PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Chartres, Nicholas; Fabbri, Alice; McDonald, Sally; Diong, Joanna; McKenzie, Joanne; Bero, Lisa

VERSION 1 – REVIEW

REVIEWER	jocelyne Benatar Auckland district health bard Auckland New Zealand
REVIEW RETURNED	13-Apr-2020

GENERAL COMMENTS	This was a well thought out study and very well presented.

REVIEWER	Arrigo Cicero University of Bologna, Italy
REVIEW RETURNED	05-May-2020

GENERAL COMMENTS	I've read with attention the paper of Chartres et al. that is potentially of interest. The background and aim of the study have been clearly defined. The methodology applied is overall correct, the results are reliable and adequately discussed. The author should only add a funnel plot for the main outcome.

REVIEWER	Rosa Sicari Institute of Clinical Physiology, Pisa, Italy
REVIEW RETURNED	21-May-2020

GENERAL COMMENTS	This is a well conducted meta-analysis clearly demonstrating that food sponsored research is biased. The statistical analysis is state of the art and the potential bias/flaws and limitations come from the studies accrued (lack of critical information in many instances). What Authors do not say and may be expanded is that nutrition studies are, in most cases, poorly designed .

REVIEWER	Jean-Philippe Drouin-Chartier Université Laval, Canada I received speaker and consulting honoraria from the Dairy Farmers of Canada in 2016 and 2018.
REVIEW RETURNED	30-May-2020

GENERAL COMMENTS	The paper by Nicolas Chartres and coll. is of great interest.

	Strengths of the paper include a comprehensive assessment of different aspects where COI could have an influence (risk of bias, effect size, concordance of conclusion vs results). Even though it is a very important subject, I question the overall research question of the paper. In nutritional epidemiology, most (if not all) data come from prospective cohort studies that were initiated years ago (e.g. the Nurses Health Studies, the EPIC, PURE, etc.). When initiated, these studies had no link with dairy industry. The design of these studies could not be influenced by industry. This element is crucial in nutritional epidemiology compared with dietary RCTs where the study sponsor truly can have an influence on the design that would favor their products. Whether the authors considered this important element is not clear in the paper. That being said, authors clearly explain where study sponsor could have an influence: risk of bias, which would impact effect size, and the concordance of the conclusion vs the results. With regard to risk of bias, authors used the ROBINS scale and found that all studies were at a high risk of bias. This finding is first surprising as it differs with other meta-analyses on dairy products that also assessed the ROB of included studies. There is usually some low ROB studies, and some with high ROB reported. This raises questions on the validity of the ROBINS scale to conduct such exercise. Could the use of the Newcastle Ottawa scale have been more useful to discriminate ROB between study vs ROBINS? It would be worth testing it as the ROB assessment is a crucial part of the methods of the current study. The importance of confounders and adjustment in analyses of included studies also needs more careful attention that goes far beyond adjusting for fruits and vegetables. To that extent, the NOS appears more informative than ROBINS as it allows to evaluate how primary confounders (e.g. age, sex, BMI, smoking status, energy intake, alcohol consumption, etc.) and secondary confounders (e.g. fruits and vegetables, etc.) were adjusted for. Also, the complexity of the relationship between dairy product consumption and cardiometabolic health is intrinsically related to the heterogeneity of dairy foods in terms of bioactive components, fat subtypes content, fermentation status, and food matrices. Thereby, authors should consider being more precise in terms of exposure and outcomes. For instance, meta-analyses of prospective cohort studies reported that total dairy consumption is not associated with CHD risk, but with a lower risk of stroke (Drouin-Chartier Adv Nutr 2016). There are also differences between dairy foods vs CHD/Stroke/total CVD risks. With the current approaches, it is very likely that authors may have missed some evidence of sponsor/COI bias as they used gross categorization of either exposure or outcomes. With finer categorizations and analyses, authors may have different results, in line with their hypothesis. Finer categorizations would also need finer assessment of confounders. Again I would recommend conducting such sensitivity analyses. Overall, it is a very interesting and relevant analysis. However, since there is no clear methods on how to evaluate the potential influence of sponsors/COIs on study results in nutritional epidemiology, I would recommend authors to conduct additional sensitivity analyses as listed above to provide a more in-depth analysis of the literature. Minor: Since the work evaluates observational studies, the use of causative language should be avoided throughout the paper (e.g. replace “effects of dairy…” by “association between dairy and …”.

REVIEWER	Charlotte Evans University of Leeds, UK

REVIEW RETURNED	05-Aug-2020

GENERAL COMMENTS	This is a well written manuscript on the effect of industry ties on the results reported on the relationship between dairy and CVD. I have no comments on the introduction, methods or results but feel the discussion lacks depth. More is needed on the future role of industry in funding public health research. should we not accept any funding from industry for studies published in scientific journals? or should we improve the reporting of COI and role of funder in the research even further than is currently the case? My view is that bias can come from many sources including scientists in universities (like myself) or charities keen to identify the diet related causes of disease so the design of experiments and reporting must be robust enough to deter against bias from any source. Should all meta-analyses of reviews provide effect estimates for studies with and without industry ties? as you mentioned, food industry ties are heterogeneous. Larger food companies that are involved in many different categories of food may be more light touch than smaller companies only producing one product type. Funding that is more arms-length from companies such as DRINC in the UK is another option for researching areas where funding is scarce and means scientists not dealing directly with industry - would this be a recommendation? if public funding was higher it may be possible to do without industry funding but that seems unlikely, at least in the near future. Selective reporting is a big issue with tobacco and soft drinks companies - funding a lot but only publishing what supports the agenda. however selective reporting didn't seem to be an issue here - could you comment on that? In summary, I would like to see a little more discussion of the difficulties of relying on industry funding and future recommendations on how to deal with this. minor comments line 60 last limitation we did not analyse low and high fat dairy separately or other products. ...may have different effects on studies of low or full fat dairy foods or other foods and drinks.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name
jocelyne benatar

Institution and Country
Auckland district health bard
Auckland
New Zealand

Please state any competing interests or state ‘None declared’:
none declared

Please leave your comments for the authors below
Comment: This was a well thought out study and very well presented
Response: We thank the reviewer for their comments

Reviewer: 2
Reviewer Name
Arrigo Cicero

Institution and Country
University of Bologna, Italy

Please state any competing interests or state ‘None declared’:
None declared

Comment: Please leave your comments for the authors below
I’ve read with attention the paper of Chartres et al. that is potentially of interest. The background and aim of the study have been clearly defined. The methodology applied is overall correct, the results are reliable and adequately discussed. The author should only add a funnel plot for the main outcome.

Response: We thank the reviewer for their comments.
While we agree with the review author that funnel plots and the tests used for examining funnel plot asymmetry could be used to assess the effect of publication bias (i.e., non-reporting of entire studies) in meta-analyses that examine the effect of an intervention on a clinical outcome, our study did not aim to assess the effect of dairy foods intake on cardiovascular disease and mortality (as outlined in our pre-registered protocol in Prospero (see L 55 & L 120). Our aim was to determine if the association of dairy foods on cardiovascular disease outcomes differ between published studies with food industry ties versus those without industry ties. Thus, assessing the potential impact of unpublished studies is not relevant.
Further, the Cochrane Collaboration who are global leaders in systematic review methods recommend that it is more valuable to conduct a thorough assessment of selective non-reporting or under-reporting of results in the studies included in a review rather than evaluate non-reporting of entire studies. This is due to the fact that because the number of studies identified in a review that have results missing for a specific analysis is known, the impact of this selective non-reporting or under reporting of results is far easier to quantify than estimating selective non-publication of an unknown number of studies. The ROBINS-E tool that we used to assess the risk of bias of the included studies within this review evaluates selective non-reporting in the domain “selection of the reported results”. We therefore feel that we have adequately assessed this bias.
Page MJ, Higgins JPT, Sterne JAC. Chapter 13: Assessing risk of bias due to missing results in a synthesis. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

Reviewer: 3
Reviewer Name
Rosa Sicari

Institution and Country
Institute of Clinical Physiology, Pisa, Italy

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
This is a well conducted meta-analysis clearly demonstrating that food sponsored research is biased. The statistical analysis is state of the art and the potential bias/flaws and limitations come from the

studies accrued (lack of critical information in many instances). What Authors do not say and may be expanded is that nutrition studies are, in most cases, poorly designed
Response: We thank the reviewer for their comments.
The consistent overall high (serious or critical) risk of bias that we identified in every study was due to the design of the risk of bias tool that we used in our review. As highlighted in our manuscript in L 192 "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." Most studies were assessed as having a critical risk of bias rating for the domain 'Bias due to confounding', thus leading to the overall high risk of bias rating. The limitations of this tool and its use of an overall risk of bias rating that does not discriminate between studies with one or several risks of bias has been discussed extensively elsewhere.
Bero, L., N. Chartres, J. Diong, A. Fabbri, D. Ghersi, J. Lam, A. Lau, S. McDonald, B. Mintzes, P. Sutton, J. L. Turton and T. J. Woodruff (2018). "The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures." Syst Rev 7(1): 242.
However, across the other domains the studies included in this review were rated consistently as low to moderate risk of bias (see Figure 2 and Supplementary File 6, L 357). While we appreciate the reviewer's suggestion, we do not feel that the result of our risk of bias assessment across the other domains allows us to make such conclusions about the design of nutrition studies overall.

Reviewer: 4
Reviewer Name
Jean-Philippe Drouin-Chartier

Institution and Country
Université Laval, Canada

Please state any competing interests or state 'None declared':
I received speaker and consulting honoraria from the Dairy Farmers of Canada in 2016 and 2018.

Please leave your comments for the authors below
Comment: The paper by Nicolas Chartres and coll. is of great interest. Strengths of the paper include a comprehensive assessment of different aspects where COI could have an influence (risk of bias, effect size, concordance of conclusion vs results).
Response: We thank the reviewer for their comments.
Comment: Even though it is a very important subject, I question the overall research question of the paper. In nutritional epidemiology, most (if not all) data come from prospective cohort studies that were initiated years ago (e.g. the Nurses Health Studies, the EPIC, PURE, etc.). When initiated, these studies had no link with dairy industry. The design of these studies could not be influenced by industry. This element is crucial in nutritional epidemiology compared with dietary RCTs where the study sponsor truly can have an influence on the design that would favor their products. Whether the authors considered this important element is not clear in the paper.
Response: Our main comparison is studies with industry ties vs. studies without industry ties. Thus, the older studies that are not industry sponsored that are mentioned by this reviewer are included in the sample of studies with no industry ties. We agree with the review author's comments that we did not see a difference in the risk of bias in the study designs between studies with industry ties (industry sponsorship and/or COI) and those without (no industry sponsorship and/or no COI) as reported in L 343 of the results. We highlight in L 489 of the discussion that this lack of difference in the risks of bias between studies with industry ties and those with no industry ties is consistent with other areas of research including nutrition, pharmaceutical and tobacco research. Therefore, as we discuss in L 512, another mechanism must be at play "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, as well as framing how the questions are asked."
Comment: That being said, authors clearly explain where study sponsor could have an influence: risk of bias, which would impact effect size, and the concordance of the conclusion vs the results.
With regard to risk of bias, authors used the ROBINS scale and found that all studies were at a high risk of bias. This finding is first surprising as it differs with other meta-analyses on dairy products that also assessed the ROB of included studies. There is usually some low ROB studies, and some with high ROB reported.
Response: We agree with the reviewer that this does appear surprising. As we highlighted in our response to Reviewer 3, the consistent overall high (serious or critical) risk of bias that we identified in these studies was due to the design of the tool we used to assess the risk of bias of each study. For example, if a study was rated as being at a 'critical' risk of bias in one domain, the overall risk of bias rating was 'critical'. Therefore, most studies were assessed as having a critical risk of bias rating for the domain 'Bias due to confounding'. The limitations of this tool and how it fails to discriminate between studies with one or several risks of bias has been discussed extensively elsewhere.
Bero, L., N. Chartres, J. Diong, A. Fabbri, D. Ghersi, J. Lam, A. Lau, S. McDonald, B. Mintzes, P. Sutton, J. L. Turton and T. J. Woodruff (2018). "The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures." Syst Rev 7(1): 242.

Comment: This raises questions on the validity of the ROBINS scale to conduct such exercise. Could the use of the Newcastle Ottawa scale have been more useful to discriminate ROB between study vs ROBINS?
Response: We selected this tool as it was adapted from the Cochrane ROBINS-I tool. ROBINS-I is the preferred tool used in Cochrane Reviews and is recommended in the Cochrane Handbook for non-randomized studies of interventions. We therefore felt that this was the most appropriate tool to use in our review.
Comment: It would be worth testing it as the ROB assessment is a crucial part of the methods of the current study.
Response: We have compared risk of bias tools for observational studies in a previous systematic review (see https://www.sciencedirect.com/science/article/pii/S016041202031761X?via%3Dihub). Many tools are available and there are advantages and disadvantages of each and, as noted above, we believe the ROBINS-E was the best tool for our study.

It is important to note that in addition to the overall risk of bias rating calculated with the ROBINS-I tool we also report the risks of bias across each domain for those studies with and without industry ties in L 351. This gives a more comprehensive understanding of the risk of bias in a group of studies, rather than just focusing on the overall risk. 'Bias in classification of exposures' was the only domain in which there was any difference between studies, with studies without industry ties or without an author with a COI more likely to have a serious or critical risk of bias rating versus those with industry ties or with an author with a COI. For all other domains, the risk of bias classifications were similarly distributed across studies with industry ties, industry sponsorship or COI versus studies with no industry ties, industry sponsorship or COI, respectively. These findings are reported in Supplementary file 6 (L357).

Comment: The importance of confounders and adjustment in analyses of included studies also needs more careful attention that goes far beyond adjusting for fruits and vegetables. To that extent, the NOS appears more informative than ROBINS as it allows to evaluate how primary confounders (e.g. age, sex, BMI, smoking status, energy intake, alcohol consumption, etc.) and secondary confounders (e.g. fruits and vegetables, etc.) were adjusted for.
Response: We agree with the reviewer's comments that confounders and adjustment in analyses of included studies goes far beyond adjusting for fruits and vegetables, which we mentioned as an example. 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. To clarify this point in the manuscript we have now edited this in L 188 to read “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)” and in sentence in L 345 to read, “An example of one of the serval confounders we identified that studies needed to control for was fruit and vegetable intake.”

Comment: Also, the complexity of the relationship between dairy product consumption and cardiometabolic health is intrinsically related to the heterogeneity of dairy foods in terms of bioactive components, fat subtypes content, fermentation status, and food matrices. Thereby, authors should consider being more precise in terms of exposure and outcomes. For instance, meta-analyses of prospective cohort studies reported that total dairy consumption is not associated with CHD risk, but with a lower risk of stroke (Drouin-Chartier Adv Nutr 2016). There are also differences between dairy foods vs CHD/Stroke/total CVD risks. With the current approaches, it is very likely that authors may have missed some evidence of sponsor/COI bias as they used gross categorization of either exposure or outcomes. With finer categorizations and analyses, authors may have different results, in line with their hypothesis. Finer categorizations would also need finer assessment of confounders. Again I would recommend conducting such sensitivity analyses.
Response: We cite the review the author highlights by Drouin-Chartier Adv Nutr 2016 in L 79 in the introduction where we discuss that there is conflicting evidence found in recent systematic reviews and meta-analyses on the association of dairy foods and several clinical outcomes of CVD, and the recommendations made in various dietary guidelines (L 76-84). Therefore, we were interested in establishing if the conflicting evidence and recommendations for the exposure of “Dairy” and clinical outcomes of CVD, was due to bias introduced by the presence of industry funding or authors with a COI with the food industry. We feel that this exposure and these outcomes were therefore appropriate to use for this current study. Further, we identified that these were the exposure and outcomes that were used in the development of the recommendations made for dairy consumption and CVD in the 2013 Australian Dietary Guidelines. We think a future study assessing finer categorizations and analyses as recommended by the reviewer would be very interesting, however, it is beyond the scope of this current review and would likely have to wait until more studies were conducted in order to achieve and adequate sample size.
National Health and Medical Research Council. A Review of the Evidence to Address Targeted Questions to Inform the Revision of the Australian Dietary Guidelines 2011. 2011. https://www.eatforhealth.gov.au/sites/default/files/content/The%20Guidelines/n55d_dietary_guidelines_evidence_report_2011.pdf

Comment: Overall, it is a very interesting and relevant analysis. However, since there is no clear methods on how to evaluate the potential influence of sponsors/COIs on study results in nutritional epidemiology, I would recommend authors to conduct additional sensitivity analyses as listed above to provide a more in-depth analysis of the literature.
Response: We again appreciate the reviewer’s comments. However, the methods that have been used to evaluate the potential influence of sponsors/COIs on study results in nutritional epidemiology have previously been used in a similar peer reviewed study that assessed the association of industry ties with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality.
Chartres, N., A. Fabbri, S. McDonald, J. Turton, M. Allman-Farinelli, J. McKenzie and L. Bero (2019). "Association of industry ties with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality: systematic review and meta-analysis." BMJ Open 9(5): e022912

We therefore feel that the current analysis is appropriate. Furthermore, such meta-research methods have been used to study funding bias across a wide variety of fields, including tobacco, pharmaceuticals, and chemicals. Again, we think a future study as recommended by the reviewer would be very interesting.

Comment: Minor: Since the work evaluates observational studies, the use of causative language should be avoided throughout the paper (e.g. replace “effects of dairy…” by “association between dairy and …”.

Response: We have changed “effects” to “association” throughout the paper in L 21, 64, 96, 107, 436

Reviewer: 5
Reviewer Name
Charlotte Evans

Institution and Country
University of Leeds, UK

Please state any competing interests or state ‘None declared’:
none

Please leave your comments for the authors below
Comment: This is a well written manuscript on the effect of industry ties on the results reported on the relationship between dairy and CVD. I have no comments on the introduction, methods or results but feel the discussion lacks depth.
Response: We appreciate the reviewer’s comments.
Comment: More is needed on the future role of industry in funding public health research. should we not accept any funding from industry for studies published in scientific journals? or should we improve the reporting of COI and role of funder in the research even further than is currently the case?
Response: This study has demonstrated that there appears to be 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. This would again suggest that there is sufficient funding from non-industry sources in nutrition research for investigators to apply for and use to fund their research, without needing to rely on food industry funding. We have now included a paragraph to reflect this recommendation in L527.
Chartres, N., A. Fabbri, S. McDonald, J. Turton, M. Allman-Farinelli, J. McKenzie and L. Bero (2019). "Association of industry ties with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality: systematic review and meta-analysis." BMJ Open 9(5): e022912
In the current study, out of 43 studies, all but one study contained a funding disclosure statement and six studies did not contain an author COI disclosure statement. We therefore did not discuss the implications a lack of COI disclosure or the role of the funder has in nutrition research. However, the aforementioned study Chartres et al. 2019, examining the association of industry ties with outcomes of studies examining the effect of wholegrain foods on CVD and mortality found that almost half of the included studies were missing author COI disclosures and discussed the possible implications.
A critical step in quantifying the influence of industry sponsorship on nutrition research (or any research) is being able to identify who the sponsors of the research are and whether the study authors have a conflict of interest with the food industry. Journals that publish nutrition research

should be responsible for the implementation of policies on disclosure and they should ensure funding sources and COI is disclosed in every study. In biomedical research, a recent analysis estimating prevalence of COI disclosure in journals conforming to the International Committee of Medical Journal Editors (ICMJE) policies found that only 22.9% of articles conformed to ICMJE disclosure standards and included a conflict of interest disclosure. A systematic analysis of nutrition journals is also needed.

Grundy Q, Dunn AG, Bourgeois FT, Coiera E, Bero L. Prevalence of disclosed conflicts of interest in biomedical research and associations with journal impact factors and altmetric scores. JAMA. 2018;319(4):408-409.

The policies the Cochrane Collaboration implement on funding and author COI are a standard that all nutrition journals could consider. It has been demonstrated that Cochrane's policy regarding the funding of systematic reviews or primary research are stricter than 11 other major medical journals. Cochrane Reviews cannot be commissioned or funded by any commercial sponsor that has a vested interest in the reviews.

Bero L. Lisa Bero: More journals should have conflict of interest policies as strict as Cochrane. 2018; https://blogs.bmj.com/bmj/2018/11/12/lisa-bero-more-journals-shouldhave-conflict-of-interest-policies-as-strict-as-cochrane/.

For author COI, other than a requirement for disclosure, few journals have restrictions. Cochrane again has the strongest policy, with all authors of Cochrane reviews required to disclose all COI according to ICMJE recommendations before publishing a protocol, review or update. Cochrane also requires that there must be a majority of authors that do not have a COI for any review and that the first author must have no COI. Such policies should be modeled in all nutrition journals.

However, failing to comply with disclosure policies is seen across multiple research areas, not just in nutrition and a number of groups including the US Institute of Medicine (IOM), the Collegium Ramazzini and the ICMJE, have all highlighted the need for increased transparency relating to COI policies.

Drazen JM, de Leeuw PW, Laine C, et al. Toward more uniform conflict disclosures--the updated ICMJE reporting form for disclosure of potential conflicts of interest. Rev Med Chil. 2010;138(7):801-803. 10.

Ramazzini. C. 7th Collegium Ramazzini Statement: Most Types of Cancer Are Not Due to Bad Luck. Available: 2015;

http://www.collegiumramazzini.org/download/17_SeventeenthCRStatement%282015%29.p df. 11.

Lo B, Field MJ. Conflict of interest in medical research, education, and practice. 2009.

Therefore, other mechanisms to identify undisclosed COI's could be used. For example, searching transparency databases of industry payments to health professionals or previously published manuscripts of the authors could identify undisclosed ties. In the United States, the Open Payments database mandated by the US Sunshine Act requires all pharmaceutical companies to report payments to US based physicians, with other countries now implementing similar databases to manage data on the disclosure of investigator COI in clinical research. A similar system to the global enactment of pharmaceutical industry transparency databases would allow the identification of undisclosed financial ties of health professionals and researchers to food companies.

Glass HE. Open Payments and the US Clinical Landscape. Therapeutic Innovation & Regulatory Science.0(0):2168479019837526

Parker L, Karanges E, and Bero L. Changes in the type and amount of spending disclosed by Australian pharmaceutical companies: an observational study. BMJ Open 2018;0:e024928. doi:10.1136/ bmjopen-2018-024928

Fabbri A, Santos A, Mezinska S, Mulinari S, Mintzes B. Sunshine Policies and Murky Shadows in Europe: Disclosure of Pharmaceutical Industry Payments to Health Professionals in Nine European Countries. Int J Health Policy Manag. 2018;7(6):504-509. Published 2018 Jun 1. doi:10.15171/ijhpm.2018.20

Finally, as all but one study contained a funding disclosure, and there was a statistically significant difference in the magnitude of effects identified in industry-sponsored studies compared to non-

industry sponsored studies, this risk of bias must be accounted for when evaluating and synthesizing a body of evidence, even when studies disclose their funding source and the authors disclose their COIs. Therefore, we have now included this recommendation in L 503-506 that “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.”

Comment: My view is that bias can come from many sources including scientists in universities (like myself) or charities keen to identify the diet related causes of disease so the design of experiments and reporting must be robust enough to deter against bias from any source.
Response: We appreciate the reviewers view on this topic. However, as noted in the previous response to the reviewer’s comments and as we have highlighted in the manuscript, there is empirical evidence across various areas of research that studies sponsored by industry are more likely to have results that favor the sponsor than studies with other sources. As we highlight in the present study in L 489 , this association is present even when accounting for methodological quality of the study as industry sponsored studies have been shown to be of equal or better internal validity than studies with no sponsorship. Therefore, even the most rigorous and well-conducted studies can still be biased by industry influence through additional mechanisms, including “the selective reporting of results, how they code events, analyse data, by spinning conclusions, as well as framing how the questions are asked” (L 512-514).
We agree with the reviewer that additional types of bias are worthy of investigation, including some we have examined such as bias in research agendas or nonfinancial interests.
Fabbri A, Lai A, Grundy Q, Bero L. The influence of industry sponsorship on the research agenda: a scoping review. Am J Public Health 2018: e1-e8. doi:10.2105/AJPH.2018.304677
Grundy Q, Mayes C, Holloway K, Mazzarello S, Thombs B, Bero L. Conflict of interest as ethical shorthand: understanding the range and nature of “non-financial conflict of interest” in biomedicine. J Clin Epidemiol 2020; 120: 1-7. https://doi.org/10.1016/j.jclinepi.2019.12.014

Comment: as you mentioned, food industry ties are heterogeneous. Larger food companies that are involved in many different categories of food may be more light touch than smaller companies only producing one product type. Funding that is more arms-length from companies such as DRINC in the UK is another option for researching areas where funding is scarce and means scientists not dealing directly with industry - would this be a recommendation? if public funding was higher it may be possible to do without industry funding but that seems unlikely, at least in the near future. Selective reporting is a big issue with tobacco and soft drinks companies - funding a lot but only publishing what supports the agenda. however selective reporting didn't seem to be an issue here - could you comment on that?

Response: As we noted in the first paragraph of our discussion,“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, 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” (L436). Unfortunately, we did not enough studies with one single sponsor to analyze differences by type of food industry sponsor.

As we highlighted in our first response to the reviewer, our current study, and a similar recent study has in fact showed that there is sufficient funding that comes from non-industry sources, including academia and government. In this study, only eight studies had a food industry funding sources, while 34 had a non-food industry-funding source.
Chartres, N., A. Fabbri, S. McDonald, J. Turton, M. Allman-Farinelli, J. McKenzie and L. Bero (2019).

"Association of industry ties with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality: systematic review and meta-analysis." BMJ Open 9(5): e022912
Further research is needed to determine the extent of selective reporting in nutrition studies. In tobacco and pharmaceutical studies, selective reporting has been detected by comparing the outcomes in published studies to 1) internal industry documents, 2) ethics protocols, 3) trial registrations, 4) regulatory documents, and 5) published protocols. However, these data sources are largely lacking for nutrition studies. Failure to publish studies in their entirety may skew the available data used in developing dietary guidelines. Therefore, these biases could be minimized, as a start, with the introduction of nutrition study registries and requirements to publish protocols.
Glass HE. Open Payments and the US Clinical Landscape. Therapeutic Innovation & Regulatory Science.0(0):2168479019837526
Dickersin K, Rennie D. The evolution of trial registries and their use to assess the clinical trial enterprise. Jama. 2012;307(17):1861-1864.
Misakian AL, Bero LA. Publication bias and research on passive smoking: comparison of published and unpublished studies. Jama. 1998;280(3):250-253.
In summary, I would like to see a little more discussion of the difficulties of relying on industry funding and future recommendations on how to deal with this.
Response: We have highlighted in this paper, in L 90, that across several fields, including nutrition research, it has been demonstrated that studies sponsored by industry are more likely to have results that favour the study sponsor than studies with other sources of sponsorship. Therefore, industry sponsorship is a risk of bias to the validity of the study results. Therefore, if researchers continue to use industry funding, it must be accounted for when evaluating and synthesizing a body of evidence: “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” (L 501-505). As stated in the previous response to the reviewer, our current study, and a similar recent study has in fact showed that there is sufficient funding that comes from non-industry sources, including academia and government. We have now included a paragraph to reflect this recommendation in L527. Although we could speculate on the difficulties of relying on industry funding, we feel this goes beyond our findings.

minor comments
line 60 last limitation we did not analyse low and high fat dairy separately or other products. ...may have different effects on studies of low or full fat dairy foods or other foods and drinks.

Response: We have now included the suggested text from the reviewer in L 468-70.

VERSION 2 – REVIEW

REVIEWER	Jean-Philippe Drouin-Chartier Université Laval, Canada I received speaker and consulting honoraria from the Dairy Farmers of Canada in 2016 and 2018.
REVIEW RETURNED	28-Sep-2020

GENERAL COMMENTS	The authors adequately addressed comments raised in the first round of review. There is, however, one element that still requires attention. The complexity of the relationship between dairy product consumption and cardiometabolic health is intrinsically related to the heterogeneity of dairy foods in terms of bioactive components, fat

	subtypes content, fermentation status, and food matrices. For instance, meta-analyses of prospective cohort studies reported that total dairy consumption is not associated with CHD risk, but with a lower risk of stroke. There are also differences between specific dairy foods with regard to the risks of specific CVD outcomes. Therefore, categorizing exposures and outcomes in a uniform manner is at the root of adequately addressing the relationship between dairy intake and cardiovascular health in meta-analyses. Failing to do so is likely to create discordant results and/or spurious associations, leading to further confusion in the field. With the current approaches, where authors pooled dairy and CVD outcomes, it is very likely that authors may have missed some evidence of sponsor/COI bias as they used gross categorization of either exposure or outcomes. With finer categorizations and analyses, authors may have had different results, in line with their hypothesis. I suggested authors to consider being more precise in terms of exposure and outcome definitions in the first round of review. Authors did not move forward with my recommendation as they considered this beyond the scope of their review. While I respect their decision, a statement in the discussion, mainly as a limitation of the study, appears critical in the current context, especially since one of the hypothesized mechanisms is potential alterations in events/exposures coding.

REVIEWER	Charlotte Evans University of Leeds, UK
REVIEW RETURNED	24-Sep-2020

GENERAL COMMENTS	I am satisfied that the suggestions put forward by the reviewers have been addressed fully.

VERSION 2 – AUTHOR RESPONSE

Reviewer 5

Comment: I am satisfied that the suggestions put forward by the reviewers have been addressed fully.

Response: We thank the reviewer for their comments.

Reviewer 4

Comment: The authors adequately addressed comments raised in the first round of review. There is, however, one element that still requires attention. The complexity of the relationship between dairy product consumption and cardiometabolic health is intrinsically related to the heterogeneity of dairy foods in terms of bioactive components, fat subtypes content, fermentation status, and food matrices. For instance, meta-analyses of prospective cohort studies reported that total dairy consumption is not associated with CHD risk, but with a lower risk of stroke. There are also differences between specific dairy foods with regard to the risks of specific CVD outcomes. Therefore, categorizing exposures and outcomes in a uniform manner is at the root of adequately addressing the relationship between dairy intake and cardiovascular health in meta-analyses. Failing to do so is likely to create discordant results and/or spurious associations, leading to further confusion in the field. With the current approaches, where authors pooled dairy and CVD outcomes, it is very likely that authors may have

missed some evidence of sponsor/COI bias as they used gross categorization of either exposure or outcomes. With finer categorizations and analyses, authors may have had different results, in line with their hypothesis. I suggested authors to consider being more precise in terms of exposure and outcome definitions in the first round of review. Authors did not move forward with my recommendation as they considered this beyond the scope of their review. While I respect their decision, a statement in the discussion, mainly as a limitation of the study, appears critical in the current context, especially since one of the hypothesized mechanisms is potential alterations in events/exposures coding.

Response: Based on the reviewer's comments, we have now included the possibility that future studies, using additional data and finer categorizations, may have different results.
"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." (L470)

VERSION 3 – REVIEW

REVIEWER	Jean-Philippe Drouin-Chartier Université Laval, Canada JPDC received speaker and consulting honoraria from the Dairy Farmers of Canada in 2016 and 2018, outside the current work.
REVIEW RETURNED	14-Oct-2020

GENERAL COMMENTS	No more comment. Thank you.