. dairy source*.mp.

31. (calcium adj15 food sourc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

32. (vitamin D adj15 food sourc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

33. (milk and (cow or goat or sheep)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

34. yogurt.mp. or Yogurt/

35. cheese.mp. or Cheese/

36. custard.mp.

37. (milk and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

38. (yogurt and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

39. Milk/

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 39

41. cardiovascular disease.mp. or exp Cardiovascular Diseases/

42. coronary*.tw.

43. heart*.tw.

44. cardia*.tw.

45. cardio*.tw.

46. myocard*.tw.

47. isch?em*.tw.

48. angina*.tw.

49. ventric*.tw.

50. tachycardi*.tw.

51. pericard*.tw.

52. endocardi*.tw.

53. atrial fibrillat*.tw.

54. arrhythmi*.tw.

55. athero*.tw.

56. arterio*.tw.

57. exp Atherosclerosis/

58. exp Arteriosclerosis/

59. HDL.tw.

60. LDL.tw.

61. VLDL.tw.

62. lipid*.tw.

63. lipoprotein*.tw.

64. triacylglycerol*.tw.

65. exp Hyperlipidemias/

66. hyperlipid*.tw.

67. hypercholesterol*.tw.

68. hypercholester?emia*.tw.

69. hypertriglycerid?emia*.tw.

70. exp Cholesterol/

71. cholesterol*.tw.

72. exp Stroke/

73. stroke*.tw.

74. CVA.tw.

75. cerebrovasc*.tw.

76. "vascular accident".tw.

77. TIA.tw.

78. cerebral vascular.tw.

79. thrombo*.tw.

80. emboli*.tw.

81. apoplexy.tw.

82. (brain adj2 accident*).tw.

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

84. Hypertension/

85. exp Blood Pressure/

86. hypertensi*.tw.

87. blood pressure*.tw.

88. systolic blood pressure.tw.

89. diastolic blood pressure.tw.

90. peripheral arter* disease*.tw.

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

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

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

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

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

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

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 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 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96

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 19 or 20 or 21 or 22

99. 40 and 97 and 98

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

101. limit 100 to humans

102. limit 101 to "all adult (19 plus years)"

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 Smoking Alcohol intake History of co-morbidities Parenteral/Fhx MI < 60 yrs PA levels SES Total energy intake Fruit & Vegetable intake *Specialised Confounders* Hormone therapy
2. CVD events	Fibre supplement (p) Magnesium supplement (p)	
3. CHD mortality (incident CVD)	Fibre supplement (p) Trans Fat (h) Polyunsaturated fat (n-6) (p) Sodium (+Na) (h)	
4. CHD events (incident CHD)	Fibre supplement (p) Trans fat (h) Magnesium supplement (p) Polyunsaturated fat (n-6) (p)	
5. Total MI	Aspirin (p) Vitamin E supplement (p)	
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

Author	Title	Reason for Exclusion
Akbaraly, T 2013[1]	Does overall diet in midlife predict future aging phenotypes? A cohort study	Dietary patterns only were assessed, not dairy foods
Anderson, LA 2011[2]	Dietary Patterns and Survival of Older Adults	No relevant outcomes were measured
Baylin, A 2003[3]	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[4]	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[5]	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[6]	Prospective investigation of major dietary patterns and risk of cardiovascular mortality in Bangladesh	Dietary patterns only were assessed, not dairy foods
Ding, M 2017[7]	Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study	Not an observational design study
Eguchi, E 2012[8]	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[9]	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[10]	Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands	No combined outcome data
Julián-Almárcegui, C 2016[11]	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[12]	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[13]	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[14]	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[15]	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[16]	Arginine intake and risk of coronary heart disease mortality in elderly men	Effects of dairy foods not measured
Paillard, F 2015[17]	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[18]	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[19]	Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study	Dietary patterns only were assessed, not dairy foods
Umesawa, M 2006[20]	Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study	No combined outcome data
van der Pols, J C 2009[21]	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[22]	Stroke and plasma markers of milk fat intake – a prospective nested case-control study	Effects of dairy foods not measured
Warensjo, E 2009[23]	Milk Fat Biomarkers and the Risk of a First Ever Acute Myocardial Infarction - A Prospective Nested Case-Control Study. Journal of the American Dietetic Association. 2009;1	Poster presentation only, full study not available
Warensjo, E 2010[24]	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 5: 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[(1)]	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[1]	Yes[a]
Al-Delaimy, WK 2003[(2)]	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[2]	No[b]
Alonso A, 2005[(3)]	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[3]	No[c]

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
Altorf-van der Kuil, W2012[4]	Cohort	Mean follow up 7·5 years	3,588 men & women	44 years	Dairy Protein T3, ≥ 27 g/day (dairy protein was calculated as protein from milk, yogurt, coffee creamer, curd, pudding, porridge, custard, whipped cream and cheese)	T1, ≤ 19 g/day	Hypertension	Industry[4]	Yes[d]
Avalos, EE 2013[5]	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[5]	No[e]
Bernstein, AM 2012[6]	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[6]	Yes[f]
Biong, A 2008[7]	Case Control		218 men & women	62.4 years	Dairy Fat, > 34.1 g/day	<14.6 g/day	First Myocardial Infarction	Industry[7]	Yes[g]

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[8]	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[8]	No[h]
Buendia, JR 2018[9]	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[9]	No[i]
Chen, M 2016[10]	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[10]	No[j]

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[(11)]	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[11]	Yes[k]
Dauchet, L 2007[(12)]	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[12]	No[l]

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[13]	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[13]	No[m]
Elwood, PC 2004[14]	Cohort	20-24 years	2,403 men	45-59 years	Milk Q4, >1 pint per day	Q1, None	Vascular Event	Non-Industry[14]	No disclosure

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
Engberink, MF 2009[15]	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[n]
Farvid, MS 2017[16]	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[15]	No[o]
Haring, B 2014[17]	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[16]	No[p]
He, K 2003[18]	Cohort	14 years	43,732 men	40-75 years	High Fat Dairy Q5, ≥1/day	Q1, <1/week	Ischaemic & Haemorrhagic Stroke	Non-Industry[17]	No[q]

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[19]	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 [18]	Yes[r]
Johansson, I 2018[20]	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[19]	No[S]
Johansson, I 2019[21]	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[20]	No[t]
Kim, D 2017[22]	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 [21]	No[u]
Larsson,S 2009[23]	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[22]	No disclosure

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
Larsson, SC 2012[24]	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[23]	No[v]
Li, K 2012[25]	Cohort	11 years	23,980 men & women	35-64 years	Dairy Calcium Q4, 780 mg/day	Q1, 188 mg/day	CVD Mortality	Non-Industry[24]	No[w]
Lin, PH 2013[26]	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[25]	No[x]
Lockheart, MSK 2007[27]	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 [26]	No disclosure
Louie, JCY 2013[28]	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[27]	No disclosure
Mazidi, M, 2018[29]	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[28]	No[y]

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[30]	Cohort	25 years	5,765 men	35-64 years	Milk T3, > 1 pint (= 0.568 liters)	T1, None	Cardiovascular Disease Deaths	Non-Industry[29]	No[z]
Nettleton, J 2008[31]	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[30]	No[aa]
Panagiotakos, D 2009[32]	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[31]	No disclosure
Patterson, E 2013[33]	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[32]	No[bb]
Praagman, J 2015 (a)[34]	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[33]	Yes[cc]

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
Praagman, J 2015 (b)[35]	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[34]	Yes[dd]
Sauvaget, C 2003[36]	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[35]	No disclosure
Snijder, MB 2008[37]	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 (≤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[36]	Yes[ee]
Soedamah-Muthu, SS 2013[38]	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 [37]	Yes[ff]
Steffen, LM 2005[39]	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[38]	No[gg]

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
Tavani, A 2002[40]	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[39]	No[hh]
Um, C 2017[41]	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-Indutry[40]	No[ii]
Umesawa, M, 2008[42]	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[41]	No[ij]

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[43]	Cohort	10 years	28,886 women	53.8 years	Total Diary 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[42]	No[kk]

* 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

Description of Funding Source (Verbatim)

1. The Hoorn Study has been made possible by the Vrije Universiteit Amsterdam and the VU University Medical Center, and by grants from the Dutch Diabetes Research Foundation, the Dutch Organization for Scientific Research, the Netherlands Heart Foundation, and the Health Research and Development Council of the Netherlands.
2. Supported by research grants HL24074, HL34594, DK36798, and CA87969 from the National Institutes of Health.
3. Supported by the Spanish Ministry of Health (grants PI040233 and G03-140), the Navarra Regional Government (PI41-2005), and the University of Navarra (línea especial Nutricio LE-97).AA was supported partially by a Fulbright fellowship and an MMA Foundation grant.
4. The Doetinchem Cohort Study was financially supported by the Ministry of Health, Welfare and Sport of the Netherlands and the National Institute for Public Health and the Environment. For the present analysis, Wageningen University was supported by the Top Institute Food and Nutrition, which is a public/private partnership that generates vision on scientific breakthroughs in food and nutrition, resulting in the development of innovative products and technologies. Partners are major Dutch Food companies and research organisations.
5. The study was supported by grants AG007181 and AG028507 from the National Institutes of Health/National Institute on Aging, and by grant DK31801 from the National Institute of Diabetes and Digestive and Kidney Diseases.
6. This study was supported by grant P01CA087969 from the National Institutes of Health, Department of Health and Human Services. A.M.B. was supported through the Harvard Human Nutrition Program.
7. The study was supported financially by the Research Council of Norway, Throne Holst's Foundation for Nutrition Research, The Norwegian Association of Margarine Producers, DeNoFa Fabrikker A/S and Tine BA. Tine BA is a dairy company.
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.
10. Supported by the NIH (grants R01 HL034594, UM1 CA176726, UM1 CA186107, R01 HL35464, R01 HL088521, R01 CA67262, HL60712, and UM1 CA167552).
11. This research was supported by a personal Dr. Dekker postdoctoral grant (2008T062) from The Netherlands Heart Foundation (JWJ Beulens).
12. The SU.VI.MAX study is supported by the Direction Générale de la Santé, the Ministère de la Santé, and the Institut Virtuel de Recherche en Santé Publique (groupe cohorte) INSERM.
13. The PURE Study is an investigator-initiated study that is funded by the Population Health Research Institute, the Canadian Institutes of Health Research (CIHR), Heart and Stroke Foundation of Ontario, support from CIHR's Strategy for Patient Oriented Research (SPOR) through the Ontario SPOR Support Unit, as well as the Ontario Ministry of Health and Long-Term Care and through unrestricted grants from several pharmaceutical companies, with major contributions from AstraZeneca (Canada), Sanofi-Aventis (France and Canada), Boehringer Ingelheim (Germany and Canada), Servier, and GlaxoSmithKline, and additional contributions from Novartis and King Pharma and from various

national or local organisations in participating countries. These include Brazil: Unilever Health Institute, Brazil; South Africa: The SA Sugar Association (SASA).

14. The Medical Research Council, the University of Wales College of Medicine and Bristol University, Food Standards Agency.
15. This work was supported by Tehran University of Medical Sciences (grant 82-603); Cancer Research UK (grant C20/A5860); the Intramural Research Program of the National Cancer Institute, US National Institutes of Health (grant Z01 CP000185-03); and various collaborative research agreements with the International Agency for Research on Cancer. M.F. was supported by a Takemi Fellowship from the Japan Pharmaceutical Manufacturers Association.
16. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).
17. This work was supported by the research grant HL35464 and CA55075 from the National Institutes of Health.
18. The study was funded by the Medical Research Council, and some aspects of the analysis were funded by The European Commission, Quality of Life and Management of Living Resources Programme, contract number QLG1-CT-2000–01643.
19. The present study was supported by the Swedish Research Council for Health, Working Life and Welfare (FORTE).
20. This research was funded by The Swedish Research Council for Health, Working Life and Welfare (FORTE), grant number 2016-00960. The Northern Sweden Diet Database has been supported by the Swedish Research Council for Health, Working Life and Welfare (FORTES) and The Swedish Research Council.
21. This research was supported by the Basic Science Research Program of the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology (NRF2016R1D1A1B03931307).
22. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was supported by Public Health Service contracts N01-CN-45165, N01-RC-45035 and N01-RC-37004 from the US National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Md. Dr. Larsson's research at the National Public Health Institute in Helsinki, Finland, was supported by a grant from the Swedish Council for Working Life and Social Research.
23. This study was supported by a research grant from the Swedish Council for Working Life and Social Research (FAS), the Swedish Research Council, and by a Research Fellow grant from Karolinska Institutet (to Dr Larsson).
24. This work was supported by supported by the Deutsche Krebshilfe (grant-No70-488-Ha I) and the Graduiertenkolleg 793: Epidemiology of communicable and chronic non-communicable disease and their inter-relationships.
25. Data collection was supported by the Department of Health in Taiwan.
26. The present study was supported by NIH NRSA T32HL007779, CVD Epidemiology and Prevention, American Heart Association – Greater Midwest Affiliate, Throne Holst's Foundation for Nutrition Research, The Norwegian Association of Margarine Producers, DeNoFa Fabriker A/S and Tine Norwegian Dairies.
27. This study was funded by Dairy Australia.

28. This manuscript was written independently; no company or institution supported it financially.
29. Funding: this study was provided with funding by a grant from the NHS Management Executive Cardiovascular Disease and Stroke Research and Development Initiative.
30. This research was supported by the National Institutes of Health grant HL73366, training grant T32 HL07779, and contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022 from the National Heart, Lung, and Blood Institute.
31. The ATTICA study was supported by research grants from the Hellenic Cardiological Society (HCS2002).
32. Supported by research grants from the Swedish Council for Working Life and Social Research and from the Swedish Research Council/Infrastructure Medicine.
33. This study was supported by an unrestricted grant from the Dutch Dairy Organization (NZO) for epidemiological analyses on dairy intake and cardiovascular diseases.
34. The present study was supported by a personal Dr Dekker postdoctoral grant (2008T062) from the Netherlands Heart Foundation (J. W. J. B.).
35. This publication is based on research performed at the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan. RERF is a private nonprofit foundation funded equally by the Japanese Ministry of Health, Labor and Welfare and the US Department of Energy through the National Academy of Sciences.
36. This particular study has been supported by a grant from the Dutch Dairy Association (NZO).
37. The Whitehall II study was supported by grants from the Medical Research Council (G0902037), the British Heart Foundation (RG/07/008/23674), the Stroke Association, the National Heart Lung and Blood Institute (5RO1 HL036310), the National Institute on Aging (5RO1AG13196) and the Agency for Health Care Policy Research (5RO1AG034454).
38. The CARDIA Study is supported by National Heart, Lung, and Blood Institute contracts N01-HC-48047, N01-HC-48048, N01-HC-48049, N01- HC-48050, and N01-HC-95095.
39. Funding: partly supported by the Italian Ministry of Health (Programmi Speciali).
40. The REGARDS research project is supported by a cooperative agreement U01 NS041588 from the National Institute of Neu- rological Disorders and Stroke, National Institutes of Health, Department of Health and Human Service. Additional support provided by the Franklin Foundation.
41. This study was supported by grants-in-aid for cancer research and by the Third Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan.
42. This work was supported by research grants CA-047988 and HL-080467 from the National Institutes of Health, Bethesda, Md.

Description of Author Disclosure Statement (Verbatim)

a) Sabita S. Soedamah-Muthu and Johanna M. Geleijnse obtained an unrestricted grant from the Dutch Dairy Association (NZO) to carry out meta-analyses on the association between dairy products and CVD.
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.
c) None of the authors had any conflicts of interest.
d) Altorf-van der Kuil W, Engberink MF, Geleijnse JM - Top Institute Food and Nutrition, PO Box 557, 6700 AN, Wageningen, The Netherlands.
e) The authors have no conflicts of interest.
f) D.M. received research grants for studying the effects of diet on cardiometabolic diseases from the National Institutes of Health; the Searle Scholar Award from the Searle Funds at The Chicago Community Trust; the Genes and Environment Initiative at the Harvard School of Public Health; and the Gates Foundation/World Health Organization Global Burden of Diseases, Injuries, and Risk Factors Study; and from GlaxoSmithKline, Sigma Tau, Pronova, and the National Institutes of Health for an investigator-initiated, not- for-profit clinical trial of fish oil and postsurgical complications. He also received ad hoc travel reimbursement and/or honoraria for research presentations from the Chicago Council, International Life Sciences Institute, Aramark, Unilever, SPRIM, Nutrition Impact, Norwegian Seafood Export Council, United Nations Food and Agricultural Organization, World Health Organization, US Food and Drug Administration, and several universities. He received ad hoc consulting fees from Foodminds and royalties from UpToDate for an online chapter on fish oil.
g) A. S. Biong is employed as a Ph.D. student in a research project funded jointly by TINE BA, a Norwegian dairy company, and the Norwegian Research Council.
h) The authors declare no conflict of interest.
i) There are no conflicts of interest.
j) None of the authors reported a conflict of interest related to the study.
k) SS-Mand MG obtained an unrestricted grant from the Dutch Dairy Association (NZO) to carry out meta-analyses on the association between dairy products and cardiovascular diseases.
l) None of the authors had any personal or financial conflicts of interest.
m) We declare no competing interests.
n) There were no conflicts of interest.
o) Conflict of interest: none declared
p) The authors have declared that no competing interests exist.
q) Competing interests: None declared.
r) SSM, JMG and AH and were supported by an unrestricted grant from the Dutch dairy industry (NZO).
s) The authors declare that they have no competing interests.
t) The authors declare no conflict of interest
u) The authors have no conflicts of interest to declare.

v) Disclosures: None.
w) Competing interests None.
x) AUTHOR DISCLOSURES None.
y) All authors have nothing to declare in relation to the subject of this paper.
z) Conflicts of interest: none.
aa) The authors have no conflicts of interest to report.
bb) Author disclosures: E. Patterson, S. C. Larsson, A. Wolk, and A. A kesson, no conflicts of interest.
cc) J.M.G and S.S.S.M received an unrestricted grant from the Dutch Dairy Organization (NZO) for epidemiological analyses on dairy intake and cardiovascular diseases.
dd) S. S. S. M. received an unrestricted research grant from the Global Dairy Platform, Dairy Research Institute and Dairy Australia for a meta-analysis project on the effect of cheese on lipids.
ee) Gerrit J. Hiddink - Dutch Dairy Association (NZO), Zoetermeer, The Netherlands.
ff) S. S. S.-M., L. V. and J. M. G. obtained an unrestricted grant from the Dutch Dairy Association (NZO) to carry out meta-analyses on the association between dairy products.
gg) None of the authors had any conflicts of interest.
hh) Conflicts of interest: none.
ii) Conflict of Interests: None.
jj) Disclosures: None.
kk) Disclosures: None.

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Supplementary File 6. Risk of bias in included studies

			Funding Source, n (%[a])					
			Sponsorship		COI		Industry Ties	
Characteristic	Category	Total N = 43	Industry N= 8	Non-Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non-Industry/ No COI N = 29
Risk of Bias Assessment								
	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)

[a] 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**
					Sauvaget, 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-Indutry	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

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)

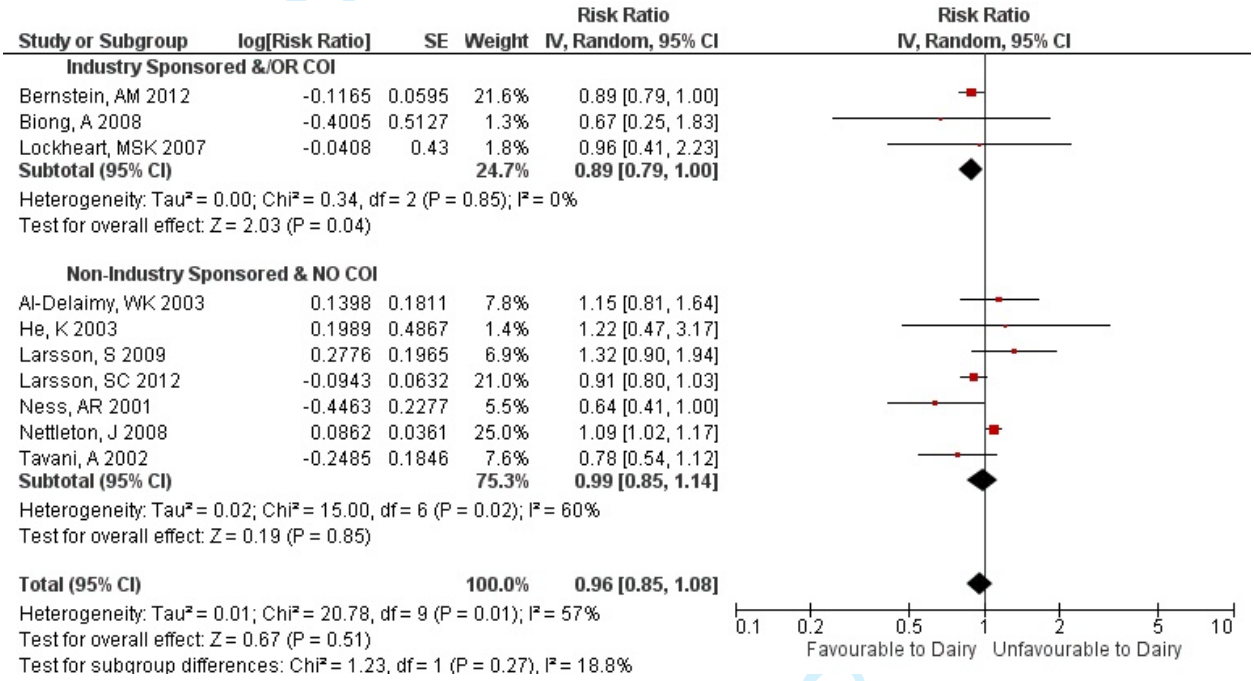
Conflicts of Interest

	COI	No/COI
Favourable	2	4
Unfavourable	8	29

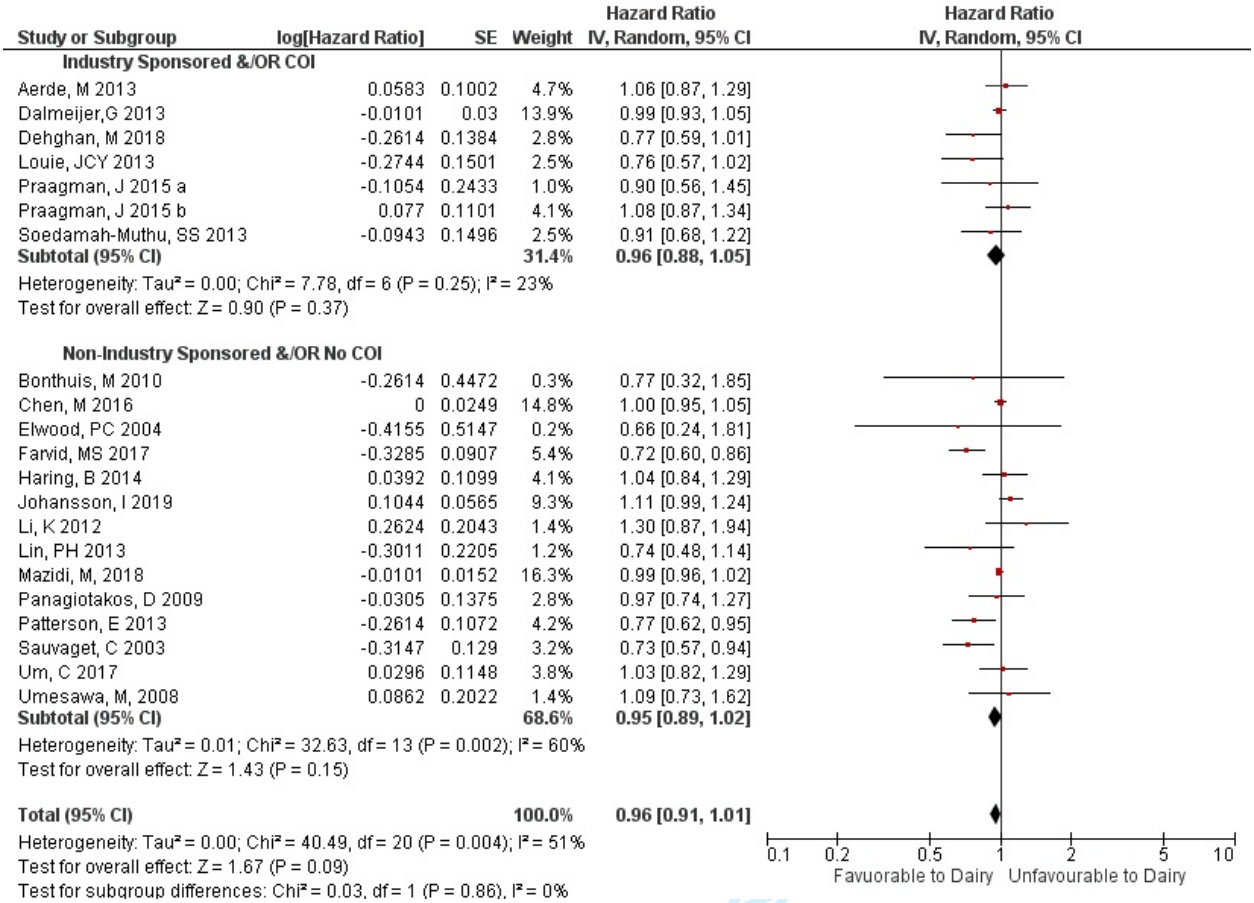
RR = 1.65 (95% CI 0.35, 7.72)

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

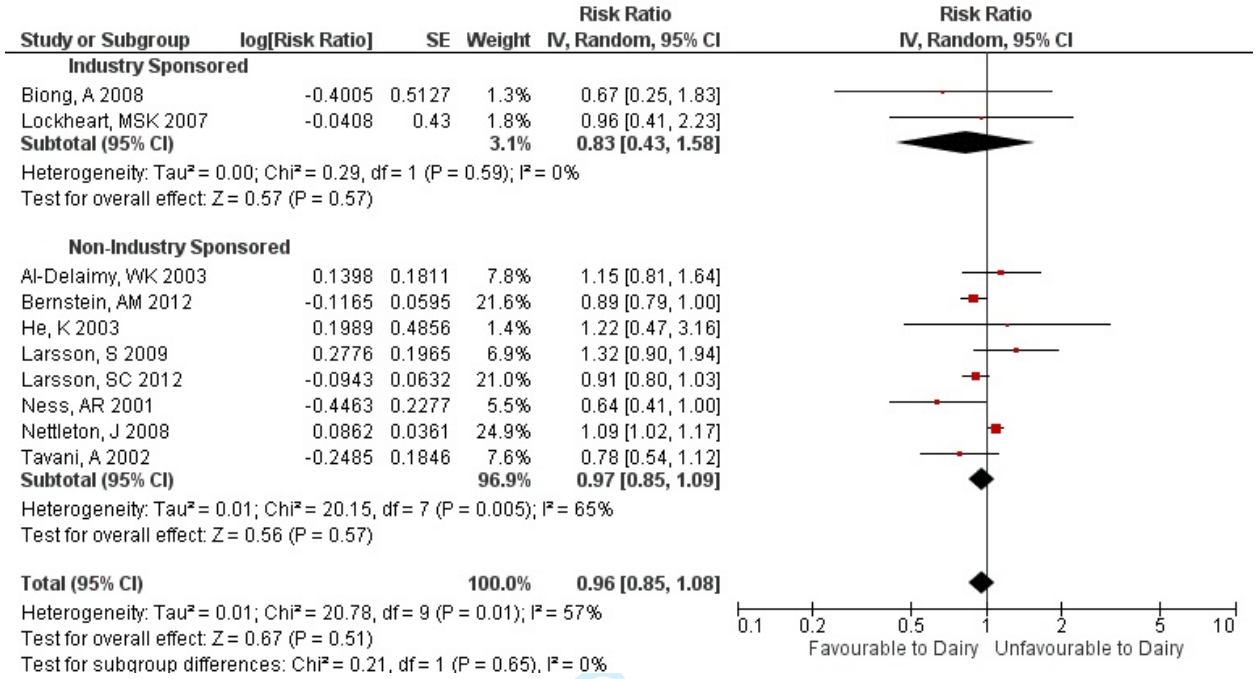
Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Risk Ratio



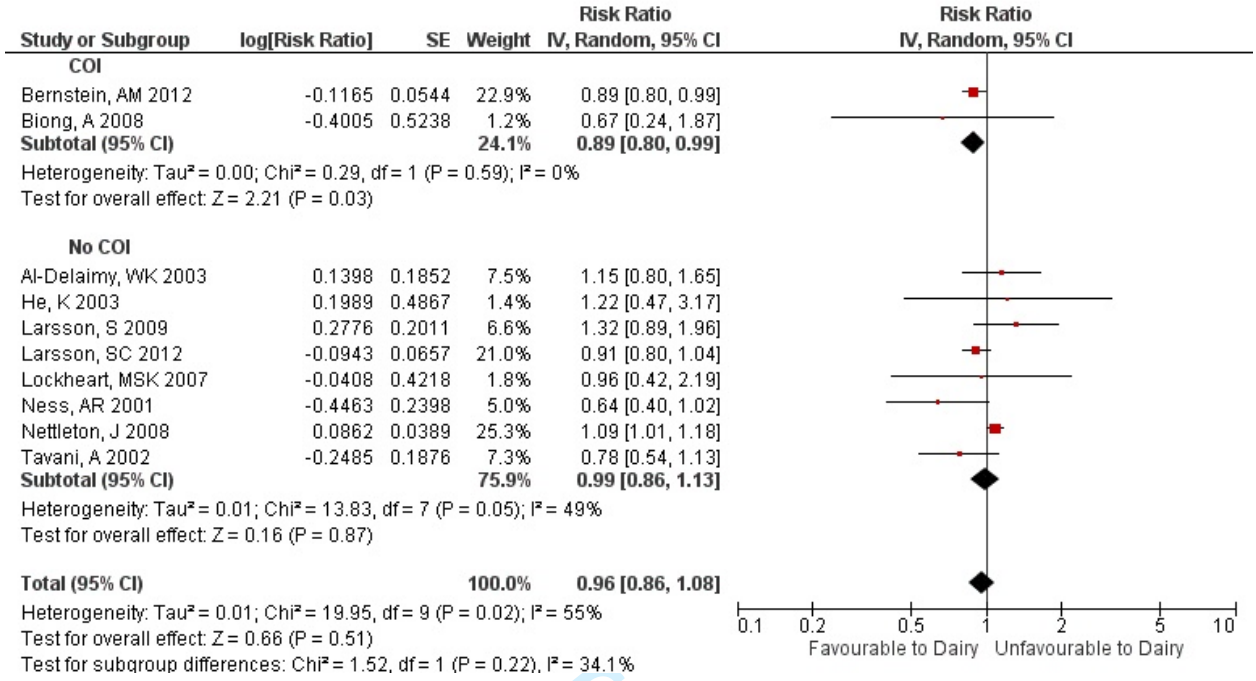
Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Hazard Ratio



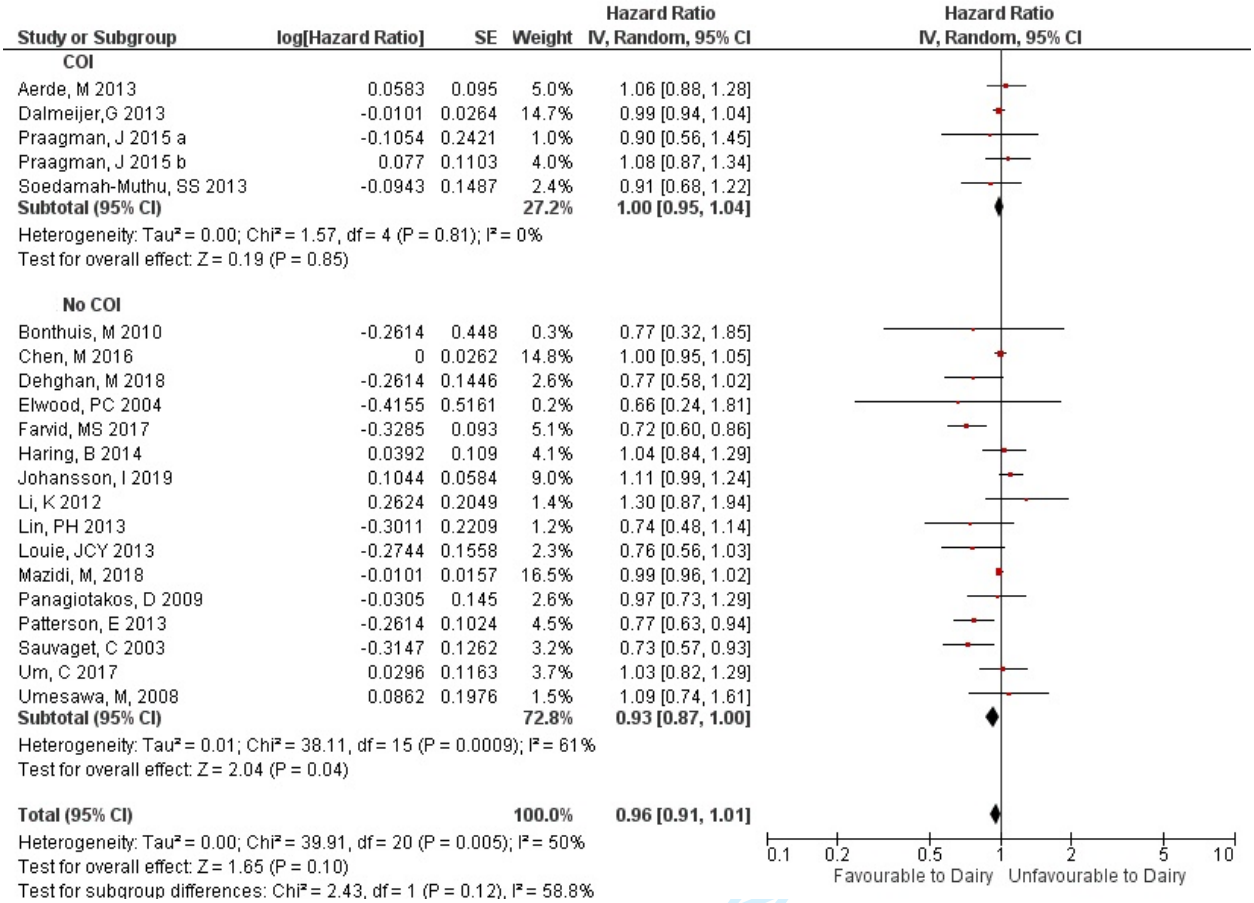
Effect Size, Cardiovascular Disease: Industry sponsorship vs no industry sponsorship, Risk Ratio



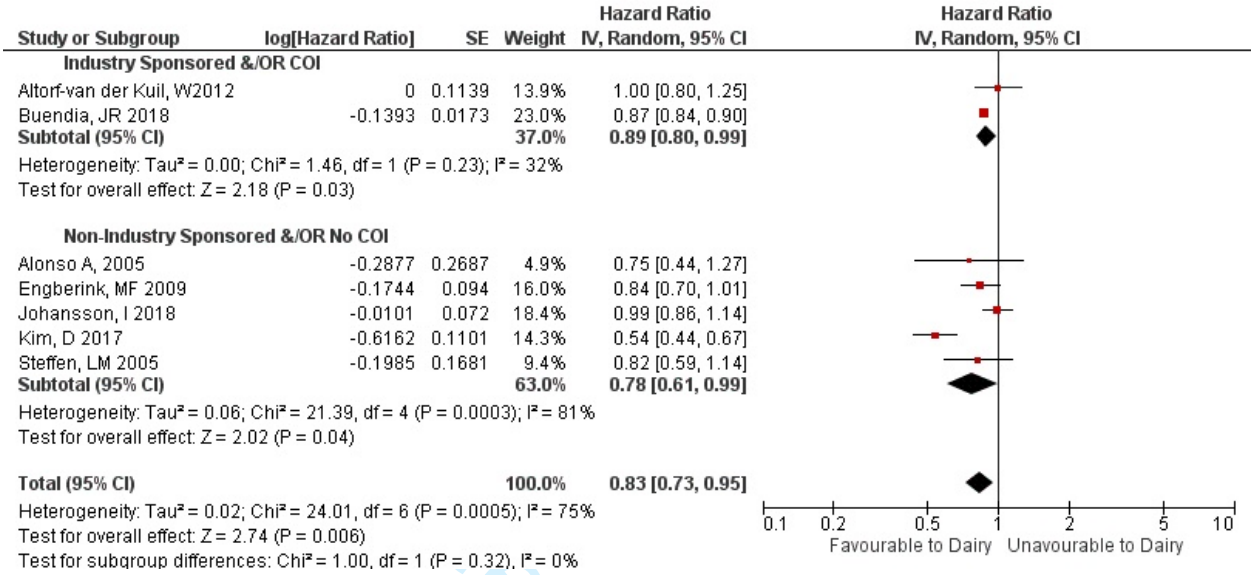
Effect Size, Cardiovascular Disease: COI vs No COI, Risk Ratio



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 #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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.	10 -11

PRISMA 2009 Checklist

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
RESULTS			
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
DISCUSSION			
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

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
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

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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:	*BMJ Open*
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
Primary Subject Heading:	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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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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Word Count: 5064

Abstract

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

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

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

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

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

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

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

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

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

Registration: Prospero ID CRD42019129659

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

Strengths and limitations of this study

- This is the first systematic review and meta-analysis to evaluate the association of food industry ties (industry sponsorship and / or author conflicts of interest (COI)) with the results, conclusions and risk of bias of primary nutrition studies examining the association of dairy foods with cardiovascular disease outcomes and mortality.
- We conducted a comprehensive search and followed explicit and well-defined inclusion and exclusion criteria for the included studies.
- For studies missing a funding or author COI disclosure, we did not contact the authors; thus we may be underestimating the number of studies with industry ties.
- The tool that we used to assess the risk of bias is still under modification, however it is unlikely any future changes to the tool will affect the risk of bias ratings.
- We did not analyse studies of low and full fat dairy separately. Industry ties may have different effects on studies of low or full fat dairy foods.

INTRODUCTION

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

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

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

The primary objective of this systematic review and meta-analysis is to determine whether:

- Studies of observational design examining the associations of dairy foods with CVD with food industry ties (industry sponsorship and / or authors with a COI) are more likely to have results and / or conclusions that are favourable to industry than those with no industry ties.

The secondary objectives of this review are to determine whether observational studies with food industry ties compared with no industry ties:

I. differ in their risk of bias;
II. have a higher level of discordance between study results and conclusions, with the conclusions more likely to be favourable compared to the results.

METHODS

We conducted a systematic review of observational studies examining the effect of dairy consumption on CVD. Our study is registered with Prospero ID CRD42019129659 (see Supplementary file 1).[19]

Search Strategy

The search included terms to locate observational studies and randomised control trials, the latter of which are for a separate systematic review. The search used was based on the Process Manual used to develop the 2013 Australian Dietary Guidelines and the guidance of an information specialist.[20] The search dates used were to ensure that we identified the studies used to inform the recommendations in these guidelines. We therefore searched the following databases from January 2000-February 2019: MEDLINE; CINAHL; PubMed; PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy used for Ovid MEDLINE on February 1, 2019 is shown in Supplementary file 2. We adapted this strategy for the other databases. We hand searched references lists of the identified studies and reviews.

Eligibility Criteria

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

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

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

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

Types of Outcome Measures

Primary Outcomes

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

1. Statistical significance of results favourable to dairy

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

2. Effect size of results

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

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'.

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,[21] the ROBINS-E[22]. 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.

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.

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

Selection of results for meta-analysis

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

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

Data Collection

From each study we extracted:

- Year of publication
- Study design (cohort or case control)
- Sample size of study
- Age of participants (combined or if reported, separately)
- Exposure duration or observation period

- How the study defined dairy (verbatim)
- Disclosure of funding source (no disclosure, yes and there is a sponsor, the authors state they received no funding for their work)
- Name of the funders of the study (verbatim)
- Role of the funders (role of the sponsor not mentioned, sponsor not involved in study design and analyses, sponsor involved, N/A)
- Disclosure of author COI (no disclosure, yes (if at least 1 author had a COI), the authors state they had no conflicts of interest to declare)
- Authors COI statement (verbatim)
- Outcomes assessed in the study (any CVD death and/or event or blood pressure/hypertension)
- The numerical results of the study (e.g., OR, HR, RR)

All extracted data from the included studies was stored in REDcap, a secure web-based application for the collection and management of data.[23] Five investigators (NC, SMc, AF, AL & JD) working independently in pairs extracted data from the included studies. Discrepancies in data extraction were resolved by consensus. If agreement could not be reached, a sixth investigator (LB) resolved the discrepancy.

Classification of industry sponsorship and author conflicts of interest

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

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

Since the number of studies with industry sponsorship or author COI was small, we also categorized studies as having "industry ties" for analysis. Studies classified as having an industry tie were industry sponsored and / or had an author COI. Otherwise, they were classified as having no industry ties.

Analysis

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

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

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

We undertook a fixed-effects test for subgroup differences (defined by industry sponsorship / authors conflict of interest) using the Chi2 test and calculated the ratio of RRs (ORs) or HRs along with 95% confidence intervals. Analyses were undertaken in Review Manager 5.3.[25]

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

Patient and Public Involvement

No patient involved

RESULTS

As shown in Figure 1, there were 1, 858 studies screened for inclusion and 43 studies were included (3 case controls, 40 cohorts). See Supplementary file 4 for 'List of excluded studies and reasons for exclusion'.

Characteristics of included Studies

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

As shown in Table 1, most characteristics were similarly distributed across studies with industry ties or no industry ties. Studies with industry ties (64%) were more likely to have sample sizes <5000 than non-industry sponsored studies (34%). A greater proportion of industry sponsored studies (100%) than non-industry sponsored studies (83%) focused on total dairy intake rather than a specific food. Details of the individual studies are in Supplementary file 5.

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

			Funding Source, n (%[a])					
			Sponsorship		COI		Industry Ties	
Characteristic	Category	Total N = 43	Industry N= 8	Non-Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non-Industry/ No COI N = 29
Sex	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)
Sample Size	<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)
Length of Follow up	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)
Type of Dairy	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)

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

* Follow up is not applicable for case control studies

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

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

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

Risk of bias in included studies

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

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

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

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

Effect Size, Cardiovascular Disease: Industry ties v no industry ties; industry sponsorship vs no industry sponsorship; COI v no COI

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

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

In our analysis comparing studies with industry sponsorship, (RR 0.83; n=2 studies) and those with no industry sponsorship, (RR 0.97; n=8 studies) we again did not find an important difference in the magnitude of RRs (ratio of RRs 0.86 (95% CI 0.44, 1.66)); P=0.65 (Supplementary file 8). However, when we compared industry sponsored studies, (HR =0.78; n=3 studies) and non-industry sponsored studies, (HR=0.97; n=18 studies) that measured the association using HRs, we found a statistically significant difference in the magnitude of the HRs (ratio of HRs 0.80 (95%CI 0.66, 0.97)); P=0.03 (Figure 3).

In our analysis comparing studies with an author with a COI (RR 0.89; n=2 studies) and those with no COI, (RR 0.99; n= 8 studies) we found no important difference in the magnitude of RRs (ratio of RRs 0.90 (95% CI 0.76-1.07)); P=0.22 (Supplementary file 8). When we compared studies with a COI, (HR =1.00; n= 5 studies) and studies with no COI, (HR=0.93; n=16 studies) that measured the association using HRs, we again found no difference in the magnitude of the HRs (ratio of HRs 1.08 (95% CI 0.99, 1.17)); P=0.12.

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

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

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

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

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

Risk of Bias Assessment by Industry Ties

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

Concordance between study results and conclusions

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

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

DISCUSSION

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

studies, [12] the funders in the studies included in this review were extremely diverse, with Big Food and trade association jointly sponsoring several studies. Thus, dairy foods are not their sole interest.

The meta-analysis of hazard ratios of CVD outcomes found that studies with industry sponsorship showed a greater benefit from dairy than studies without industry sponsorship, and this difference was statistically significant. The meta-analysis of risk ratios of CVD outcomes found a similar estimate; however, this was not statistically significant. The likely reason for this was that the meta-analysis of RRs had fewer studies, and so the ratio of RRs could not be as precisely estimated. We found no evidence of a clinically important difference in the magnitude of effect between studies with industry ties or authors with a COI compared to those with no industry ties or no COI for other outcomes.

For every study, the overall risk of bias was classified as high (meaning either serious or critical). Therefore, differences in the risk of bias across studies with and without industry ties would not seem to provide an explanation for our findings. However, the version of the ROBINS-E tool that we used may not have been able to adequately discriminate across the studies, as perhaps is indicated by the uniformity in risk of bias classification.[26] Therefore, we cannot rule out the possibility that differences in bias across studies with and without industry ties may partly explain our findings.

Strengths and limitations of this review

Our review was prospectively registered in Prospero.[19] We followed explicit inclusion and exclusion criteria, conducted a comprehensive search across multiple databases and hand searched reference lists for the included studies.

For those studies missing a funding or author COI disclosure, we did not contact the authors and we therefore may be underestimating the number of studies with industry ties. The tool that we used to assess the risk of bias is still under development, however it is unlikely any future changes to the tool will affect the risk of bias ratings.[22] We did not analyse studies of low and full fat dairy or other types of dairy products separately. Industry ties may have different effects on studies of low or full fat dairy foods or other foods and drinks. A final limitation of our study is that we relied on definitions of exposures and outcomes that were

used in the original studies included in our analyses. Using finer categorizations of exposures and outcomes would not provide a sufficient sample size to do our analyses. However, future studies, using additional data and finer categorizations, may have different results.

Agreements and disagreements with other studies or reviews

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

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

Implications for clinicians, policy makers and future research

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

made in dietary guidelines should account for the potential influence of industry sponsorship on evidence of health effects. Nutrition studies included in systematic reviews used in the development of dietary guidelines should be assessed using empirical methods to identify 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 domain. The University of California, San Francisco's Navigation Guide assesses both author conflicts of interest and funding sources as a risk of bias in human and animal studies. [29] As the study designs used in nutrition are the same as those used to evaluate the harms of an exposure in environmental health, dietary guideline committees could consider adopting this tool to evaluate the risk of bias of the studies included in the systematic reviews used to develop dietary guidelines.

Industry sponsors may bias research via different mechanisms, including the design and conduct of a study, the selective reporting of results, how they code events, analyse data, by spinning conclusions,[11] as well as framing how the questions are asked.[30–32] It has been suggested that the dairy industry may preferentially fund research on topics which will provide them with more favourable outcomes.[33] The influence of the food industry on the research agenda has been demonstrated in an examination of research topics covered by samples of randomised controlled trials included in systematic reviews of nutrition studies and obesity.[34] It was shown that most food industry studies focused on the manipulations of specific nutrients, and not on dietary behaviours, therefore limiting the public health relevance of rigorous evidence available for use in both systematic reviews and dietary guidelines.[34] The topics examined in cohort studies on the relationship of nutrition and obesity, which tend to focus on more complex exposures than trials, did not demonstrate a similar influence of funding source. However, the disclosure of food industry sponsorship was low, making a comparison difficult.[35]

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

studies.[16] To eliminate this risk of bias from nutrition research, investigators should use only non-industry sources to fund their research.

Conclusion

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

Acknowledgements: We thank Agnes Lau, University of California, San Francisco, for her assistance with data collection.

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

Funding: This work was supported by Australian Health and Medical Research Council Project Grant APP 1139997. Nicholas Chartres is a recipient of the James Millner PhD Scholarship in Pharmacy from the University of Sydney.

Competing interests: None declared.

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

Patient consent for publication: Not required.

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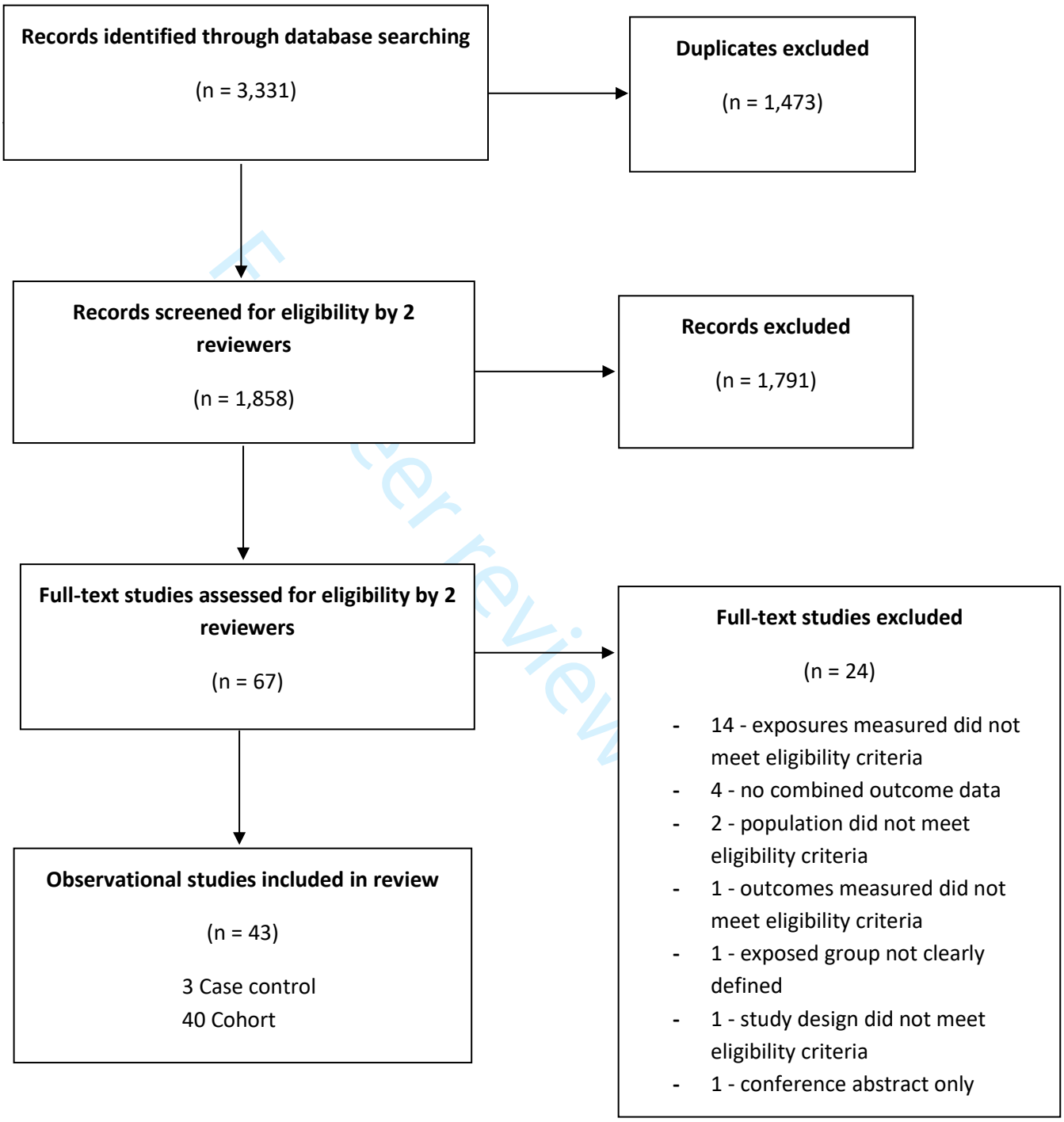
Figures

Figure 1. Study Flow Diagram

Figure 2. Risk of Bias in Included Studies

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

Figure 1. Study Flow Diagram



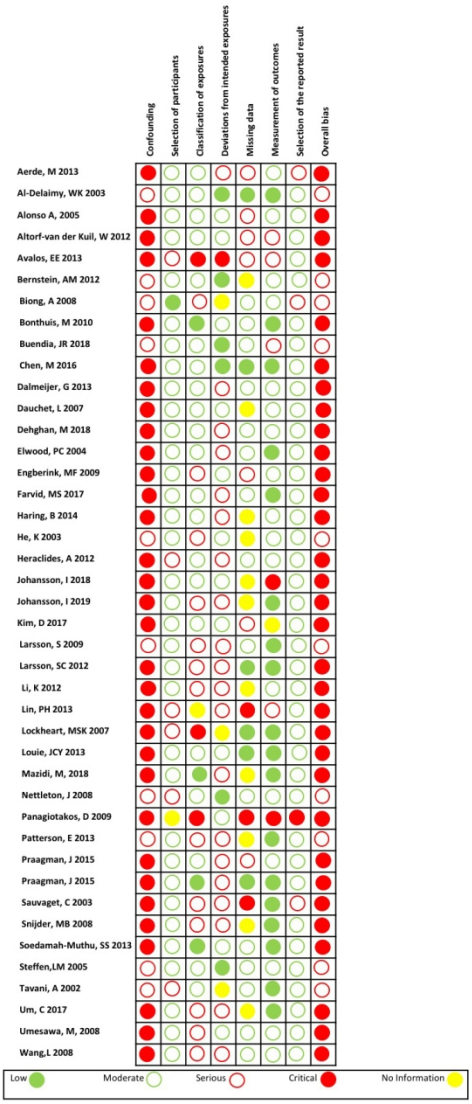


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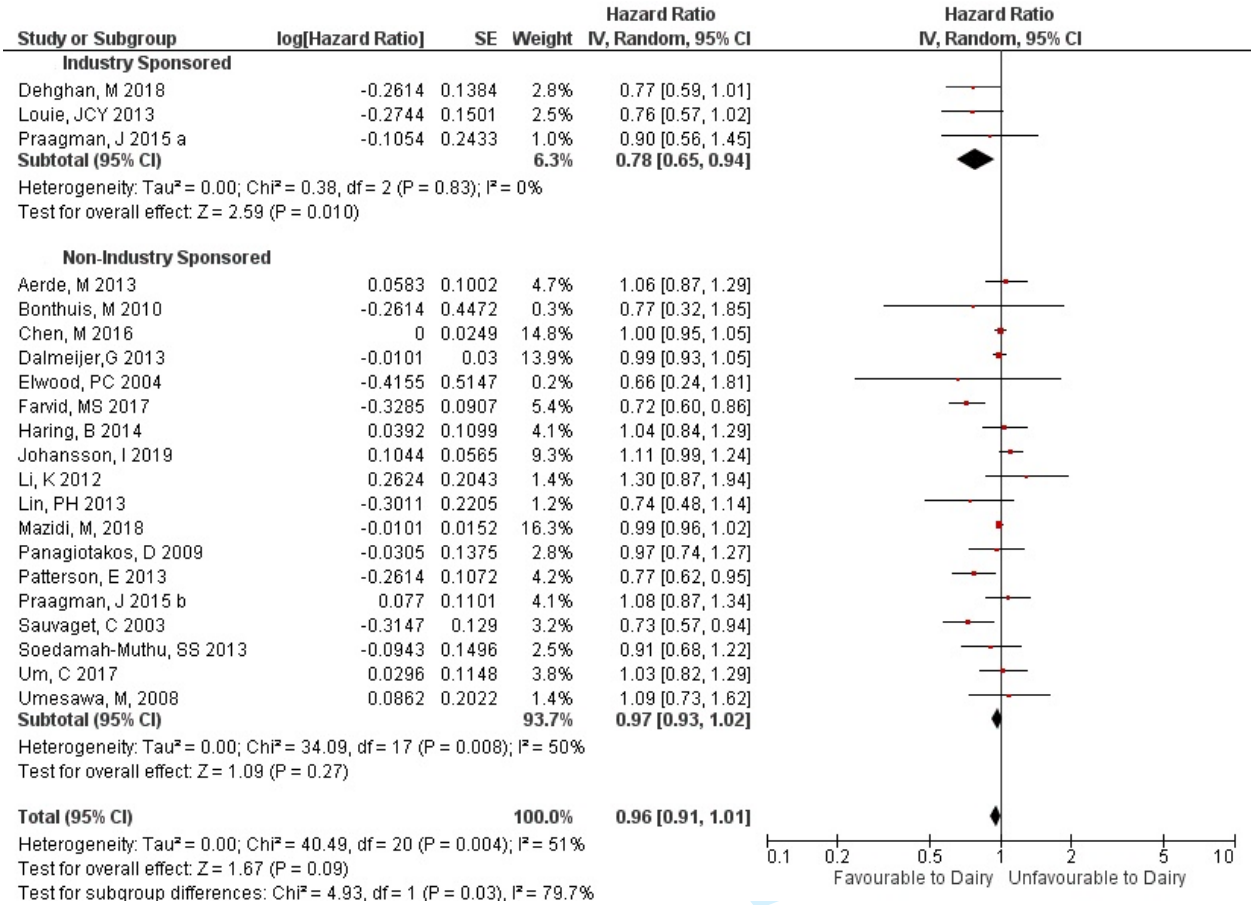
Figure 3. Effect Size, Cardiovascular Disease, Industry sponsorship vs no Industry sponsorship, Hazard Ratio



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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:

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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

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6. * Named contact.

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

Nicholas Chartres

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Mr Chartres

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8. Named contact address

Give the full postal address for the named contact.

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

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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.

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

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

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

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

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 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.

c. Secondary Outcome 1 (Risk of Bias tool for studies)

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

‘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

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

No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
Yes

Care of the elderly
No

Child health
No

Complementary therapies

No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
Yes

Rehabilitation
No

Respiratory disorders
No

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.

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 newregistrations 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.

25. dairy consumption.mp.

26. dairy food*.mp.

27. Dairy Products/ or dairy product*.mp.

28. dairy serv*.mp.

29. dairy type*.mp.

30. dairy source*.mp.

31. (calcium adj15 food sourc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

32. (vitamin D adj15 food sourc*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

33. (milk and (cow or goat or sheep)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

34. yogurt.mp. or Yogurt/

35. cheese.mp. or Cheese/

36. custard.mp.

37. (milk and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

38. (yogurt and (skim or full fat or low fat)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

39. Milk/

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 39

41. cardiovascular disease.mp. or exp Cardiovascular Diseases/

42. coronary*.tw.

43. heart*.tw.

44. cardia*.tw.

45. cardio*.tw.

46. myocard*.tw.

47. isch?em*.tw.

48. angina*.tw.

49. ventric*.tw.

50. tachycardi*.tw.

51. pericard*.tw.

52. endocardi*.tw.

53. atrial fibrillat*.tw.

54. arrhythmi*.tw.

55. athero*.tw.

56. arterio*.tw.

57. exp Atherosclerosis/

58. exp Arteriosclerosis/

59. HDL.tw.

60. LDL.tw.

61. VLDL.tw.

62. lipid*.tw.

63. lipoprotein*.tw.

64. triacylglycerol*.tw.

65. exp Hyperlipidemias/

66. hyperlipid*.tw.

67. hypercholesterol*.tw.

68. hypercholester?emia*.tw.

69. hypertriglycerid?emia*.tw.

70. exp Cholesterol/

71. cholesterol*.tw.

72. exp Stroke/

73. stroke*.tw.

74. CVA.tw.

75. cerebrovasc*.tw.

76. "vascular accident".tw.

77. TIA.tw.

78. cerebral vascular.tw.

79. thrombo*.tw.

80. emboli*.tw.

81. apoplexy.tw.

82. (brain adj2 accident*).tw.

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

84. Hypertension/

85. exp Blood Pressure/

86. hypertensi*.tw.

87. blood pressure*.tw.

88. systolic blood pressure.tw.

89. diastolic blood pressure.tw.

90. peripheral arter* disease*.tw.

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

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

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

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

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

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

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 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 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96

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 19 or 20 or 21 or 22

99. 40 and 97 and 98

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

101. limit 100 to humans

102. limit 101 to "all adult (19 plus years)"

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 Smoking Alcohol intake History of co-morbidities Parenteral/Fhx MI < 60 yrs PA levels SES Total energy intake Fruit & Vegetable intake *Specialised Confounders* Hormone therapy
2. CVD events	Fibre supplement (p) Magnesium supplement (p)	
3. CHD mortality (incident CVD)	Fibre supplement (p) Trans Fat (h) Polyunsaturated fat (n-6) (p) Sodium (+Na) (h)	
4. CHD events (incident CHD)	Fibre supplement (p) Trans fat (h) Magnesium supplement (p) Polyunsaturated fat (n-6) (p)	
5. Total MI	Aspirin (p) Vitamin E supplement (p)	
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

Author	Title	Reason for Exclusion
Akbaraly, T 2013[1]	Does overall diet in midlife predict future aging phenotypes? A cohort study	Dietary patterns only were assessed, not dairy foods
Anderson, LA 2011[2]	Dietary Patterns and Survival of Older Adults	No relevant outcomes were measured
Baylin, A 2003[3]	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[4]	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[5]	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[6]	Prospective investigation of major dietary patterns and risk of cardiovascular mortality in Bangladesh	Dietary patterns only were assessed, not dairy foods
Ding, M 2017[7]	Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study	Not an observational design study
Eguchi, E 2012[8]	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[9]	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[10]	Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands	No combined outcome data
Julián-Almárcegui, C 2016[11]	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[12]	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[13]	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[14]	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[15]	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[16]	Arginine intake and risk of coronary heart disease mortality in elderly men	Effects of dairy foods not measured
Paillard, F 2015[17]	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[18]	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[19]	Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study	Dietary patterns only were assessed, not dairy foods
Umesawa, M 2006[20]	Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study	No combined outcome data
van der Pols, J C 2009[21]	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[22]	Stroke and plasma markers of milk fat intake – a prospective nested case-control study	Effects of dairy foods not measured
Warensjo, E 2009[23]	Milk Fat Biomarkers and the Risk of a First Ever Acute Myocardial Infarction - A Prospective Nested Case-Control Study. Journal of the American Dietetic Association. 2009;1	Poster presentation only, full study not available
Warensjo, E 2010[24]	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.
7. Ding M, Huang T, Bergholdt HK, et al. Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study. *Bmj.* 2017;356:j1000.
8. Eguchi E, Iso H, Tanabe N, et al. Healthy lifestyle behaviours and cardiovascular mortality among Japanese men and women: the Japan collaborative cohort study. *European heart journal.* 2012;33(4):467-477.
9. Geleijnse JM, Mertens E, Markey O, et al. Dietary Patterns in Relation to Cardiovascular Disease Incidence and Risk Markers in a Middle-Aged British Male Population: Data from the Caerphilly Prospective Study. *Nutrients.* 2017;9(1):75.
10. Goldbohm RA, Chorus AMJ, Galindo Garre F, et al. Dairy consumption and 10-y total and cardiovascular mortality: a prospective cohort study in the Netherlands. *American Journal of Clinical Nutrition.* 2011;93(3):615-627 613p.
11. Julián-Almárcegui C, Vandevijvere S, Gottrand F, et al. Association of heart rate and blood pressure among European adolescents with usual food consumption: The HELENA study. *Nutrition, Metabolism & Cardiovascular Diseases.* 2016;26(6):541-548.
12. Larsson SC, Wolk A, Bäck M. Dietary patterns, food groups, and incidence of aortic valve stenosis: A prospective cohort study. *International Journal of Cardiology.* 2018.
13. Lupton BS, Fonnebo V, Sogaard AJ, et al. The Finnmark Intervention Study: is it possible to change CVD risk factors by community-based intervention in an Arctic village in crisis? *Scandinavian Journal of Public Health.* 2003;31(3):178-186.
14. Meyer J, Doring A, Herder C, et al. Dietary patterns, subclinical inflammation, incident coronary heart disease and mortality in middle-aged men from the MONICA/KORA Augsburg cohort study. *European journal of clinical nutrition.* 2011;65(7):800-807.
15. Michaelsson K, Melhus H, Warensjo E, et al. Long term calcium intake and rates of all cause and cardiovascular mortality: community based prospective longitudinal cohort study. *Bmj.* 2013;346:f228.
16. Oomen CM, van Erk MJ, Feskens EJ, et al. Arginine intake and risk of coronary heart disease mortality in elderly men. *Arteriosclerosis, thrombosis, and vascular biology.* 2000;20(9):2134-2139.
17. Paillard F, Bruckert E, Naelten G, et al. Cardiovascular risk and lifestyle habits of consumers of a phytosterol-enriched yogurt in a real-life setting. *Journal of Human Nutrition & Dietetics.* 2015;28(3):226-235 210p.
18. Praagman J, Beulens JW, Alssema M, et al. 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. *American Journal of Clinical Nutrition.* 2016;103(2):356-365.
19. Streppel MT, Sluik D, van Yperen JF, et al. Nutrient-rich foods, cardiovascular diseases and all-cause mortality: the Rotterdam study. *European journal of clinical nutrition.* 2014;68(6):741-747.
20. Umesawa M, Iso H, Date C, et al. Dietary intake of calcium in relation to mortality from cardiovascular disease: the JACC Study. *Stroke.* 2006;37(1):20-26.
21. van der Pols JC, Gunnell D, Williams GM, et al. Childhood dairy and calcium intake and cardiovascular mortality in adulthood: 65-year follow-up of the Boyd Orr cohort. *Heart.* 2009;95(19):1600-1606.
22. Warensjo E, Smedman A, Stegmayr B, et al. Stroke and plasma markers of milk fat intake--a prospective nested case-control study. *Nutrition Journal.* 2009;8:21.

23. Warensjo E, Sjogren P, Cederholm T, et al. Milk Fat Biomarkers and the Risk of a First Ever Acute Myocardial Infarction - A Prospective Nested Case-Control Study. *Journal of the American Dietetic Association.* 2009;109(9, Supplement):A51.
24. Warensjö E, Jansson JH, Cederholm T, et al. Biomarkers of milk fat and the risk of myocardial infarction in men and women: a prospective, matched case-control study. *American Journal of Clinical Nutrition.* 2010;92(1):194-202 199p.

Supplementary file 5: 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[(1)]	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[1]	Yes[a]
Al-Delaimy, WK 2003[(2)]	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[2]	No[b]
Alonso A, 2005[(3)]	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[3]	No[c]

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
Altorf-van der Kuil, W2012[4]	Cohort	Mean follow up 7·5 years	3,588 men & women	44 years	Dairy Protein T3, ≥ 27 g/day (dairy protein was calculated as protein from milk, yogurt, coffee creamer, curd, pudding, porridge, custard, whipped cream and cheese)	T1, ≤ 19 g/day	Hypertension	Industry[4]	Yes[d]
Avalos, EE 2013[5]	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[5]	No[e]
Bernstein, AM 2012[6]	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[6]	Yes[f]
Biong, A 2008[7]	Case Control		218 men & women	62.4 years	Dairy Fat, > 34.1 g/day	<14.6 g/day	First Myocardial Infarction	Industry[7]	Yes[g]

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[8]	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[8]	No[h]
Buendia, JR 2018[9]	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[9]	No[i]
Chen, M 2016[10]	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[10]	No[j]

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[(11)]	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[11]	Yes[k]
Dauchet, L 2007[(12)]	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[12]	No[l]

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[13]	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[13]	No[m]
Elwood, PC 2004[14]	Cohort	20-24 years	2,403 men	45-59 years	Milk Q4, >1 pint per day	Q1, None	Vascular Event	Non-Industry[14]	No disclosure

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
Engberink, MF 2009[15]	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[n]
Farvid, MS 2017[16]	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[15]	No[o]
Haring, B 2014[17]	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[16]	No[p]
He, K 2003[18]	Cohort	14 years	43,732 men	40-75 years	High Fat Dairy Q5, ≥1/day	Q1, <1/week	Ischaemic & Haemorrhagic Stroke	Non-Industry[17]	No[q]

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[19]	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 [18]	Yes[r]
Johansson, I 2018[20]	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[19]	No[S]
Johansson, I 2019[21]	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[20]	No[t]
Kim, D 2017[22]	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 [21]	No[u]
Larsson,S 2009[23]	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[22]	No disclosure

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
Larsson, SC 2012[24]	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[23]	No[v]
Li, K 2012[25]	Cohort	11 years	23,980 men & women	35-64 years	Dairy Calcium Q4, 780 mg/day	Q1, 188 mg/day	CVD Mortality	Non-Industry[24]	No[w]
Lin, PH 2013[26]	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[25]	No[x]
Lockheart, MSK 2007[27]	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 [26]	No disclosure
Louie, JCY 2013[28]	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[27]	No disclosure
Mazidi, M, 2018[29]	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[28]	No[y]

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[30]	Cohort	25 years	5,765 men	35-64 years	Milk T3, > 1 pint (= 0.568 liters)	T1, None	Cardiovascular Disease Deaths	Non-Industry[29]	No[z]
Nettleton, J 2008[31]	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[30]	No[aa]
Panagiotakos, D 2009[32]	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[31]	No disclosure
Patterson, E 2013[33]	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[32]	No[bb]
Praagman, J 2015 (a)[34]	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[33]	Yes[cc]

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
Praagman, J 2015 (b)[35]	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[34]	Yes[dd]
Sauvaget, C 2003[36]	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[35]	No disclosure
Snijder, MB 2008[37]	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 (≤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[36]	Yes[ee]
Soedamah-Muthu, SS 2013[38]	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 [37]	Yes[ff]
Steffen, LM 2005[39]	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[38]	No[gg]

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
Tavani, A 2002[40]	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[39]	No[hh]
Um, C 2017[41]	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-Indutry[40]	No[ii]
Umesawa, M, 2008[42]	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[41]	No[ij]

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[43]	Cohort	10 years	28,886 women	53.8 years	Total Diary 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[42]	No[kk]

* 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

Description of Funding Source (Verbatim)

1. The Hoorn Study has been made possible by the Vrije Universiteit Amsterdam and the VU University Medical Center, and by grants from the Dutch Diabetes Research Foundation, the Dutch Organization for Scientific Research, the Netherlands Heart Foundation, and the Health Research and Development Council of the Netherlands.
2. Supported by research grants HL24074, HL34594, DK36798, and CA87969 from the National Institutes of Health.
3. Supported by the Spanish Ministry of Health (grants PI040233 and G03-140), the Navarra Regional Government (PI41-2005), and the University of Navarra (línea especial Nutricio LE-97).AA was supported partially by a Fulbright fellowship and an MMA Foundation grant.
4. The Doetinchem Cohort Study was financially supported by the Ministry of Health, Welfare and Sport of the Netherlands and the National Institute for Public Health and the Environment. For the present analysis, Wageningen University was supported by the Top Institute Food and Nutrition, which is a public/private partnership that generates vision on scientific breakthroughs in food and nutrition, resulting in the development of innovative products and technologies. Partners are major Dutch Food companies and research organisations.
5. The study was supported by grants AG007181 and AG028507 from the National Institutes of Health/National Institute on Aging, and by grant DK31801 from the National Institute of Diabetes and Digestive and Kidney Diseases.
6. This study was supported by grant P01CA087969 from the National Institutes of Health, Department of Health and Human Services. A.M.B. was supported through the Harvard Human Nutrition Program.
7. The study was supported financially by the Research Council of Norway, Throne Holst's Foundation for Nutrition Research, The Norwegian Association of Margarine Producers, DeNoFa Fabrikker A/S and Tine BA. Tine BA is a dairy company.
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.
10. Supported by the NIH (grants R01 HL034594, UM1 CA176726, UM1 CA186107, R01 HL35464, R01 HL088521, R01 CA67262, HL60712, and UM1 CA167552).
11. This research was supported by a personal Dr. Dekker postdoctoral grant (2008T062) from The Netherlands Heart Foundation (JWJ Beulens).
12. The SU.VI.MAX study is supported by the Direction Générale de la Santé, the Ministère de la Santé, and the Institut Virtuel de Recherche en Santé Publique (groupe cohorte) INSERM.
13. The PURE Study is an investigator-initiated study that is funded by the Population Health Research Institute, the Canadian Institutes of Health Research (CIHR), Heart and Stroke Foundation of Ontario, support from CIHR's Strategy for Patient Oriented Research (SPOR) through the Ontario SPOR Support Unit, as well as the Ontario Ministry of Health and Long-Term Care and through unrestricted grants from several pharmaceutical companies, with major contributions from AstraZeneca (Canada), Sanofi-Aventis (France and Canada), Boehringer Ingelheim (Germany and Canada), Servier, and GlaxoSmithKline, and additional contributions from Novartis and King Pharma and from various

national or local organisations in participating countries. These include Brazil: Unilever Health Institute, Brazil; South Africa: The SA Sugar Association (SASA).
14. The Medical Research Council, the University of Wales College of Medicine and Bristol University, Food Standards Agency.
15. This work was supported by Tehran University of Medical Sciences (grant 82-603); Cancer Research UK (grant C20/A5860); the Intramural Research Program of the National Cancer Institute, US National Institutes of Health (grant Z01 CP000185-03); and various collaborative research agreements with the International Agency for Research on Cancer. M.F. was supported by a Takemi Fellowship from the Japan Pharmaceutical Manufacturers Association.
16. The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C).
17. This work was supported by the research grant HL35464 and CA55075 from the National Institutes of Health.
18. The study was funded by the Medical Research Council, and some aspects of the analysis were funded by The European Commission, Quality of Life and Management of Living Resources Programme, contract number QLG1-CT-2000–01643.
19. The present study was supported by the Swedish Research Council for Health, Working Life and Welfare (FORTE).
20. This research was funded by The Swedish Research Council for Health, Working Life and Welfare (FORTE), grant number 2016-00960. The Northern Sweden Diet Database has been supported by the Swedish Research Council for Health, Working Life and Welfare (FORTES) and The Swedish Research Council.
21. This research was supported by the Basic Science Research Program of the National Research Foundation of Korea (NRF), funded by the Ministry of Education, Science, and Technology (NRF2016R1D1A1B03931307).
22. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study was supported by Public Health Service contracts N01-CN-45165, N01-RC-45035 and N01-RC-37004 from the US National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Md. Dr. Larsson's research at the National Public Health Institute in Helsinki, Finland, was supported by a grant from the Swedish Council for Working Life and Social Research.
23. This study was supported by a research grant from the Swedish Council for Working Life and Social Research (FAS), the Swedish Research Council, and by a Research Fellow grant from Karolinska Institutet (to Dr Larsson).
24. This work was supported by supported by the Deutsche Krebshilfe (grant-No70-488-Ha I) and the Graduiertenkolleg 793: Epidemiology of communicable and chronic non-communicable disease and their inter-relationships.
25. Data collection was supported by the Department of Health in Taiwan.
26. The present study was supported by NIH NRSA T32HL007779, CVD Epidemiology and Prevention, American Heart Association – Greater Midwest Affiliate, Throne Holst's Foundation for Nutrition Research, The Norwegian Association of Margarine Producers, DeNoFa Fabriker A/S and Tine Norwegian Dairies.
27. This study was funded by Dairy Australia.

28. This manuscript was written independently; no company or institution supported it financially.
29. Funding: this study was provided with funding by a grant from the NHS Management Executive Cardiovascular Disease and Stroke Research and Development Initiative.
30. This research was supported by the National Institutes of Health grant HL73366, training grant T32 HL07779, and contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022 from the National Heart, Lung, and Blood Institute.
31. The ATTICA study was supported by research grants from the Hellenic Cardiological Society (HCS2002).
32. Supported by research grants from the Swedish Council for Working Life and Social Research and from the Swedish Research Council/Infrastructure Medicine.
33. This study was supported by an unrestricted grant from the Dutch Dairy Organization (NZO) for epidemiological analyses on dairy intake and cardiovascular diseases.
34. The present study was supported by a personal Dr Dekker postdoctoral grant (2008T062) from the Netherlands Heart Foundation (J. W. J. B.).
35. This publication is based on research performed at the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan. RERF is a private nonprofit foundation funded equally by the Japanese Ministry of Health, Labor and Welfare and the US Department of Energy through the National Academy of Sciences.
36. This particular study has been supported by a grant from the Dutch Dairy Association (NZO).
37. The Whitehall II study was supported by grants from the Medical Research Council (G0902037), the British Heart Foundation (RG/07/008/23674), the Stroke Association, the National Heart Lung and Blood Institute (5RO1 HL036310), the National Institute on Aging (5RO1AG13196) and the Agency for Health Care Policy Research (5RO1AG034454).
38. The CARDIA Study is supported by National Heart, Lung, and Blood Institute contracts N01-HC-48047, N01-HC-48048, N01-HC-48049, N01- HC-48050, and N01-HC-95095.
39. Funding: partly supported by the Italian Ministry of Health (Programmi Speciali).
40. The REGARDS research project is supported by a cooperative agreement U01 NS041588 from the National Institute of Neu- rological Disorders and Stroke, National Institutes of Health, Department of Health and Human Service. Additional support provided by the Franklin Foundation.
41. This study was supported by grants-in-aid for cancer research and by the Third Term Comprehensive Ten-Year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare of Japan.
42. This work was supported by research grants CA-047988 and HL-080467 from the National Institutes of Health, Bethesda, Md.

Description of Author Disclosure Statement (Verbatim)

a) Sabita S. Soedamah-Muthu and Johanna M. Geleijnse obtained an unrestricted grant from the Dutch Dairy Association (NZO) to carry out meta-analyses on the association between dairy products and CVD.
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.
c) None of the authors had any conflicts of interest.
d) Altorf-van der Kuil W, Engberink MF, Geleijnse JM - Top Institute Food and Nutrition, PO Box 557, 6700 AN, Wageningen, The Netherlands.
e) The authors have no conflicts of interest.
f) D.M. received research grants for studying the effects of diet on cardiometabolic diseases from the National Institutes of Health; the Searle Scholar Award from the Searle Funds at The Chicago Community Trust; the Genes and Environment Initiative at the Harvard School of Public Health; and the Gates Foundation/World Health Organization Global Burden of Diseases, Injuries, and Risk Factors Study; and from GlaxoSmithKline, Sigma Tau, Pronova, and the National Institutes of Health for an investigator-initiated, not- for-profit clinical trial of fish oil and postsurgical complications. He also received ad hoc travel reimbursement and/or honoraria for research presentations from the Chicago Council, International Life Sciences Institute, Aramark, Unilever, SPRIM, Nutrition Impact, Norwegian Seafood Export Council, United Nations Food and Agricultural Organization, World Health Organization, US Food and Drug Administration, and several universities. He received ad hoc consulting fees from Foodminds and royalties from UpToDate for an online chapter on fish oil.
g) A. S. Biong is employed as a Ph.D. student in a research project funded jointly by TINE BA, a Norwegian dairy company, and the Norwegian Research Council.
h) The authors declare no conflict of interest.
i) There are no conflicts of interest.
j) None of the authors reported a conflict of interest related to the study.
k) SS-Mand MG obtained an unrestricted grant from the Dutch Dairy Association (NZO) to carry out meta-analyses on the association between dairy products and cardiovascular diseases.
l) None of the authors had any personal or financial conflicts of interest.
m) We declare no competing interests.
n) There were no conflicts of interest.
o) Conflict of interest: none declared
p) The authors have declared that no competing interests exist.
q) Competing interests: None declared.
r) SSM, JMG and AH and were supported by an unrestricted grant from the Dutch dairy industry (NZO).
s) The authors declare that they have no competing interests.
t) The authors declare no conflict of interest
u) The authors have no conflicts of interest to declare.

v) Disclosures: None.
w) Competing interests None.
x) AUTHOR DISCLOSURES None.
y) All authors have nothing to declare in relation to the subject of this paper.
z) Conflicts of interest: none.
aa) The authors have no conflicts of interest to report.
bb) Author disclosures: E. Patterson, S. C. Larsson, A. Wolk, and A. A kesson, no conflicts of interest.
cc) J.M.G and S.S.S.M received an unrestricted grant from the Dutch Dairy Organization (NZO) for epidemiological analyses on dairy intake and cardiovascular diseases.
dd) S. S. S. M. received an unrestricted research grant from the Global Dairy Platform, Dairy Research Institute and Dairy Australia for a meta-analysis project on the effect of cheese on lipids.
ee) Gerrit J. Hiddink - Dutch Dairy Association (NZO), Zoetermeer, The Netherlands.
ff) S. S. S.-M., L. V. and J. M. G. obtained an unrestricted grant from the Dutch Dairy Association (NZO) to carry out meta-analyses on the association between dairy products.
gg) None of the authors had any conflicts of interest.
hh) Conflicts of interest: none.
ii) Conflict of Interests: None.
jj) Disclosures: None.
kk) Disclosures: None.

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Supplementary File 6. Risk of bias in included studies

			Funding Source, n (%[a])					
			Sponsorship		COI		Industry Ties	
Characteristic	Category	Total N = 43	Industry N= 8	Non-Industry N=35	COI N =10	No COI N=33	Industry /COI N = 14	Non-Industry/ No COI N = 29
Risk of Bias Assessment								
	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)

[a] 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**
					Sauvaget, 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-Indutry	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

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)

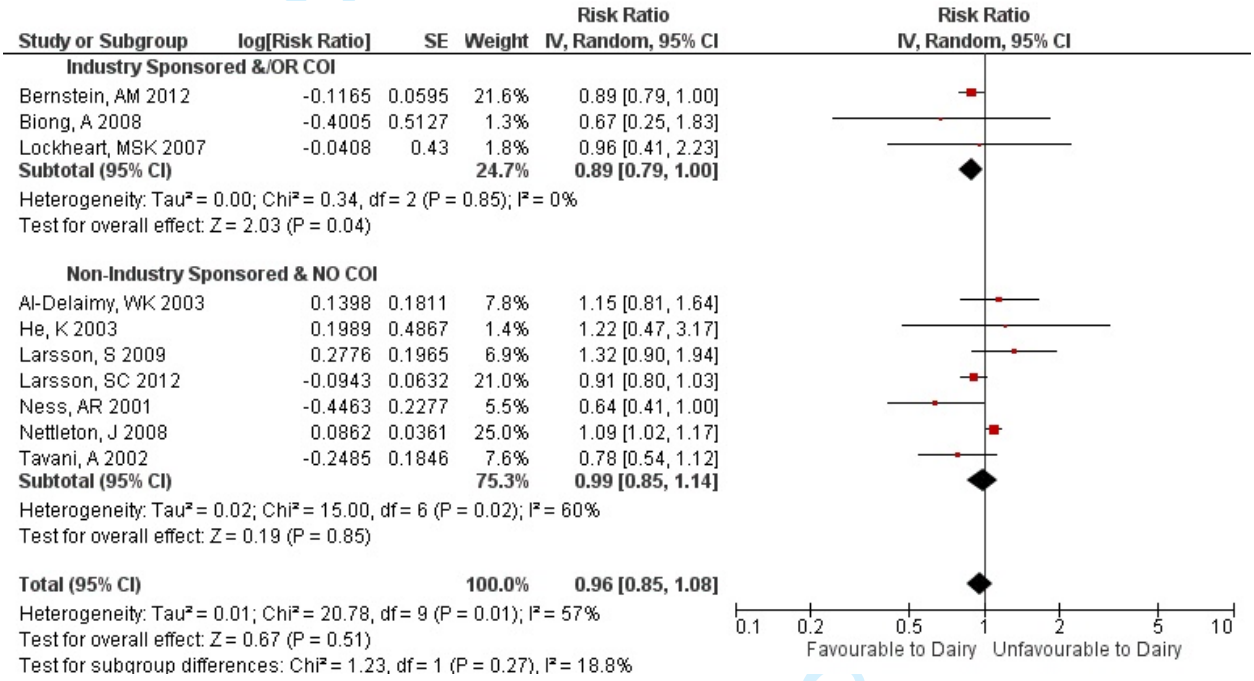
Conflicts of Interest

	COI	No/COI
Favourable	2	4
Unfavourable	8	29

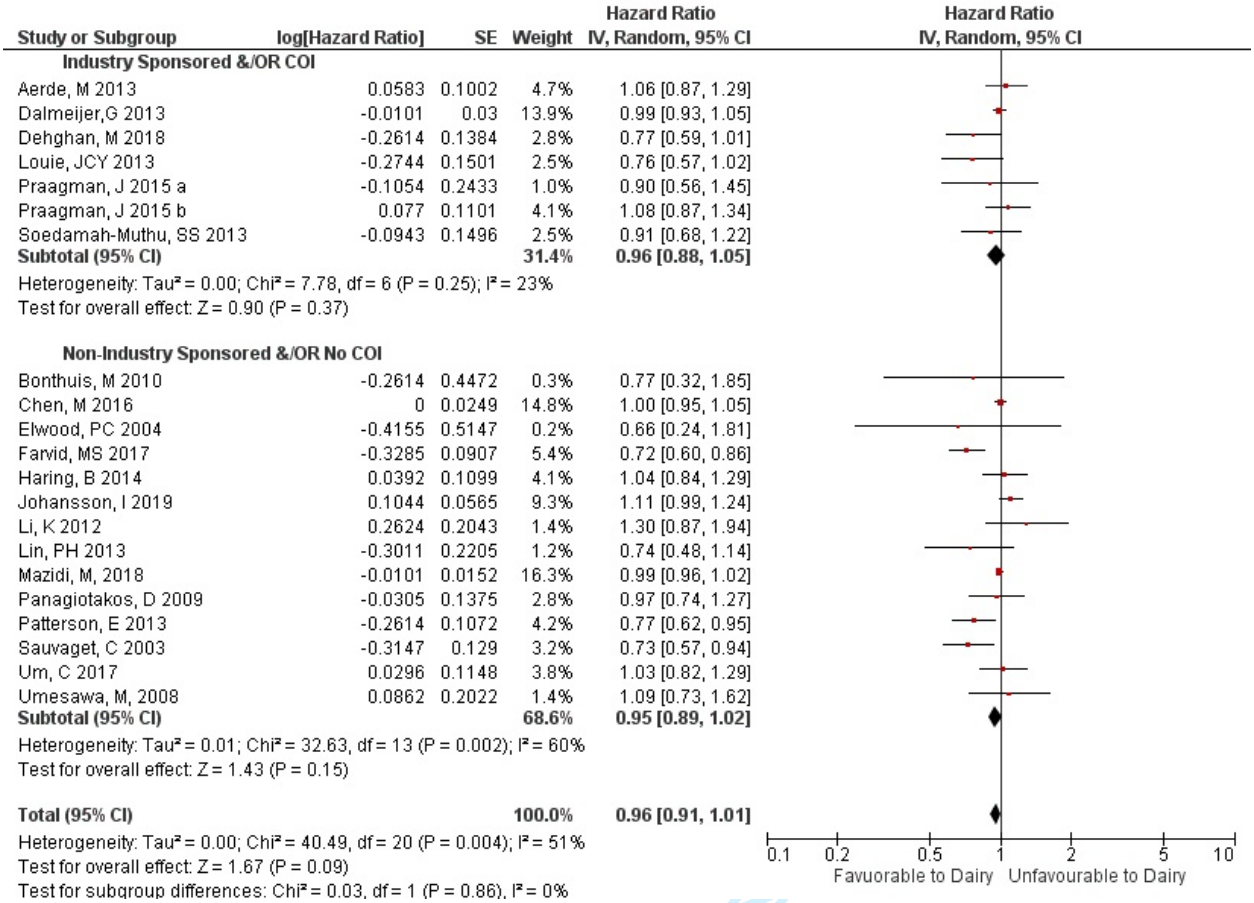
RR = 1.65 (95% CI 0.35, 7.72)

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

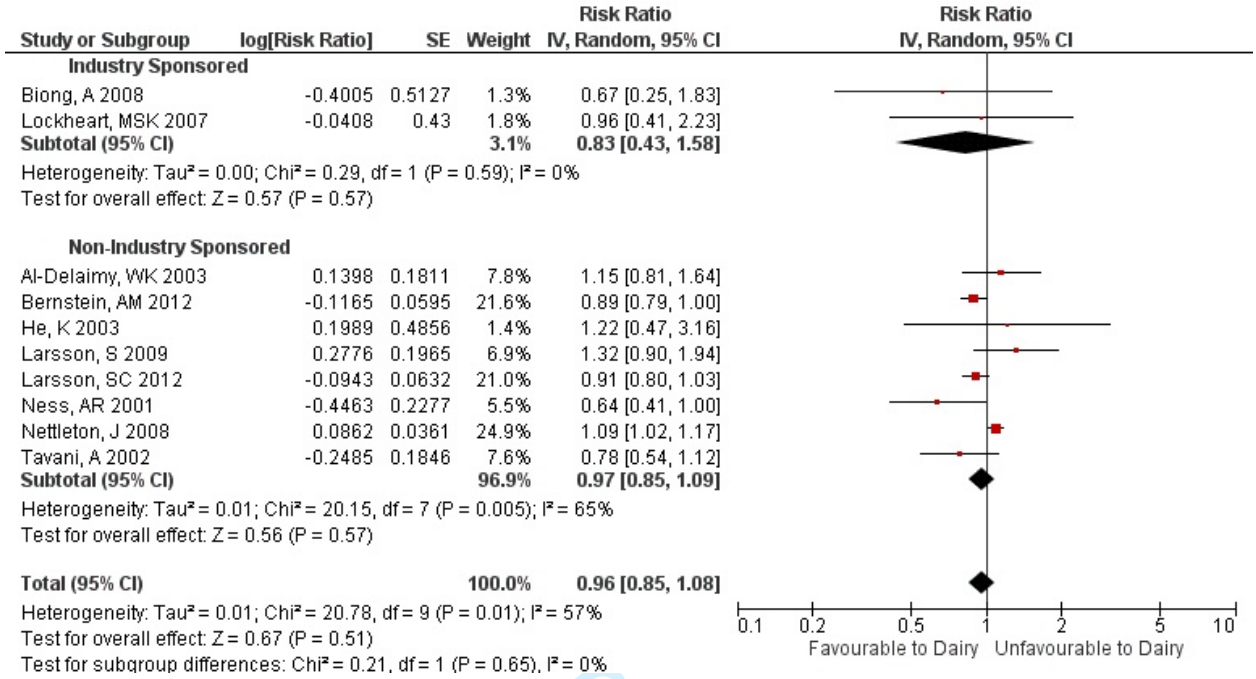
Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Risk Ratio



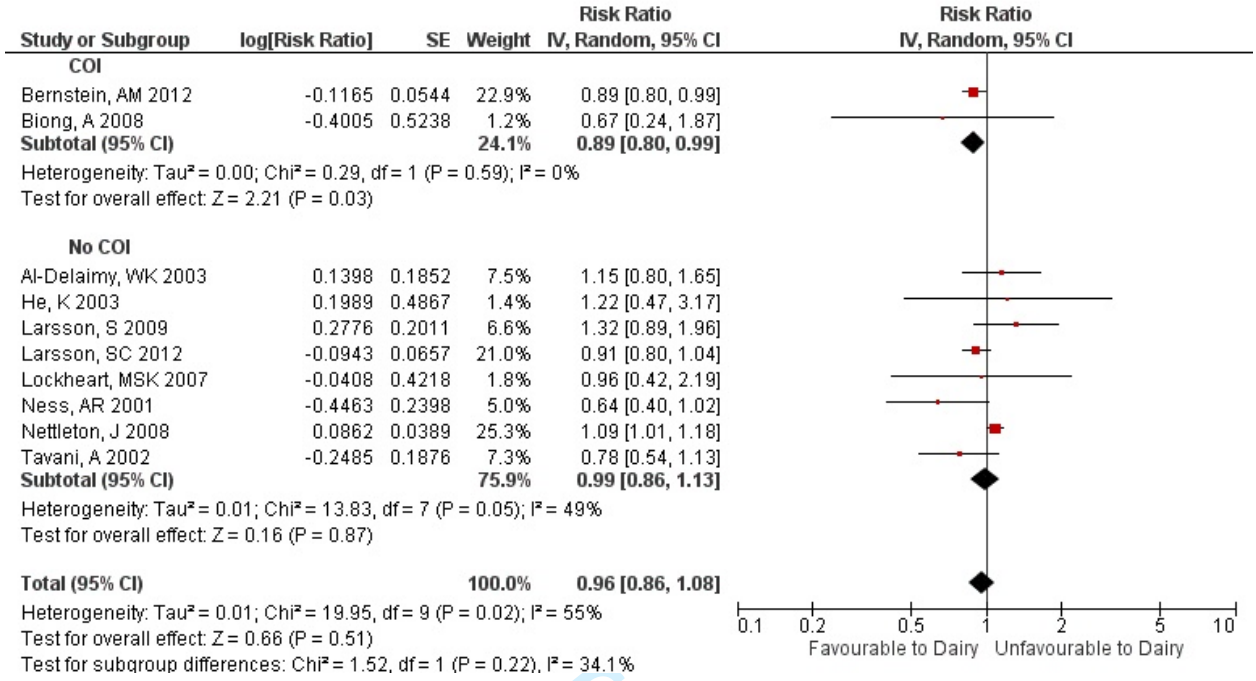
Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Hazard Ratio



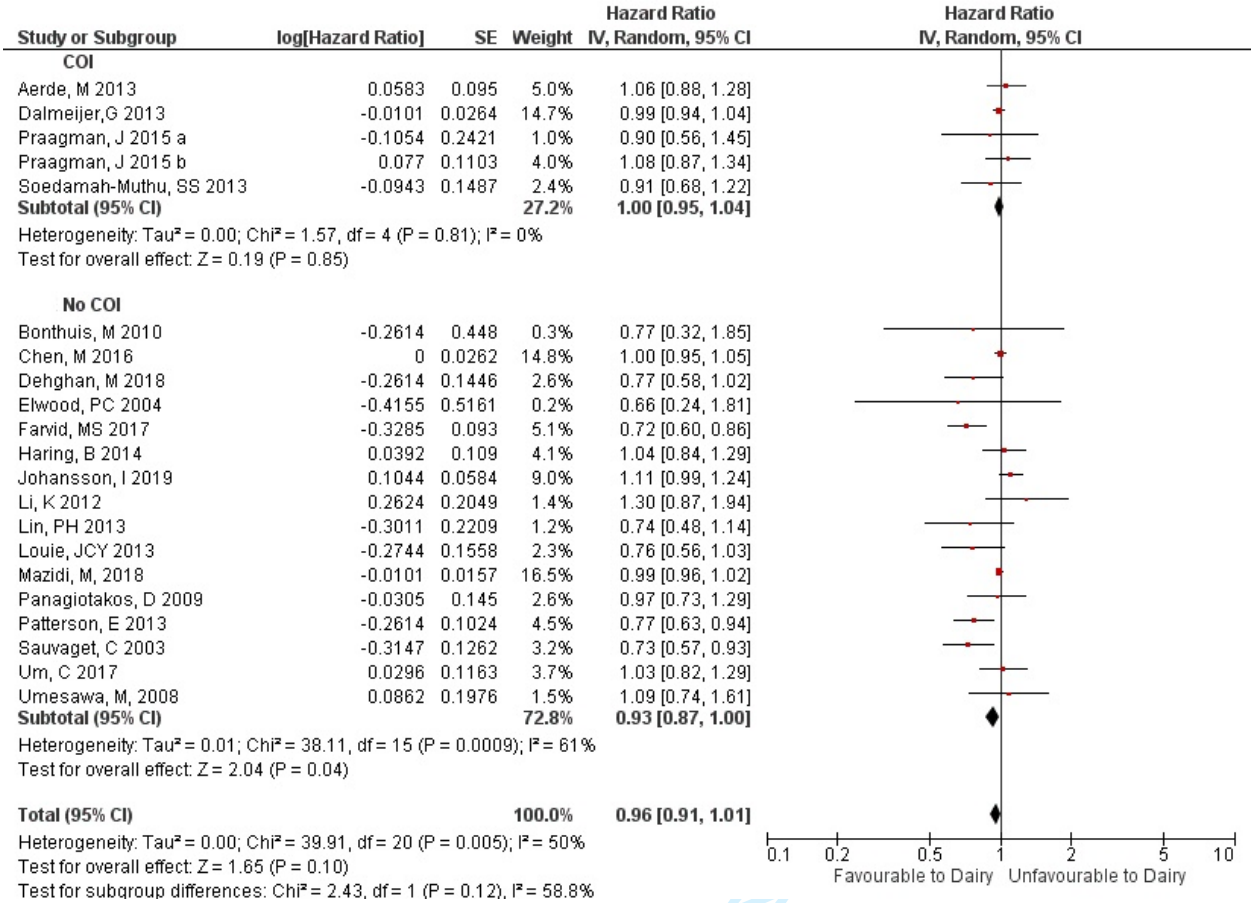
Effect Size, Cardiovascular Disease: Industry sponsorship vs no industry sponsorship, Risk Ratio



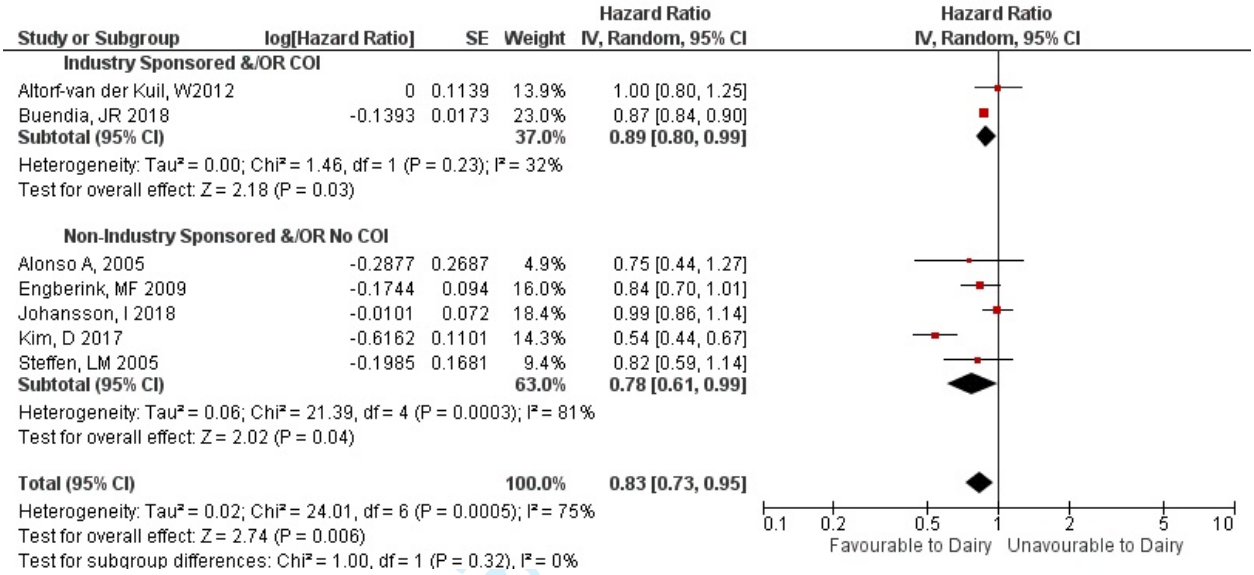
Effect Size, Cardiovascular Disease: COI vs No COI, Risk Ratio



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 #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
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
INTRODUCTION			
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
METHODS			
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.	10 -11

PRISMA 2009 Checklist

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
RESULTS			
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
DISCUSSION			
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

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	19
FUNDING			
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

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