Reducing Bias in Public Health Guidelines

Nicholas Chartres

A thesis submitted to fulfil requirements for the degree of DOCTOR OF PHILOSOPHY

School of Pharmacy, Faculty of Medicine and Health,

The University of Sydney

Statement of Originality

I Nicholas Chartres, declare that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Nicholas Chartres Date: 07/06/2019

Reducing Bias in Public Health Guidelines

Abstract

Background and Objectives

Bias in research and the methods used for developing public health guidelines may put the public's health at risk. This dissertation explores three possible sources of influence on the recommendations made in public health guidelines:

- *Commercial Influences on Nutrition Research:* Primary research studies and systematic reviews form the evidence base for dietary guidelines. The association between funding sources and the outcomes of nutrition studies was therefore explored;
- *Methods Used for Public Health Guideline Development*: Heterogenous methodologies used in the development of public health guidelines may lead to conflicting recommendations. I conducted a systematic analysis of the methods used in their development;
- S*ocial Influences on Public Health Guideline Development:* The interactions within guideline groups may be a significant influence on the final recommendations made. I aimed to understand the experiences of the participants involved in developing public health guidelines.

Methods

My methods included: 1) Meta-analysis and systematic review to measure bias in primary nutrition research; 2) Content analysis to understand the methods used in synthesising evidence for public health guidance development; and 3) Qualitative analysis of interviews to understand social influences on guideline development.

Results

My major findings were: I found an association with industry sponsorship with the outcomes of studies, even when controlling for the internal validity between the studies; I established heterogenous methodologies are being used by organisations that conduct hazard identification and risk assessment; and I identified that the public health guideline process in Australia is a divided one.

Conclusions

Through greater transparency of funding practices, the development of nutrition study registries and improvements in risk of bias tools used to evaluate the evidence, industry influence on the outcomes of nutrition studies relevant to dietary guidelines can be accounted for. Further, the use of standardised, transparent methodological processes and collaboration between systematic review teams and guideline groups will lead to increased comparability and validity of guidelines and ensure that the recommendations made from them will protect the public's health.

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v. Associations between industry involvement and study characteristics at the time of trial registration in medical research

List of publications

First author publications relating to this Thesis

Published Manuscripts

- **Chartres N**, Fabbri A, Bero LA. Association of Industry Sponsorship with Outcomes of Nutrition Studies: A Systematic Review and Meta-analysis. *JAMA Internal Medicine*. 2016;176(12):1769-77.
- **Chartres N**, Bero LA, Norris SL. A review of methods used for hazard identification and risk assessment of environmental hazards. *Environ Int.* 2019;123:231-239.
- **Chartres N,** Fabbri A, McDonald S, et al. 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.* 2019;9(5):e022912.

Submitted Manuscripts

- **Chartres N**, McDonald S, Turton J, Allman-Farinelli M, Mckenzie JR, Bero LA. The association of industry sponsorship with findings of randomised controlled trials examining the effect of wholegrain foods on cardiovascular disease outcomes: Systematic review and Meta-analysis. (under review)
- **Chartres N**, Fabbri A, McDonald S, Diong J, Mckenzie JR, Bero LA. 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. (under review)
- **Chartres N**, Grundy Q, Parker L, Bero L. "It's not smooth sailing": Bridging the gap between methods and content expertise in public health guideline development. (under review)

Additional publications related to the work presented in this Thesis[1]

Published Manuscripts

- Fabbri A, **Chartres N**, Scrinis G, Bero LA. Study sponsorship and the nutrition research agenda: analysis of randomized controlled trials included in systematic reviews of nutrition interventions to address obesity. *Public health nutrition.* 2017;20(7):1306-1313.
- Fabbri A, **Chartres N**, Bero LA. Study sponsorship and the nutrition research agenda: analysis of cohort studies examining the association between nutrition and obesity. *Public health nutrition.* 2017;20(17):3193-3199.
- de Rezende LFM, Rey-Lopez JP, de Sa TH, **Chartres N**, Fabbri A, Powell L, Stamatakis E, Bero L. Reporting bias in the literature on the associations of health-related behaviors and statins with cardiovascular disease and all-cause mortality. *PLoS biology.* 2018;16(6):e2005761.
- Bero L, **Chartres N**, Diong J, et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. *Syst Rev.* 2018;7(1):242.

Submitted Manuscripts

- Seidler LA, Hunter K, **Chartres N**, Askie L. Associations between industry involvement and study characteristics at the time of trial registration in medical research. (under review)

[1] These publications are listed in the Appendix as the PhD candidate is not the lead author but has contributed to these studies as a co-author.

Authorship Attribution Statement

Chapter One of this Thesis includes the publications:

i. Association of industry sponsorship with outcomes of nutrition studies: A Systematic Review and Meta-analysis

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

iii. The association of industry sponsorship with findings of randomised controlled trials examining the effect of wholegrain foods on cardiovascular disease outcomes: Systematic review and Meta-analysis

iv. The association of industry ties with outcomes of studies examining the effect of dairy foods intake with cardiovascular disease and mortality: Systematic review and Meta-analysis

For each study I designed and wrote the protocol, wrote the search strategy, undertook the literature search, screened the title and abstracts for inclusion, extracted the data, undertook data analysis and wrote the drafts of the manuscript.

Chapter Two of this Thesis includes the publication:

i. A Review of Methods Used for Hazard Identification and Risk Assessment of Environmental Hazards

For this study I designed and wrote the protocol, undertook the search for included organisations, extracted the data, undertook content analysis and wrote the drafts of the manuscript.

Chapter Three of this Thesis includes the publication:

i. "It's not smooth sailing": Bridging the gap between methods and content expertise in public health guideline development

For this study I designed and initiated the study, conducted the interviews, undertook data analysis and wrote the drafts of the manuscript.

The Appendix of this Thesis includes the publications:

i. Study Sponsorship and the Nutrition Research Agenda: Analysis of randomized controlled trials included in systematic reviews of nutrition interventions to address obesity

For this study I extracted the data, undertook data analysis and contributed to the writing of the final manuscript.

ii. Study sponsorship and the nutrition research agenda: Analysis of cohort studies examining the association between nutrition and obesity

For this study I conceived the study and designed the data collection tool, extracted the data, undertook data analysis and contributed to the writing of the final manuscript.

iii. Reporting bias in the literature on the associations of health-related behaviors and statins with cardiovascular disease and all-cause mortality

For this study I assessed the risk of bias in all included systematic reviews and contributed to the writing of the final manuscript.

iv. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures

For this study I evaluated articles using the ROBINS-E tool, provided critical revision of the manuscript and approved the final manuscript.

v. Associations between industry involvement and study characteristics at the time of trial registration in medical research

For this study I provided critical revision of the manuscript and approved the final manuscript.

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Supervisor Name: Lisa Bero

Signature: [redacted] Date: 07/06/2019

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Introduction

Synopsis

Entering the second year of my Master of Human Nutrition degree at Deakin University, I had decided to undertake a unit of research on obesity policy. I had always thought that obesity was a highly complex issue, driven primarily through poor personal choices around diet and exercise. I knew that 'junk foods', those highly processed commodities that I enjoyed on an occasional basis, weren't great for me. I had also assumed that educational resources such as dietary guidelines and the food pyramid would guide the public to make personal choices that were consistent with healthy eating. I believed that having these foods available in our food system was not such a bad thing. My then supervisor suggested a topic for my research project on 'Big Food' (otherwise known as multinational food and beverage companies with huge and concentrated market power), and the strategies they use to distract the public from the harms of their products.[1] As I soon discovered, using similar techniques from the playbook of 'Big Tobacco', 'Big Food' was just as harmful to the public's health.[1-3] One such strategy used by the food industry was the funding of research, such as on the harms of sugar sweetened beverages.[4,5] My focus as a nutritionist had now changed from educating people about how to make healthy personal choices, to understanding and combatting corporate influence on health behaviours.

Apart from the influence 'Big Food' was having on the dietary behaviours of the public, I also began to question why there appeared to be so much confusion around dietary advice when Australia had national dietary guidelines. While I had read conflicting systematic reviews on whether saturated fat was bad for my health, or whether dairy really did protect me from heart disease, I still felt confident that I could use the dietary guidelines as my main resource to offer guidance to the members of the public around what constituted a healthy diet. As a nutritionist, I had always believed without

question that the Australian Dietary Guidelines were the gold standard for dietary advice; that the guidelines were developed by the best experts in the nutrition field who had evaluated all the evidence using systematic methods and had then synthesised the results into recommendations.[6] But, why was there conflicting evidence out there, contrary to their recommendations? Why was there any confusion or debate around the recommendations made in the Dietary Guidelines? What else needed to be considered? What else could influence them? These were the questions I had often asked myself.

This dissertation has allowed me to empirically investigate both these areas of interest and concern, both as a nutritionist and public health researcher, that is; the commercial influence of the food industry on nutrition research, and the biases that are present due to the methodological challenges and limitations of developing public health guidelines, such as the dietary guidelines.

In Chapter One of this dissertation, using previously validated, rigorous methods, I have systematically evaluated the association of food industry sponsorship and authors with a conflict of interest with the food industry and the results, effect sizes, conclusions and risk of bias of primary nutrition studies that are used in the development of dietary guidelines.[7] In order to assess bias across a body of evidence it is necessary to focus on specific topics. I focus on dietary recommendations around whole grain intake and dairy intake as recommendations regarding these foods vary globally. This research will help dietary guideline committees quantify the influence these commercial funders may have on the evidence reviews as part of the guideline process and the advice offered to the public.

In Chapter Two, I study the methods used for the development of public health guidelines, as opposed to clinical practice guidelines. The methods used to develop guidelines that review observational studies of exposures, such as diet or environmental exposures, are not as well developed as methods for clinical practice guidelines.[8-12] By comparing current methods and processes that are used in the development of hazard identification and risk assessments of hazardous exposures against recommended best practice frameworks, I have identified current gaps in how evidence is evaluated and synthesised in forming these types of public health guidelines and assessments. This work will help inform organisations and agencies producing these types of guidelines and assessments on how to reduce potential biases in the development process and in forming the recommendations that are made from them.

In Chapter Three, I have sought to gain an in-depth understanding of the guideline development process. Specifically, I was interested in understanding influences other than the methodological processes that are described in guideline development handbooks. I have conducted the first empirical investigation into public health guideline development in Australia. By understanding the perspectives and opinions of the review groups responsible for evaluating and synthesising the evidence and that of the working committees that develop the guideline recommendations, I have extended previous work into how public health guidelines are developed.[13-15] These experiences help explain the social processes and influences involved in public health guideline development and suggest areas where further guidance can be developed for review teams and guideline development groups.

In Chapter Four, I have proposed solutions to the challenges that are presented in the first three chapters, specifically, recommendations to minimise these various biases in developing public health guidelines. Through improved methods to quantify these biases and greater transparency in how

evidence is produced, evaluated and finally synthesised into recommendations, policy makers, health practitioners and the public that use these guidelines will have greater confidence in the recommendations made from them.

Commercial Influences on Research

The primary interest of a corporation is to maximise its profits. Therefore, when industry funds research to either show the benefits or reduced harms of their products, a conflict of interest exists and a bias may be present.[2] Bias is "the systematic error or deviation from the true results or inferences of a study".[16] It has been empirically demonstrated in several fields (e.g. pharmaceutical, tobacco and chemical) that corporate research sponsorship and authors with a conflict of interest are associated with publishing studies with outcomes that favour the corporate interest.[17-26] These favourable outcomes result from a variety of biases in how the studies are designed, conducted or disseminated.[27]

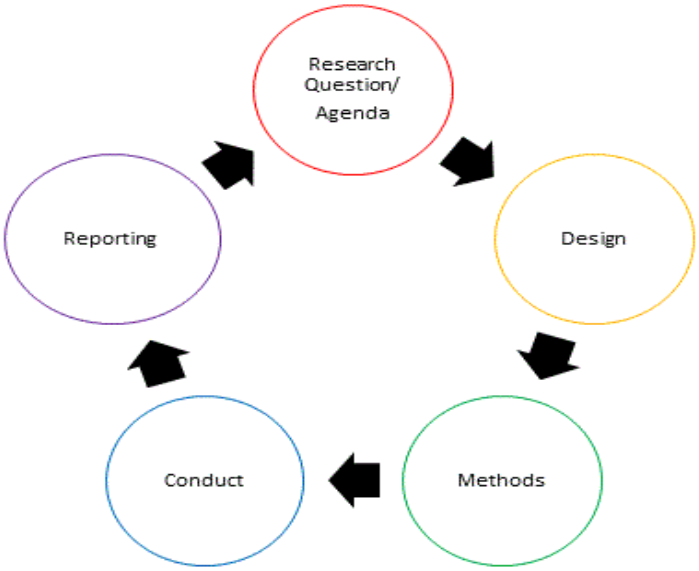
One of the largest examinations on the influence of industry sponsorship, published in 2017, investigated whether industry sponsored drug and device studies had more favourable results, conclusions, effect size, and lower risks of bias, compared with studies having other sources of sponsorship.[28] The review of more than 75 studies, including cross-sectional studies, cohort studies, systematic reviews and meta-analyses, found that industry sponsored studies more often reported favourable efficacy results and favourable conclusions. Importantly, these favourable results were demonstrated even when other methodological biases had been controlled for and the studies had similar risks of bias across several of domains.[29] This means that the studies have similar internal validity, but pose the question in different way, or only publish the favourable outcomes. Therefore,

the main factor contributing to differences in the outcomes of the studies was the presence of industry funding. A similar review of studies examining food industry influence on research outcomes had not been conducted and the first manuscript from this dissertation fills this gap (Chapter 1, 'Association of industry sponsorship with outcomes of nutrition studies: Systematic Review and Meta-analysis).

The association of studies reporting more favourable outcomes with author conflicts of interest is an area that has not been examined to the same level as industry sponsorship. While some studies have shown an association,[30-34] others have not.[35-37] One recent study that demonstrated this association assessed whether study results, conclusions and risk of bias of reviews on the effects of artificially sweetened beverage consumption and weight outcomes differed based on the review sponsors or if the authors had a financial conflict of interest.[33] Along with a high non-disclosure rate of author financial conflicts of interest statements, reviews conducted by authors with a conflict of interest with the food industry were seven times more likely to report favourable conclusions, than those with no conflict of interest with the food industry. Again, there was no difference in the risk of bias between the reviews and the major factor that could therefore influence the outcome was the presence of an author with a conflict of interest.

Bias can be introduced throughout each stage of the research process as depicted in Figure1. Corporate sponsors may bias the research process via the research agenda and the questions that they ask, the way a study is designed and conducted, and through the selective publication of the study results.[25,27,38]

Figure 1. Image adapted from: Odierna DH, Forsyth SR, White J, Bero LA. The cycle of bias in health research: a framework and toolbox for critical appraisal training. [27]



Bias in research agendas. Industry influence on the research agenda has been demonstrated across different industry sectors.[39] By funding distracting research to suggest that other components of indoor air were more harmful to health than tobacco, the tobacco industry successfully influenced and undermined the research agenda on the harms of second-hand smoke.[18,38] Recent examinations of historical internal industry documents of the cane and beet sugar industry have shown that similar tactics were employed to influence the dental research agenda on dental caries and cardiovascular disease.[40,41] The sugar industry supported research to protect itself from potentially financially damaging data on the harms of its products. An analysis of industry documents demonstrated that for over a decade during the 1960's the sugar industry attempted to influence the research agenda and focus of the National Caries Program to deflect attention away from the

harms of sugar in causing caries. Amongst other tactics, the sugar industry funded reach into a potential vaccines and enzymes that would limit the effect of dental plaque.[40] Also during the 1960's, as evidence began to emerge of the association of sucrose with cardiovascular disease, the sugar industry again attempted to shift the focus away from the harms of its products and onto saturated fats.[41]

Apart from these case studies, a systematic analysis examining the association between funding sources and the research agenda in nutrition research has not been conducted. We examined the research topics of nutrition interventions to address obesity in randomised controlled trials (see Appendix i. 'Study sponsorship and the nutrition research agenda: analysis of randomised controlled trials included in systematic reviews of nutrition interventions to address obesity')[42] and cohort studies (see Appendix ii. 'Study sponsorship and the nutrition research agenda: analysis of cohort studies examining the association between nutrition and obesity').[43]

In our first study examining randomised controlled trials, we found that industry funded trials involved the manipulation of specific nutrients and were much less likely to fund trials that address dietary behaviours, compared to non-industry funded trials.[42] Therefore, by examining narrow nutrient focused questions, and not relevant questions on dietary behaviours, the evidence available to answer important public health questions in nutrition, may be limited. In our second study that included 121 cohort studies, only approximately 8% of the studies were industry funded, despite a 95% disclosure rate of funding source.[43] While there was no significant difference in the research agenda by funding sources, the analysis was limited by the low proportion of industry funded studies. The observational studies in this sample looked at more complex exposures such as foods and dietary patterns and as demonstrated in our analysis of randomised controlled trials, industry has been shown to fund research mainly around single nutrients.

In a further investigation to assess the potential for bias in the research agenda, publications and their research topics that resulted from food industry-funded projects on human health were examined.[44] Food industry supported projects were identified from food company websites and the publications that resulted from these funded projects, identified by searching PubMed. The authors of the study found that only two companies (Coca-Cola and Mars) out of ten analysed provided sufficient detail to analyse their research projects. It was found that physical activity was the topic in over 40% of the 204 publications that resulted from 37 disclosed research projects, while approximately 22% focused on nutrients. Highly processed foods were examined in only 10% of the publications. These findings that showed the food industry is more likely to sponsor studies focusing on nutrients than foods or dietary patterns is consistent with our previous work that examined the research topics in a sample of published cohort studies on nutrition and obesity.[42,43] Further, these findings show that industry funded research can also shape the research agenda away from nutrition as a health issue and divert attention to physical activity. Although more research is needed on industry influence on the research agenda, my focus has been on examining bias in the research methods.

Bias in research methods. Methodological risks of bias can have an influence on the outcomes of intervention studies in humans.[29] These biases occur when the study design has features, such as a lack of blinding or flawed outcome assessment, that allow for a systematic error to occur in the magnitude or direction of the results. For example, in clinical trials that test the efficacy of drugs, studies that do not randomise participants, or blind those individuals responsible for conducting the outcome assessment to the interventions that participants have received, overestimate the efficacy of the drugs. Studies with these design flaws are also less likely to report statistically significant adverse effects, when compared to trials that randomise participants and blind the outcome assessors.[45,46] However, the influence of methodological biases on the effect size and direction of

study results has not been examined in nutrition research. I have conducted a series of studies to address this gap (see Chapter 1: 'Association of industry sponsorship with outcomes of nutrition studies: A Systematic Review and Meta-analysis'; 'The association of industry ties with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality: Systematic review and Meta-analysis'; 'The association of industry sponsorship with findings of randomised controlled trials examining the effect of wholegrain foods on cardiovascular disease outcomes: Systematic review and Meta-analysis'; and 'The association of industry ties with outcomes of studies examining the effect of dairy foods intake with cardiovascular disease and mortality: Systematic review and Meta-analysis').

Bias in reporting of results. Reporting bias refers to lack of publication of outcomes, while publication bias refers to lack of publication of whole studies. By not reporting statistically significant results and through the selective reporting of certain outcomes with statistically significant results, reporting bias threatens the validity of research results. Selective publication can skew the evidence available for making important decisions around health outcomes by over inflating the benefits or underestimating the harms of interventions.[47] Reporting bias has been extensively assessed for drug studies using a variety of methods, including conducting quantitative estimates of publication bias to estimate the proportion of unpublished studies or comparing trial registry entries or protocols to published studies to identify unpublished outcomes.[48] As protocols are virtually unavailable for nutrition studies, little research on reporting bias has been conducted. We conducted initial research to estimate publication bias in nutrition studies.

We assessed the risk of publication bias in the epidemiological evidence on health-related behaviours that included studies examining the association of tobacco, alcohol, diet, physical activity, and sedentary behaviour with cardiovascular disease mortality and all-cause mortality. We

compared the level of publication bias to research on a drug, statins (in primary prevention). (Appendix iii. 'Reporting bias in the literature on the associations of health-related behaviours and statins with cardiovascular disease and all-cause mortality'). We identified publication bias in approximately 20% of health-related behaviour meta-analyses according to small study effect (22%) and excess significance (24%) tests, but in none of the statin-related meta-analyses. While we also found evidence of excess significance bias in 26% of the studies on diet compared to 0% in the meta-analyses on statins. Therefore, this preliminary evidence suggests that meta-analysis of nutrition studies may provide inaccurate estimates of the preventative effects on cardiovascular disease and all-cause mortality due to the presence of publication bias.

Even when studies report unfavourable results, "spin" on conclusions may lead to the overemphasis of nonsignificant results as demonstrating an effect, or the over emphasis of secondary outcomes and the minimising of the non-significant primary outcomes.[49] A previous examination into spin in biomedical research was investigated across 35 reports in clinical trials, observational studies, diagnostic accuracy studies, systematic reviews, and meta-analyses, with the authors hypothesising that the funding source could be one factor associated with spin.[50] The findings were inconclusive however, although the authors stated that it was possibly due the heterogeneity of the included papers. Therefore, further research into this area is required. Spin in nutrition research has not yet been examined, although my research examines the concordance of research results and conclusions, with studies reporting unfavourable results with favourable conclusions (see Chapter 1: 'The association of industry ties with outcomes of studies examining the effect of wholegrain foods on cardiovascular disease and mortality: Systematic review and Meta-analysis'; 'The association of industry sponsorship with findings of randomised controlled trials examining the effect of wholegrain foods on cardiovascular disease outcomes: Systematic review and Meta-analysis'; and

'The association of industry ties with outcomes of studies examining the effect of dairy foods intake with cardiovascular disease and mortality: Systematic review and Meta-analysis').

Commercial influence in nutrition research

These previous examinations into commercial influence on pharmaceutical, tobacco and chemical research has led to important changes and strategies to counter potential biases due to corporate sponsorship. International reforms include the prospective registration of pharmaceutical trials to allow data to become more accessible, calls for greater transparency on industry funding of research and disclosure of conflicts of interest, and stricter policies on how to manage conflicts of interest.[51-53] Importantly, an examination of these corporate influences on other areas of research is relevant to nutrition research, as regardless of the exposure or intervention being studied, the same biases may exist and the methods that can be employed to reduce their impact on the results of studies are the same.[54] However, there has been little empirical study of commercial influence on nutrition research to stimulate such reforms for nutrition research or to support reforms that may be unique to nutrition.

In recent years, the influence of food industry sponsorship on nutrition research has been discussed extensively by Dr Marion Nestle[55] and there has been increasing awareness of the influence that the sugar industry has been attempting to exert on academics and their research.[56,57] Further, there have been several studies that have examined the relationship between research sponsored by the food industry and the conclusions and design features of studies compared to research sponsored by other funders.[4,5,58-60] However, these studies have only focused on 'Big Food' and when assessing the influence of the funding source, they have not controlled for other factors that may have impacted on the research outcomes, including the internal validity or risk of bias of the studies. To date there

has not been a systematic evaluation of these commercial influences across a wide range of primary nutrition studies.

Primary research studies and systematic reviews form the evidence base for dietary guidelines. Dietary guidelines not only inform health practitioners, but also the wider public and policy makers on what dietary choices are required to reduce the incidence of the ever-growing risk of diseases such as diabetes, cardiovascular disease and cancer. With increasing debate over whether the dietary guidelines may be biased,[61] coupled with concerns about bias in nutrition research, [55,62] the need to assess the evidence used in the development of dietary guidelines has never been more pressing than it is today. These concerns around the credibility of the dietary guidelines not only destabilise the confidence consumers and health practitioners have in the recommendations made in them, but it may also undermine policies to regulate the food industry such as regulation of marketing practices, taxes and the use of food labelling.[63-65] Therefore, similar rigorous assessments of the evidence for bias that have already been conducted in other areas of health, such as in drug studies, was required in nutrition research. Empirical studies of bias related to commercial sponsorship and conflicts of interest will provide information on the credibility of the primary nutrition studies that underpin the systematic reviews that are used in dietary guideline development. In sum, there had been no systematic analysis of the extent of food industry sponsorship and authors with a conflict of interest across the full spectrum of nutrition research, including the primary studies that are used in the development of dietary guidelines.

In Chapter One of this dissertation, I offer a unique contribution to the evidence on the extent of commercial influence on nutrition research by examining the risks of bias in the design and conduct of nutrition studies. The chapter assesses whether studies sponsored by the food industry or who have an author with a conflict of interest with the food industry are more likely to report favourable

results, effect sizes, conclusions or differ in their methods compared to studies with other sources of sponsorship or that have authors without a conflict of interest with the food industry. Taken together with our work on industry influence on the research agenda and reporting bias, this work will allow for a more complete understanding of commercial influence on nutrition research.

The results of this work will help improve methods used to evaluate the validity of primary nutrition studies included in systematic reviews that form the evidence base for the recommendations made in dietary guidelines. It will also help in determining if reforms to how nutrition research is designed, conducted, evaluated and funded are required.

Biases in Methods Used for Public Health Guideline Development

Corporate sponsorship and conflicts of interest within a body of evidence and conflicts of interest in the context of the committee's responsible for guideline development pose separate challenges for maintaining the integrity of a guideline. As discussed above, there is some evidence that the presence of authors with a conflict of intertest introduces biases that influence research results in favour of the study sponsor.[17,23] The management of conflicts of interest of guideline committee members, despite organisations such as the such the World Health Organization (WHO) and the National Institute for Health and Care Excellence (NICE) containing explicit policies around the management of conflict of interest of guideline development groups, remains unsatisfactory in many organisations responsible for developing guidelines.[66-69]

There are two principal types of guidelines related to health: clinical practice and public health. Clinical practice guidelines offer recommendations on how health care practitioners can optimise care for patients with specific clinical conditions.[70-72] They may provide guidance on how to prevent, diagnose, treat or offer long-term care on any aspect of a condition.[70] Public health guidelines offer recommendations to prevent specific diseases or to improve the health of a population.[70] Public health interventions may be delivered at the individual level, initiating direct and immediate change, or they may lead to changes in multi-sectoral policies, with an indirect effect on health.[73]

Public health guidelines pose specific challenges to their development that make them unique to clinical practice guidelines. Although methods for conducting systematic reviews and developing guidelines for clinical practice guideline are well established,[8,16] methods for the development of guidelines related to public health issues are still evolving.[74-76]

One of the greatest challenges of developing public health guidelines and assessments is that unlike clinical practice guidelines, the evidence supporting a public health intervention is often derived from observational studies such as cohort studies, case controls, or time series analyses. Although the methods for assessing the quality or risks of bias in the evidence from randomised controlled trials are well developed,[29] there are concerns around the methods for assessing the quality of observational studies. For example, the risk of bias in non-randomised studies of exposures (ROBINS-E) tool was developed by building upon tools previously developed for risk of bias assessment of randomised trials.[77] To assess its useability, we applied the tool to over 70 studies of exposure that are commonly used in the development of public health guidelines, including environmental risk, dietary exposure and drug harm (See Appendix iv. 'The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures').[78] Our study identified both practical and methodological concerns about the tool with

recommendations for the development of a simpler, empirically based on bias tool to assist in the development of credible public health guidelines.

In areas of public health related to nutrition and the harms of exposures of environmental hazards, the National Academies of Science (NAS) have recommended a move towards improving the methods used in the development of these types of guidelines and assessments to reduce potential biases and enhance their credibility.[9] Amongst several potential enhancements to improving the methodological processes used both in dietary guidelines and assessments of the harms of chemicals, the NAS has strongly recommended the use of systematic reviews to evaluate the evidence. However, the recent evaluation of an international sample of dietary guidelines identified concerns with the current methods employed for the systematic reviews used and how evidence from these reviews is synthesised into final recommendations.[10-12]

In recent years, there has been growing scrutiny around the methods used in the assessment of hazardous environmental exposures conducted by various national and international organisations and agencies. For example, the above referenced NAS report scrutinised methods used by the United States Environmental Protection Agency (USEPA) and the International Agency for Research on Cancer (IARC) has recently reviewed its methods for conducting environmental hazard assessments. The processes and methodologies used in the development of these guidelines and assessments may vary significantly among the organisations that develop them. This could lead to conflicting conclusions, and debate around what assessments are most valid. For example, the different statements on the harms of environmental hazards, such as those surrounding glyphosate[79,80] and bisphenol-A (BPA)[81,82] by various organisations around the world, leave both the public and policy-makers confused. While there are many factors that influence the implementation of guidelines that go beyond the scope of this current dissertation, differing opinions on the what

the most valid assessment are may impact the implementation of the recommendations that are made from them.

In 2011, the NAS conducted a review of the United States Environmental Protection Agencies Integrated Risk Information System (IRIS) Process.[9] The IRIS program is responsible for developing toxicologic assessments of environmental contaminants, including hazard identifications and dose-response assessments of chemicals related to cancer and noncancer endpoints. The program was formed to create consistency in the toxicologic assessments within the agency and soon became relied upon by federal, state, and international agencies for setting regulatory standards, establishing exposure guidelines, and estimating potential risks to those populations exposed to chemicals. The review by the NAS, however, identified several deficiencies in the methods and approaches being used in the completion of IRIS assessments. The review and future reports on the program have made specific recommendations on how evidence should be identified, selected, evaluated and integrated across different streams to make final conclusions on the potential harms of these exposures. The recommendations made by the NAS to reduce bias in this process are transferrable to all public health guidelines, as the methods used to evaluate and synthesise observational studies of exposures, such as diet or environmental exposures, are the same.

Building on from this review into the IRIS program, we sought to conduct the first systematic analysis and comparison of the methods and processes used by the various national and international organisations responsible for conducting hazard identification and / or risk assessments of environmental hazards. Our analysis was based on the recommendations made to the IRIS program by the NAS. In Chapter Two of this dissertation, I explore the current methodological practices and procedures of these organisations, comparing them to a framework I devised based on the recommendations from the NAS to the IRIS program and discuss any current knowledge gaps to

inform the development of future methods used in this area of public health. This work will aim to improve the methods used to reduce bias and to increase the credibility of the conclusions that are made from assessment of exposure studies, such as studies of environmental exposures.

Social Influences on Public Health Guideline Development

In addition to the potential biases that may be brought into the development of public health guidelines via the primary studies that are included, or the methods used to select, evaluate and synthesise the evidence used in their formation, the interactions within guideline groups and how they are facilitated may be a significant influence on the final recommendations. Lessons learned in clinical practice guidelines suggest that how guideline development groups function influences how the evidence is processed, and therefore affects the quality of the guidelines.[83,84]

There have been various case studies that have explored both the social processes[13] and methodological challenges[14,15] involved in the development of public health guidelines and how the recommendations are made, both in the United Kingdom with the NICE and the WHO respectively. In a study that explored how NICE advisory groups function, the authors identified that advisory group members conceptualised the guideline development task differently, with some prioritising the evidence in informing their decision making, while others their disciplinary expertise. While the diversity of opinions in these groups brought tensions, it was seen to be vital in making informed judgements, relevant to making recommendations.[13] To improve the GRADE (The Grading of Recommendations Assessment, Development and Evaluation) process and facilitate its uptake, participants involved with the development of WHO guidelines identified similar challenges,

including clinical expertise and practical experiences sometimes taking precedence over the evidence in discussions about recommendations. Additionally, they found that power dynamics within the guideline group where experienced members could dominate, may affect considerations.[14] GRADE methodologists instead reported that they experienced tensions with the WHO panels that did not understand the GRADE process and that there was a need for better understanding and support of their roles in the guideline development process.[15]

Chapter Three of this dissertation makes a unique contribution to the public health guideline development process in Australia and internationally, as it aims to understand the experiences and perspectives of the two key groups of people involved in developing public health guidelines and statements for the National Health and Medical Research Council (NHMRC); the independent groups contracted and responsible for conducting the systematic searches and evaluations of the quality of the evidence; and those on the working committee. Chapter Three explores this process and its potential implications for future public health guideline development in Australia, with the aim to enhance the processes and methods for public health guidelines. My findings will directly inform the ongoing development of the NHMRC "Guidelines for Guidelines" report, which will have chapters developed specifically for the development of public health guidelines.[85]

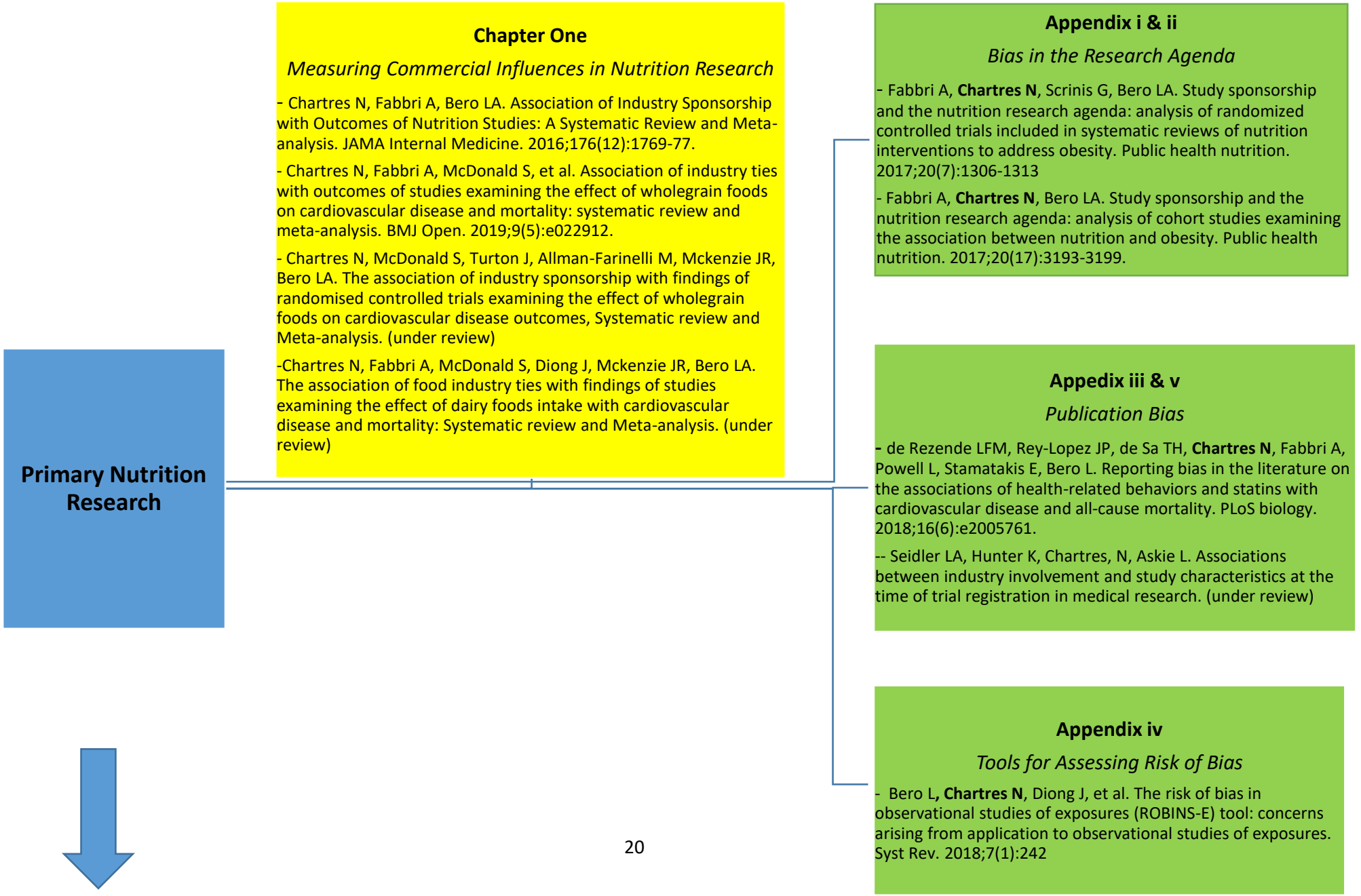
In Chapter Four of this dissertation I discuss health and policy implications of these findings, potential solutions to the key issues identified, and future steps to continue to improve both the credibility of primary studies that form the evidence base and the methods used in developing rigorous guidelines to protect the public's health.

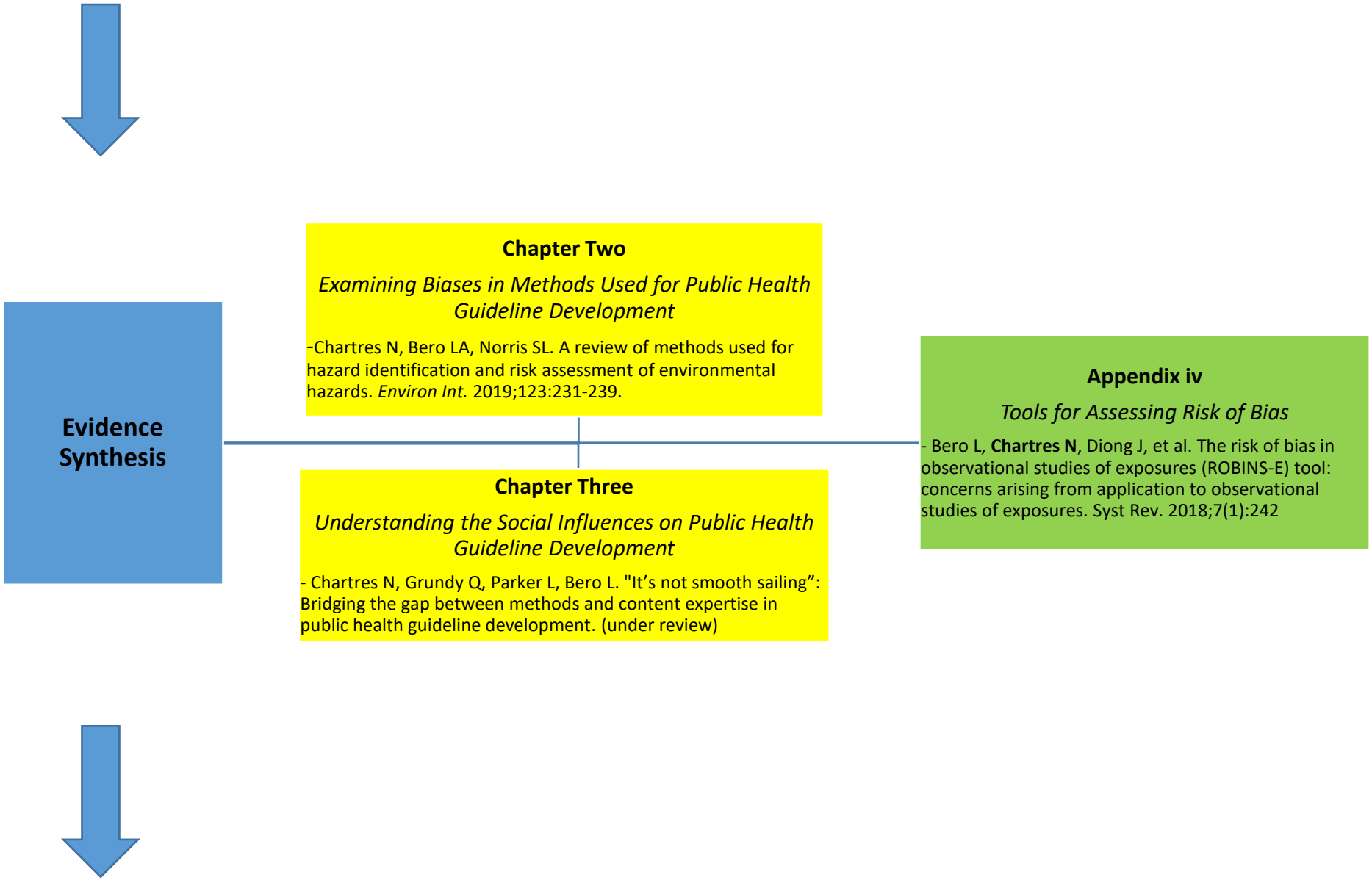
Summary

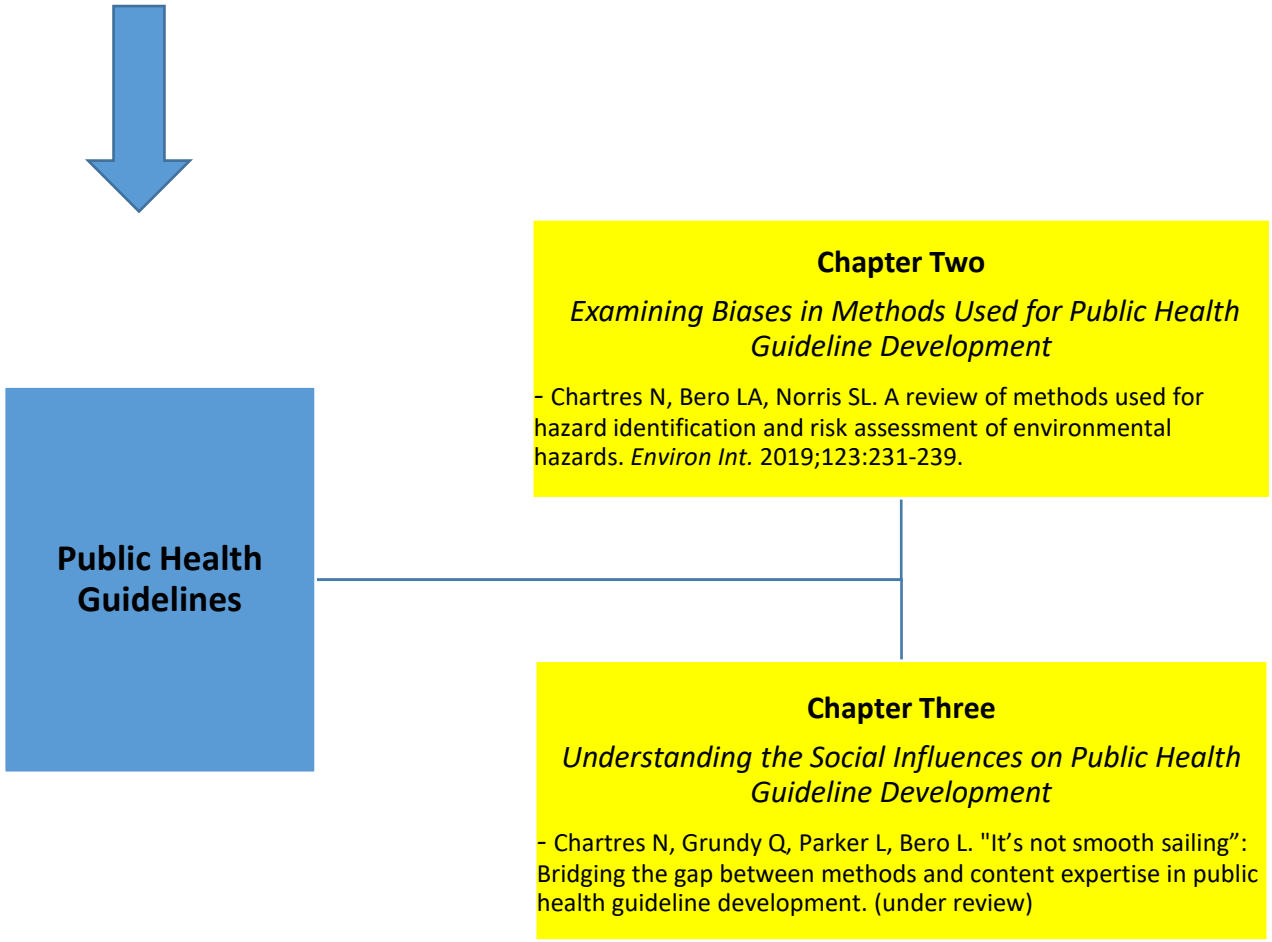
My dissertation and publications contribute to understanding bias in nutrition research and public health guideline development. Figure 2 illustrates how my publications relate to the primary themes of studying bias in primary nutrition research, evidence synthesis methods, and guideline development. This body of evidence was created using a variety of methods:

- meta-analysis and systematic review to measure bias in primary nutrition research (Chapter One);
- content analysis to understand the methods used in synthesising evidence for public health guidance development (Chapter Two);
- qualitative analysis of interviews using Grounded Theory to understand social influences on guideline development (Chapter Three).

Figure 2. Contribution to understanding bias in nutrition research and public health guideline development




Evidence Synthesis
Chapter Two
Examining Biases in Methods Used for Public Health Guideline Development
-Chartres N, Bero LA, Norris SL. A review of methods used for hazard identification and risk assessment of environmental hazards. Environ Int. 2019;123:231-239.
Chapter Three
Understanding the Social Influences on Public Health Guideline Development
- Chartres N, Grundy Q, Parker L, Bero L. "It's not smooth sailing": Bridging the gap between methods and content expertise in public health guideline development. (under review)
Appendix iv
Tools for Assessing Risk of Bias
- Bero L, Chartres N, Diong J, et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. Syst Rev. 2018;7(1):242


Public Health Guidelines
Chapter Two
Examining Biases in Methods Used for Public Health Guideline Development
- Chartres N, Bero LA, Norris SL. A review of methods used for hazard identification and risk assessment of environmental hazards. Environ Int. 2019;123:231-239.
Chapter Three
Understanding the Social Influences on Public Health Guideline Development
- Chartres N, Grundy Q, Parker L, Bero L. "It's not smooth sailing": Bridging the gap between methods and content expertise in public health guideline development. (under review)

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Chapter One

Measuring Commercial Influences in Nutrition Research

Publication details

This chapter contains the following manuscripts:

1. **Chartres N**, Fabbri A, Bero LA. Association of Industry Sponsorship with Outcomes of Nutrition Studies: A Systematic Review and Meta-analysis. *JAMA Internal Medicine*. 2016;176(12):1769-77.
2. **Chartres N,** Fabbri A, McDonald S, et al. 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.* 2019;9(5):e022912.
3. **Chartres N**, McDonald S, Turton J, Allman-Farinelli M, Mckenzie JR, Bero LA. The association of industry sponsorship with findings of randomised controlled trials examining the effect of wholegrain foods on cardiovascular disease outcomes: Systematic review and Meta-analysis. (under review)
4. **Chartres N**, Fabbri A, McDonald S, Diong J, Mckenzie JR, Bero LA. 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. (under review)

Overview

As discussed in the introduction of this dissertation, bias may be introduced in any stage of the research process, including the questions that are asked, in the design and conduct of a study and through the publication of the study results. We previously examined the association between funding source and the research agenda in nutrition research and found that corporate funders are likely to sponsor studies that examine specific nutrients and do not consider the level of food processing (see Appendix i. 'Study sponsorship and the nutrition research agenda: analysis of randomised controlled trials included in systematic reviews of nutrition interventions to address obesity''[1] and Appendix ii. 'Study sponsorship and the nutrition research agenda: analysis of cohort studies examining the association between nutrition and obesity').[2] In this Chapter we therefore sought to measure the influence of food industry sponsorship on the research methods.

While there have been previous examinations into the relationship between research sponsored by the food industry and the conclusions of studies, there has been little study of difference in the design features of studies sponsored by industry vs. other sponsors. In addition, these studies have only focused on a narrow range of nutrition research topics such as sugar sweetened beverages and have not controlled for other factors that may have affected the research results, including the internal validity or risk of bias of the studies, when assessing the influence of funding source. Only one methodological study examined the association of author conflicts of interest and conclusions, and found a statistically significant association between them.[3] Chapter One addresses these gaps by examining the association of both funding source and author conflicts of interest with the outcomes and methods of nutrition studies.

My hypothesis was that studies funded by the food industry and /or that had authors with conflicts of interest with the food industry, were more likely to have results and conclusions that would favour the sponsor, than studies without industry funding or authors with a conflict of interest. I tested this hypothesis by using meta-analytic techniques to quantify the association of industry sponsorship and authors conflicts with the direction and magnitude of the results, effect size and conclusions. My secondary hypothesis was that studies with or without industry ties would be similar in risks of bias as has been shown in examinations of the association of funding source with risks of bias in drug studies.[4]

In our first systematic review and meta-analysis, 'Association of Industry Sponsorship with Outcomes of Nutrition Studies: A Systematic Review and Meta-analysis' we sought to assess the evidence on industry influence across all nutrition research by measuring whether food industry sponsorship of nutrition studies is associated with outcomes that favour the sponsor. We found that the few studies that have examined biases in nutrition research were limited in scope and had not assessed the effect of industry sponsorship on the results or internal validity of the included studies or throughout the entire research process.

The following three systematic reviews and meta-analyses in Chapter One filled this gap in knowledge. We did this by measuring the association of food industry sponsorship and authors with a conflict of interest with the food industry and the study results, conclusions and risk of bias in studies measuring the effect of foods recommended in dietary guidelines, such as wholegrains and dairy foods and specific health outcomes, such as cardiovascular disease.

Selection of study topics

To establish the questions and body of evidence relevant to recent dietary recommendations, we assessed a review of the questions used in the development of dietary guidelines from 2010-2015 in the Food and Agricultural Organization of the United Nations (FAO) database.[5] For example, if a guideline recommendation was related to wholegrain intake and cardiovascular disease, we reviewed the entire body of evidence relevant to this question. The rationale for this was we sought to identify foods that the food industry may have an interest in testing to establish health benefits and develop products with these foods or ingredients, to help market their food products. For example, the food industry attempts to test formulated wholegrain products, such as breakfast cereals. As the overarching aim of this dissertation was to reduce bias in public health guidelines, the evidence base on which they are built, must be assessed for bias. We therefore sought to review the entire body of evidence used in each recommendation that we selected, to measure bias in the results that are used in forming these recommendations.

Our analyses provide the first empirical examination and quantitative data on the effects of food industry sponsorship and author conflict of interest on the magnitude and direction of results, conclusions and risk of bias of the primary nutrition studies used in the development of dietary guidelines. We found an association of industry sponsorship and authors with a conflict of interest with the outcomes of studies, even when controlling for risk of bias or internal validity between the studies. As discussed in the following chapters of this dissertation, this new knowledge on funding bias that has been shown to influence research outcomes can be used to improve how nutrition studies used in public health guidelines, such as dietary guidelines, and nutrition policy, are assessed and accounted for in evidence synthesis. In the following chapters, we will also explore the necessary steps to minimise bias throughout the entire guideline development process.

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MANUSCRIPT 1

The association of industry sponsorship with outcomes of nutrition studies: a systematic review and meta-analysis

(JAMA Intern Med 2016; 176(12):1769-1777. doi: 10.1001/jamainternmed.2016.6721)

Nicholas Chartres, MHumNutr, PhD candidate, University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia

Alice Fabbri, MD, PhD candidate, University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia

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

Corresponding author: Prof. Lisa Bero, lisa.bero@sydney.edu.au

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Abstract

Importance: Food industry sponsorship of nutrition research may bias research reports, systematic reviews, and dietary guidelines.

Objective: To determine if food industry sponsorship is associated with effect sizes, statistical significance of results, and conclusions of nutrition studies with findings that are favorable to the sponsor and, secondarily, to determine whether nutrition studies differ in their methodological quality depending on whether they are industry-sponsored.

Data sources: OVID MEDLINE, PubMed, Web of Science and Scopus from inception until October 2015; the reference lists of included reports.

Study selection: Reports that evaluated primary research studies or reviews and that quantitatively compared food industry sponsored studies with those that had no or other sources of sponsorship.

Data extraction: Two reviewers independently extracted data from each report and rated its quality using the ratings of the Oxford Centre for Evidence-Based Medicine, ranging from a highest quality rating of 1 to a lowest of 5.

Main outcomes and measures: Results (statistical significance and effect size) favorable to the sponsor and conclusions favorable to the sponsor. If data were appropriate for meta-analysis, we used an inverse variance DerSimonian-Laird random-effects model.

Results: Of 775 reports reviewed, 12, with quality ratings ranging from 1 to 4, met the inclusion criteria. Two reports, with data that could not be combined, assessed the association of food industry sponsorship and the statistical significance of research results; neither found an association. One report examined effect sizes and found that studies sponsored by the food industry reported significantly smaller harmful effects for the association of soft drink consumption with energy intake and body weight than those not sponsored by the food industry. Eight reports, including 340 studies, assessed the association of industry sponsorship with authors' conclusions. Although industry sponsored studies were more likely to have favorable conclusions than non-industry sponsored

studies, the difference was not significant, RR: 1.31 (95% CI: 0.99 to 1.72). Five reports assessed methodological quality; none found an association with industry sponsorship.

Conclusions and Relevance: Although industry-sponsored studies were more likely to have conclusions favorable to industry than non–industry-sponsored studies, the difference was not significant. There was also insufficient evidence to assess the quantitative effect of industry sponsorship on the results and quality of nutrition research. These findings suggest but do not establish that industry sponsorship of nutrition studies is associated with conclusions that favor the sponsors, and further investigation of differences in study results and quality is needed.

INTRODUCTION

Dietary guidelines provide recommendations to reduce the risk of conditions such as obesity, diabetes and cardiovascular disease. Even when dietary guidelines have been based on systematic reviews,[1] the evidence has been criticized for being biased[2] and guidelines contain conflicting recommendations.[3,4] Recent scrutiny of the funding practices of transnational food companies[5] has heightened concerns about the credibility of nutrition research and how sponsorship affects the findings.[6-9] It is important to know whether funding source influences the statistical significance of the results or the effect sizes of nutrition studies and should, therefore, be considered when assessing biases in these studies.[10]

Considerable evidence suggests that industry sponsorship of research is associated with outcomes that favor the sponsor.[11-14] Examinations of pharmaceutical and tobacco industry sponsored research show that, even when controlling for methodological biases, industry sponsored studies are more likely to have results that favor the sponsor's product than studies with other sources of sponsorship.[11,15,16] Industry sponsors can influence the outcomes of a study in many ways, including the framing of the research questions, the design and conduct of the study, selective reporting of results, and 'spin' on conclusions.[17-19] Food companies appear to use tactics similar to those of the tobacco industry to influence research. [13,20,21]

Prior assessments of the influence of industry sponsorship and conflicts of interest in nutrition research have had conflicting results.[22,23] It is unclear whether studies of sponsorship bias in nutrition research have controlled for other potential biases, such as methodological quality, that could also influence research outcomes. We conducted a systematic review of studies examining the association of industry sponsorship with the statistical significance of results, effect sizes, and conclusions of nutrition research.

Our objectives were to determine whether: (1) Published nutrition studies with food industry sponsors are more likely to have results and/ or conclusions that are favorable to the industry; and (2) Published nutrition studies sponsored by industry differ in their methodological quality compared with studies with other or no sponsors.

METHODS

Inclusion and exclusion criteria

This review includes published reports that were designed to quantitatively compare food industry and non-food industry sponsored samples of primary nutrition research studies (such as cohort studies) or reviews. We excluded conferences presentations, opinion pieces and letters to the editor. We had no language restrictions.

Primary Outcomes

We hypothesized that studies with food industry sponsorship would be more likely to have favorable results and conclusions than those without industry sponsorship. We assessed two primary outcomes:

1. Results (statistical significance and effect size) favorable to the sponsor.

For studies of health benefits, favorable results were defined as those that were statistically significant (e.g. $P < 0.05$ or 95% confidence interval excluding the possibility of no difference) in favor of the sponsor's product(s) or diet. For studies of harms, favorable results were defined as those where harms were not statistically significant (e.g. $P > 0.05$ or 95% confidence interval including the possibility of no difference) or results that had a statistically significant measure of harm in the comparator group.

We also determined whether each report assessed the magnitude of effect size estimates as an outcome. The effect size measures the standardized mean difference between groups; an effect size of 0 means there is no difference. Since the effect size is a measure of the magnitude of an effect, it can be compared across different outcome measures.

2. Conclusions favorable to the sponsor.

Conclusions that suggested the nutrition intervention or exposure being studied was beneficial to health and / or safe were considered favorable to the study sponsor. Otherwise, the conclusions were considered unfavorable.

Secondary Outcome

We determined whether each report compared the methodological quality of industry vs. non-industry sponsored studies.

Search Strategy

We searched Ovid MEDLINE, PubMed, Web of Science, and Scopus (inception to October 2015) (Supplemental file 1). We hand searched the references lists of all included reports to identify any additional relevant reports that the electronic searches missed.

Selection of studies

Two investigators (NG & LB) independently screened the titles and abstracts of all retrieved records for obvious exclusions, and then applied our inclusion criteria to the full text of the remaining reports. Any discrepancies were resolved by consensus. Reasons for exclusion are in Supplemental file 2.

Data extraction

Two assessors (NG & AF) independently extracted data from each included report; a third assessor (LB) adjudicated any disagreements. We contacted the authors of two reports to acquire missing data.

Rating system to evaluate the quality of evidence

Two investigators (NG and LB) independently rated the quality of the included reports using the Oxford Centre for Evidence-based Medicine ratings; with a highest rating of 1 to a lowest of 5. The quality ratings are: 1= Properly powered and conducted randomized clinical trial; systematic review with meta-analysis; 1a = systematic review without meta-analysis; 2= Well-designed controlled trial without randomization; prospective comparative cohort trial; 3= Case-control studies; retrospective cohort study; 4 = Case series with or without intervention; cross-sectional study; 5 = Opinion of respected authorities; case reports.[24]

Statistical Analysis

To test our hypothesis that studies with food industry sponsorship would be more likely to have favorable conclusions than those without industry sponsorship, we conducted a meta-analysis using Review Manager 5.3 software (The Cochrane Collaboration). We assessed statistical heterogeneity using the I^2 statistic, a statistic that quantifies the variability in effect estimates that is due to heterogeneity rather than chance. Because heterogeneity was substantial (defined as an $I^2 > 50\%$), we used an inverse variance DerSimonian-Laird random-effects model for the meta-analysis. Due to the lack of homogeneous data on statistical significance of results or effect size, we could not quantitatively synthesize data (i.e., conduct a meta-analysis) on these outcomes.

RESULTS

Search results and Characteristics of included reports

As shown in Figure 1, 775 references were identified and 12 reports met the inclusion criteria.

Table 1 summarizes the characteristics of the included reports. The quality of the reports ranged from 1 to 4. The 12 reports were published between 2003 and 2014. The median number of included studies was 68.5 (range: 17 to 2539). Four reports included randomized controlled trials (RCTs) only, 2 included reviews only and 6 included a mix of study designs. Four reports focused on the effects of sugar-sweetened beverage consumption and 4 focused on a broad range of interventions to reduce obesity.

The reports defined industry sponsorship in different ways (Table 1). Nine reports examined associations of industry sponsorship and reported outcomes. Three reports examined both industry sponsorship and author conflicts of interest together, while 1 of these examined industry sponsorship and author conflicts of interest separately.

The most commonly studied outcome was the association of industry sponsorship with conclusions (8 reports); five reports assessed only conclusions. Supplemental file 3 shows how conclusions that were favorable to the sponsor were defined and measured in the reports. Only 1 report assessed the association of industry sponsorship with effect size estimates and 2 measured the association with statistical significance of the results.

Of the 12 reports, 1 was industry funded and 8 were not; 1 report had no external funding and for 2 reports funding was not disclosed (Table 2). Authors of 3 reports had financial ties to the food industry; for 6 reports, the authors stated they had no conflicts of interest and for 3 reports author conflicts of interest were not disclosed.

Methodological “quality” was assessed in 5 reports using a variety of definitions and tools (Table 3).

Summary of Findings

Statistical significance: Industry sponsored versus non-industry sponsored studies

Neither of the 2 reports that examined the association between industry sponsorship and the statistical significance of results found an association. Both of these reports were systematic reviews (quality rating 1a). The results of the reports could not be combined because they measured statistical significance in different ways (per study versus all individual outcomes). One report containing 70 RCTs measuring the efficacy and harm of synbiotics, probiotics and prebiotics (foods or supplements that aim to stimulate the growth of beneficial gut bacteria) found no significant association between funding source and statistically significant results for 7 of the 8 clinical outcomes examined. Overall, industry sponsored studies reported 20.6% (73/354) of all clinical outcomes as favorable compared to non-industry sponsored studies, which reported 16.7% (9/54) as favorable.[25] The second report examining 19 RCTs assessing calcium supplementation in healthy children found that there was insufficient variability in the study results to measure any association between study sponsorship and results; almost all study results found a statistically significant improvement in bone health outcomes.[26]

Effect size: Industry sponsored versus non-industry sponsored studies

Only 1 report including 88 observational studies and RCTs examining sugar-sweetened beverages and various health outcomes assessed the relationship between industry sponsorship and effect size.[27] The report was a systematic review that analyzed RCTs and observational studies in separate meta-analyses (quality rating 1). For the harmful outcome of energy intake, overall effect size was smaller in industry [0.05, 95% CI: 0.04, 0.07] compared to non-industry [0.23, 95% CI: 0.22, 0.24] ($P<0.006$) sponsored studies, and for the outcome of body weight, effect size was also smaller in industry [0.02, 95% CI: 0.01, 0.04] versus non-industry [0.10, 95% CI: 0.09, 0.11] ($P<.006$) sponsored studies. However, no significant difference in effect size was observed among RCTs.

Conclusions: Industry sponsored versus non-industry sponsored studies

Eight reports, including 340 studies, examined the association of sponsorship and conclusions, and all could be combined in a meta-analysis (Figure 2). Although industry sponsored studies were more likely to have favorable conclusions than non-industry sponsored studies, the difference was not significant, RR: 1.31 (95% CI: 0.99 to 1.72).

We conducted 2 additional analyses to explore heterogeneity. Two of the 8 reports defined industry sponsorship as a combination of study sponsorship and author conflicts of interest, and these could not be separated for analysis.[22,28] We conducted a sensitivity analysis excluding these 2 reports and found similar results RR: 1.20 (95% CI: 0.93 to 1.54), $I^2 = 42\%$. In addition, two reports included only reviews and not primary research studies.[22,29] Exclusion of these from the analysis produced similar results RR: 1.11 (95% CI: 0.92 to 1.34), $I^2 = 5\%$.

One report, with quality rating 1a, examined the association of author conflicts of interest and conclusions.[23] This report examined the health risks and nutritional value of genetically modified foods and found a significant association between author conflicts of interest and favorable study conclusions; 100% (41/41) of studies with author conflicts of interest reached favorable conclusions compared to 76% (39/51) without author conflicts of interest, RR 1.31 (95% CI: 1.12 to 1.52).

Methodological quality: Industry sponsored versus non-industry sponsored studies

Five reports compared the methodological quality of industry sponsored with non-industry sponsored studies (Table 3). No reports examined the association of authors' conflicts of interest with methodological quality. One report assessed risk of bias of the included studies using Cochrane methodology[33] and found there was no significant association of industry sponsorship and random sequence generation, allocation concealment, blinding, or selective reporting.[25] Industry sponsored studies had significantly less missing data than non-industry sponsored studies[33]. Three reports used

different tools to assess methodological quality using a score (e.g., primary and review Quality Criteria Checklist and Chalmers method) (Table 3), and found no differences in quality scores between industry and non-industry sponsored studies.[29,36,37] One report measured quality using CONSORT and found that reporting was equivalent, regardless of funding.[38] CONSORT, however, is a guideline for reporting trials and does not assess how they are actually conducted or the means to reduce bias.[34,35]

DISCUSSION

Our review identifies a gap in empirical evidence on the association of industry sponsorship or authors' conflicts of interest and the outcomes of nutrition research. The majority of the reports examined only the effects of sponsorship on conclusions. Influence on conclusions is important to study because the relationship between industry sponsorship and conclusions favorable to the study sponsor has been previously demonstrated in tobacco, [13] pharmaceutical [11] and environmental toxin research.[39] 'Spin' on conclusions, which has been identified as a tactic used in other industries, [16,40] can influence how research is interpreted,[19,40] and can undermine the credibility of research reports. From the standpoints of developing systematic reviews, dietary guidelines and other evidence-based advice, the results are more relevant than the conclusions; for example, only the results are included in systematic reviews.

Our findings suggest that there is insufficient evidence to assess the quantitative effect of industry sponsorship on the results of nutrition research and, thus, account for this bias in systematic reviews. The two reports that assessed the association of sponsorship and the statistical significance of research results found no association.[25,26] This may be because there was insufficient power to compare industry and non-industry sponsored studies, as most of the studies were industry sponsored. In addition, funding sources of nutrition studies are often not disclosed.[5] Improved disclosure of funding sources and larger samples for analysis should make it possible to assess the association of funding source with statistical significance of study results, as well as effect sizes. It is

important to determine whether industry sponsorship affects the results of nutrition research, as has been shown for pharmaceutical industry funding of drug research.[11]

Food industry sponsorship and methodological quality

Our review found that industry sponsored studies were equal or better in quality than those with other funding sources. However, methodological quality was usually measured using tools that derived quality scores. The use of quality scores can be problematic, because the choice of scale can influence the results of meta-analyses. Individual study domains should be assessed instead.[41] These findings are consistent with previous examinations of pharmaceutical and tobacco research showing that industry sponsored studies are of equal or better quality to non-industry funded studies.[11,15,42] Industry sponsorship can influence research results in a variety of ways. Methodological quality is only one characteristic that can influence study outcomes. Sponsors can also frame research questions to produce a desirable outcome or to generate research that diverts attention from certain questions. For example, the tobacco industry funded research on the adverse health effects of indoor air components other than tobacco smoke to distract from the evidence on harms associated with environmental tobacco smoke exposure .[15] Sponsors can influence how the study is actually conducted and whether the results of the study are published in full or not. [43] Although industry sponsorship has been associated with selective reporting of research outcomes that favor the sponsor, [44] this practice was not assessed in any of the reports we reviewed. The association of research sponsorship with the design and reporting of nutrition research should be examined.

Strengths and limitations of the review

We conducted a comprehensive search and followed explicit and well-defined inclusion and exclusion criteria for the reports. Authors of reports were also contacted for additional data. We reported on all outcomes and rated the quality of all the reports we included.

The limited number of studies that met our inclusions criteria prevented the conduct of statistical analyses of the relationship between industry sponsorship and study results. We could not quantitatively synthesize data for all outcomes because the reports were heterogeneous. They included different topics and designs of studies and classified industry sponsorship in different ways. In addition, we only included data on sponsorship that was disclosed, and did not seek to identify industry funding or other associations that were not disclosed in the publications.

Implications

The scrutiny of the funding practices of large transnational food companies[6,7] has threatened the credibility of nutrition research and researchers.[5] However, without empirical work examining the association of industry sponsorship with the results of nutrition research, researchers, policy makers and the public have no way of quantifying and understanding the extent of industry influence on the data. It is challenging to rigorously assess the association of industry sponsorship with research outcomes. The quality of the reports we examined varied. Research to quantify the influence of industry sponsorship on effect estimates can be improved by obtaining complete and accurate data on sponsors of research and conflicts of interest of sponsors and authors, and focusing on specific research questions and study designs. Thus, bias in study methods, as well as bias related to sponsorship, can be measured.

Most of the studies included in our review focused on sponsorship by large transnational food companies. However, conflicts of interest in nutrition research are complex because they encompass more than financial relationships with the manufacturers of the food products being tested.[45] For example, there is a conflict of interest if an investigator receives royalties from selling their own dietary advice. In addition, trade organizations representing different food groups also sponsor nutrition research. [46,47] Therefore, it is important to know if the extent and mechanisms of bias are similar across different types of sponsors.

Previous research documenting the influence of industry sponsorship on research in other health-related fields has led to international reforms to make data more accessible, conflicts of interest and funding more transparent, and to calls for stricter standards and policies for managing conflicts of interest, critiquing and reporting evidence, and conducting systematic reviews.[10,48,49] Similar research is needed to help refine methods for evaluating studies used in systematic reviews that form the basis of dietary guidelines. Such research should also determine whether 1) biases associated with industry conflicts of interest require policies for disclosure and management similar to those now widely accepted in clinical research, 2) mechanisms to reduce publication bias, such as study registries or open access data, should be considered for nutrition studies, and 3) research agendas should be revised to produce studies that are relevant to population health.

In conclusion, our findings suggest, but do not establish, that industry sponsorship of nutrition studies is associated with conclusions that favor the sponsors, but not differences in study quality. Our findings also suggest that there is insufficient evidence to assess the quantitative effect of industry sponsorship on the results of nutrition research and, thus, account for this bias in systematic reviews.

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LB had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1. Characteristics of the 12 Reports

Report	Number and type of studies	Quality Rating*	Topic	Comparison as defined in included study**	Outcomes measured
Bes-Rastrollo 2013	17 systematic reviews	1	Effect of sugar-sweetened beverages on weight gain or obesity	COI with food industry[1] vs. no COI with food industry (Combined industry sponsorship & author COI)	Conclusions
Diels 2011	94 intervention, composition or simulation studies	1a	Health risks and nutritional value of genetically modified foods (GM foods)	COI with food industry[2] vs. no COI with food industry (Combined industry sponsorship & author COI).	Conclusions
Kaiser 2012	38 RCTs	3	Quality reporting scores in obesity and nutrition RCTs	Industry sponsorship[3] vs. no industry sponsorship[4]	Quality
Lesser 2007	206 intervention, observation and reviews	1a	Health effects of soft drinks, juice and milk	Industry sponsorship[5] vs. no industry sponsorship	Conclusions
Levine 2003	67 research articles and reviews	4	Safety and efficacy of the fat substitute olestra	COI with food industry[6] vs. no COI with food industry (Combined industry sponsorship & author COI)	Conclusions
Massoug-bodji 2014	20 reviews - systematic, non-systematic and meta-analysis	1a	Effect of sugar-sweetened beverage consumption and body weight	Industry sponsorship[7] vs. no industry sponsorship	Conclusions Quality
Mugambi 2013	67 completed and 3 ongoing RCTs	1a	The efficacy and safety of synbiotics, probiotics and prebiotics supplementation in infant formula	Industry sponsorship[8] vs. no industry sponsorship[9]	Results Conclusions Quality
Myers 2011	2539 Intervention, observational studies and reviews	3	Research report quality of nutrition research	Industry sponsorship[10] vs. no industry sponsorship[11]	Quality
Nkansah 2009	19 RCTs	1a	Calcium supplementation	Industry sponsorship[12] vs. no industry sponsorship	Results Conclusions

			and bone health in children		
Thomas 2009	63 RCTs	3	Quality reporting in long term interventions to reduce obesity	Industry Sponsorship[13] vs no industry sponsoship[14]	Quality
Vartanian 2007	88 RCTs and observational studies, analyzed separately	1	Association of soft drink consumption with nutrition and health outcomes	Industry sponsorship[15] vs. no industry sponsorship	Results (effect size)
Wilde 2012	79 observational studies, intervention studies and reviews	3	Obesity- related research	Industry sponsorship[16] vs. No industry sponsorship[17]	Conclusions

RCT = randomized controlled trial; COI = conflicts of interest

*quality ratings: 1= Properly powered and conducted randomized clinical trial; systematic review with meta-analysis; 1a = systematic review without meta-analysis; 2= Well-designed controlled trial without randomization; prospective comparative cohort trial; 3= Case-control studies; retrospective cohort study; 4 = Case series with or without intervention; cross-sectional study; 5 = Opinion of respected authorities; case reports

**definitions of industry sponsorship used in each report:

1. COI with food industry = Financial industry funding or the disclosure of potential conflicts of interest of the authors
2. COI with food industry = Funding COI, at least one sponsor classified as industry or Professional COI, at least one of the authors is affiliated with industry

   *This review also separated Funding COI and Professional COI in their analysis
3. Industry sponsorship = Industry funded studies plus mixed funding mixed

4. No industry sponsorship = Non-industry funded studies plus private foundation or governmental funding
5. Industry Sponsorship = Articles funded entirely by industry
6. COI with food industry = Articles with at least 1 Proctor & Gamble (P&G) author or acknowledged P&G support or articles with at least 1 non-P&G food industry author or acknowledged non-P&G food industry support
7. Industry sponsorship = Industry funded
8. Industry sponsorship = Industry funding or support
9. No Industry sponsorship = Non-Industry. It did not include None/Not Clear
10. Industry sponsorship = Industry funding. This category contained food manufacturing companies (n=100), pharmaceutical companies (n=81), commodity groups (n=13), and other funders (n=17)
11. No industry sponsorship = Comparisons were made in research report quality between government, university/hospital and non-profit, separately
12. Industry sponsorship = Industry funding/mixed funding. This included nutritional supplement industry.
13. Industry sponsorship = Industry supported. Industry was listed as funding the study, an author was employed by a for-profit company making the product or service under study, or both. This category contained drug industry sponsored studies. Only data from the non-drug industry sponsored studies were included in our analysis
14. No industry sponsorship = None. No industry support was noted in the paper, and no author was an employee of a for profit company making the produce or service under study
15. Industry sponsorship = Industry funded by the food industry
16. Industry sponsorship = Financial sponsorship from the federal government's semi-public generic commodity promotion or “checkoff” programs for Fluid Milk and Dairy
17. No industry sponsorship = Financial sponsorship from the National Institutes of Health (NIH)

Table 2: Funding sources and author conflicts of interest in the 12 reports

Report	Funding Source*	Disclosed author conflicts of interest**
Bes-Rastrollo 2013	None	None
Diels 2011	None disclosed	None Disclosed
Kaiser 2012	Non Industry[a]	Yes[1]
Lesser 2007	Non Industry[b]	None
Levine 2003	Non Industry[c]	Yes (minor)[2]
Massoug-bodji 2014	Non Industry[d]	None
Mugambi 2013	Non Industry[e]	None
Myers 2011	Industry[f]	None
Nkansah 2009	Non Industry[g]	None
Thomas 2009	Non Industry[h]	Yes[3]
Vartanian 2007	Non Industry[i]	None Disclosed
Wilde 2012	None Disclosed	None Disclosed

*** Funding source** as disclosed in the included report:

a. Supported in part by National Institute of Health grant

b. This study was supported by a grant from the Charles H. Hood foundation and discretionary funds from the Department of Medicine, Children's Hospital Boston to DSL.

c. This study was funded by J. Levine and J. D. Gussow.YLB Supported by a development grant from the Foundation Lucie et Andre´ Chagnon. YLB received an educational grant from the Fonds de Recherche du Québec, Societée et Culture.

d. Stellenbosch University Faculty of Medicine and Health Sciences, South Africa.

e. North American Branch of the International Life Sciences Institute (which receives food industry sponsorship).

f. The study was supported in part by funding through the California Tobacco-Related Disease Research Program (TRDRP) grant entitled 'Corporate Strategies: Design, Conduct, Publication of Research 2004 (Cycle XIII) 13RT-0108H' awarded to L.B.

g. This research was supported in part by NIH grant. This work was supported in part by the Rudd Foundation.

****Author conflicts of interest** as disclosed in the included report

1. Dr Allison has received grants, honoraria, donations, royalties, and consulting fees from numerous publishers, food, beverage, pharmaceutical companies, and other commercial and non-profit entities with interests in obesity and randomized controlled trials
2. A. Eccher has provided statistical expertise on market research studies for food companies.
3. DBA has received grants, honoraria, consulting fees, and donations from numerous food, pharmaceutical, and other companies as well as on-profit organizations and government agencies with interests in obesity-related issues.

Table 3. Summary of assessments of methodological quality in 5 reports

Report	Instrument Used*	Findings
Kaiser 2012	Chalmers method[1]	Equal Quality: Overall Chalmers Index quality score (out of 100): Industry sponsorship, M= 84.5 (s.d.=7.04) vs No Industry sponsorship, M=79.4 (s.d. = 13.00). Wilcoxon matched-pairs signed-ranks test Z = -0.966, P = 0.334 (two tailed)
Massougbodji 2014	Assessment of Multiple Systematic Reviews (AMSTAR) [2] and the Quality Criteria Checklist for reviews (QCC)[3]	Equal Quality: No study comparison, only a statement "Quality scores were not related to the source of Funding"
Mugambi 2013	The Cochrane Collaboration's tool for assessing risk of bias in RCTs[4]	Equal Quality: There was no statistical association found between funding and methodological quality in 4 out of 6 domains. Industry sponsored studies were at a lower risk of bias for missing data than non-industry sponsored studies.
Myers 2011	Quality Criteria Checklist (QCC) -Primary Research[3] and the Review Research QCC [3]	Equal Quality: Industry sponsored research reports no more likely to receive a neutral (OR 1.38, 95% CI of OR 0.98–1.95) or negative quality rating (OR 1.90, 95% CI of OR 0.95–3.81) vs government (reference, OR 1.00)
Thomas 2008	CONSORT Statement[5]	Equal Quality: Industry sponsorship (non-drug studies only) vs No industry sponsorship Estimated Mean Difference 2.31 (95% CI−0.70 to 5.31), (p=0.1287)

*Tools used to assess quality:

[1] Chalmers Method: Produces a weighted score for RCT quality that assesses the study protocol (with randomization and blinding weighted most heavily), statistical analysis and presentation of results. Points are awarded for the quality of reporting of trial information, not the quality of the study design itself.[30]

[2]AMSTAR (Assessment of Multiple Systematic Reviews): This tool calculates a quality score for reviews based on review design, research strategy, selection of articles, data abstraction process, assessment of the scientific quality of the studies included in the review, evaluation of publication bias, or mention of possible conflicts of interest. The maximum score is 9 for a qualitative systematic review and 11 for a meta-analysis.[31]

[3]Quality Checklist Criteria (QCC) for primary research and for reviews: These tools were developed by the American Dietetic Association for assessing nutrition studies. Both tools include a mix of questions about reporting (e.g., were statistical tests adequately described) and how a study was conducted (e.g., were statistical tests appropriate?). The QCC for primary research calculates a score based on questions related to 10 domains (e.g., subject selection, blinding, outcomes, analysis) and the QCC for reviews calculates a score based on questions related to 10 domains (e.g., search strategy, study selection, analysis, etc.).[32]

[4]Cochrane Collaboration tool: The Cochrane Risk of Bias tool for Randomized Trials rates each of the following domains - sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues' – as being at a high risk of bias, low risk of bias, or unclear risk of bias. An overall score is not calculated.[33]

[5]CONSORT (Consolidated Standards of Reporting Trials): This tool is a 25-item checklist describing what should be reporting in a randomized controlled trial in the following sections: title/abstract, introduction, methods, results, discussion.[34,35]

Figure 1. Study flow diagram of included studies

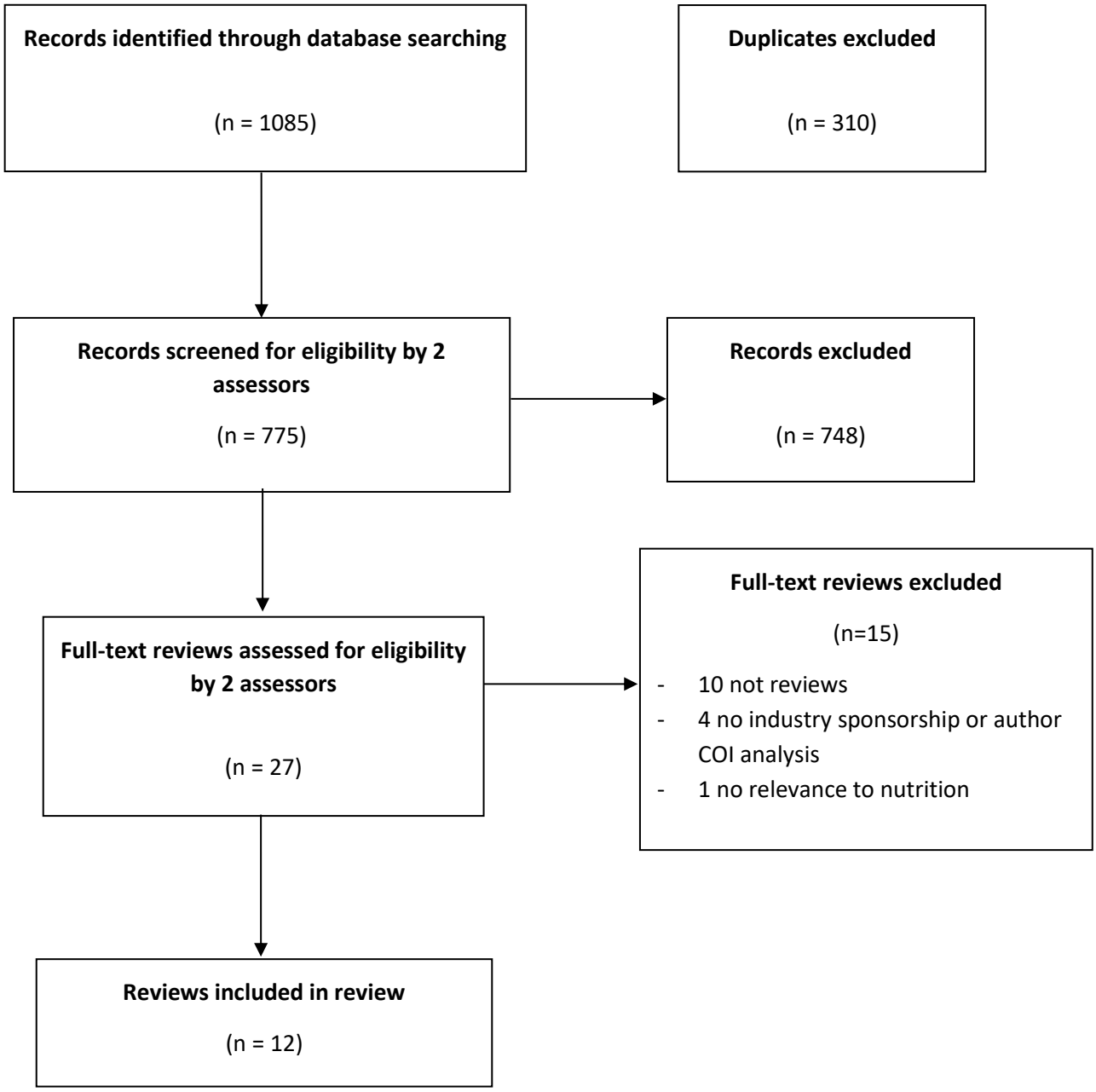
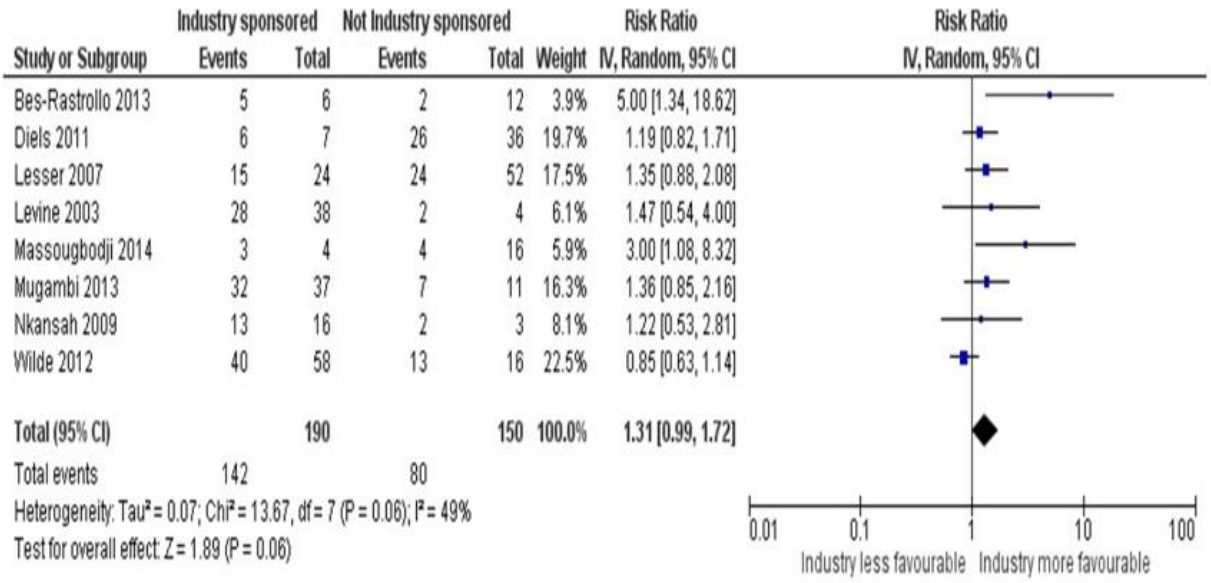


Figure 2. Favorable conclusions in industry vs. non-industry sponsored studies



Supplemental File 1. Search Strategy for Ovid Medline

1. Food/ or exp Food Industry/ or exp Food Habits/

2. exp Beverages/

3. exp Diet/

4. exp Food Habits/ or "nutrition* intervention*".mp.

5. exp Nutrition Policy/

6. exp Nutritive Value/

7. "food industry".mp. or exp Food Industry/

8. (nutrition* and (intervention* or science or studies or values or management or support or treatment)).tw.

9. (diet* and (intervention* or science or studies or values or management or support or treatment)).tw.

10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11. "financial support".mp. or exp Financial Support/

12. "industry sponsored research".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]

13. "Industry funding".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]

14. "Industry payment".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]

15. "private funding".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]

16. "funding source".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]

17. "funding opportunities".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]

18. "industry funded".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]

19. "reporting bias".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]

20. "industry bias".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]

21. "financial conflict* of interest".tw.

22. "conflict* of interest".tw.

23. "non financial conflict* of interest".tw.

24. "Conflict of Interest"/

25. "industry sponsorship".mp.

26. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27. (review* or "systematic review*" or "content analysis" or "content analyses" or cohort).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]

28. 10 and 26 and 27

Supplemental File 2. List of Excluded Studies

Study	Reason for exclusion
Adams 2007(1)	Not relevant to nutrition
Brownell 2009(2)	Commentary not review
Chowdhury 2014(3)	No industry sponsorship or COI analysis
Galbraith-Emami 2013(4)	No industry sponsorship or COI analysis
Gudzune 2015(5)	No industry sponsorship or COI analysis
Jacobson 2005(6)	Commentary not review
James 2002(7)	Commentary not review
Katan 2007(8)	Commentary not review
Lazzerini 2013(9)	No industry sponsorship or COI analysis
Lubans 2013(10)	Letter not review
Pezzuto 2008(11)	Commentary not review
Rock 1999(12)	Commentary not review
Rowe 2009(13)	Commentary not review
Stuckler 2012(14)	Commentary not review
Tappenden 2015(15)	Commentary not review

References of Excluded Studies

1. Adams PJ. Assessing whether to receive funding support from tobacco, alcohol, gambling and other dangerous consumption industries. Addiction. 2007.
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7. James JE. 'Third-party' threats to research integrity in public-private partnerships. Addiction. 2002.
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9. Lazzerini M, Rubert L, Pani P. Specially formulated foods for treating children with moderate acute malnutrition in low- and middle-income countries. The Cochrane database of systematic reviews. 2013;6:Cd009584.
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11. Pezzuto JM. Grapes and human health: A perspective. Journal of agricultural and food chemistry. 2008.
12. Rock CL. Conflict of interest: an important issue in nutrition research and communications. Journal of the American Dietetic Association. 1999;99(1):31-2.
13. Rowe S, Alexander N, Clydesdale F, Applebaum R, Atkinson S, Black R, et al. Funding food science and nutrition research: financial conflicts and scientific integrity. Nutr Rev. 2009;67(5):264-72.
14. Stuckler D, Nestle M. Big food, food systems, and global health. PLoS medicine. 2012.
15. Tappenden KA. A unifying vision for scientific decision making: the Academy of Nutrition and Dietetics' Scientific Integrity Principles. Journal of the Academy of Nutrition and Dietetics. 2015;115(9):1486-90.

Supplemental File 3. Coding of Conclusions

Study	Definition of Favorable Conclusions in the Review	Reliability Measure
Bes-Rastrollo, 2013	SRs were considered to have a conclusion of a positive association when they concluded that SSB consumption may increase the risk of weight gain or overweight/obesity. By contrast, SRs were considered to have a conclusion of no positive association when they concluded that there was insufficient evidence to assess the risk of SSB consumption on weight gain or obesity, or when they presented contradictory results without stating any definitive conclusion about the association.	Two researchers, blinded to the authors' financial conflicts of interest and stated sources of funding, independently extracted the conclusions stated in the articles. The agreement between the researchers was 93.3% (Kappa index: 0.86; p,0.001); disagreement was resolved through a third researcher's assessment, to reach a consensus. Based on these conclusions, we classified the SRs into those that had found a positive association versus those that had not for the relationship between SSB consumption and weight gain or obesity.
Diels, 2011	Each article was classified based on the following criteria: 1. Favorable – If the co-investigator finds that no statement were made that cast the product in a negative light and, at the same time, the conclusions suggest one or more of the following: (a) Beneficial health effects. (b) Increased nutritional value. (c) Absence of adverse health effects. (d) Equivalence in nutritional value between the GM product and the non-GM reference line, if the GM product was not developed with the aim to increase nutritional value. 2. Unfavorable – If the co-investigator finds that no statements were made that cast the product in a positive light and, at the same time the conclusions suggest one or more of the following: (a) Absence of expected beneficial health effects. (b) Adverse health effects. (c) Lower nutritional value of the GM product when compared to the non-GM reference line. (d) Equal nutritional value of the GM product, when compared to the non-GM reference line, if the GM product	Two independent co-investigators classified the conclusions of each article as generally ''favorable'', ''unfavorable'' or ''neutral''. None of the co-investigators had any prior knowledge of the classification produced by their peers and had access only to the article sections relevant to their task.

	was developed with the aim to increase nutritional value. 3. Neutral – If the co-investigator finds the study is inconclusive or criteria for a favorable or unfavorable classification were not met. Finally, the two co-investigators exchanged classification data. An article was excluded if no consensus was reached on assigned categories.	
Lesser, 2007	Article conclusions were classified as ''favorable,'' ''neutral,'' or ''unfavorable'' by two investigators who had no knowledge of financial sponsors. Favorable—if both coinvestigators agreed that: (1) the conclusions suggested beneficial health effects or absence of expected adverse health effects, and (2) no statements were made that cast the product in a negative light. Unfavorable—if both coinvestigators agreed that: (1) the conclusions suggested adverse health effects or absence of expected beneficial health effects, and (2) no statements were made that cast the product in a positive light. Neutral—if the coinvestigators agreed that the conclusions were neither favorable nor unfavorable, or if the coinvestigators could not agree on classification.	The study coordinator provided two coinvestigators (CBE and DSL) with each article's abstract and discussion/conclusion section (as available). The coinvestigators classified article conclusions independently and then met to resolve discrepancies, using the categories outlined below.
Levine, 2003	The articles were reviewed and classified as supportive, neutral, or critical with respect to the use of olestra by criteria defined as follows: Supportive: Emphasizes safety/efficacy; recommends use; criticizes authors questioning safety/efficacy. Neutral: Concludes that there is insufficient information to assess safety/efficacy; makes no recommendations about use; equitably assesses opposing views. Critical: Emphasizes concerns about safety/efficacy; recommends	The articles were first assessed by 2 raters Independently (J.L. and J.G.), 1 of whom did and 1 of whom did not make a conscious effort to ignore authors' stated affiliations. When the independent rankings of the first 2 raters were compared, there were 19 discrepancies (for only 1 article the difference was supportive vs critical; for 2 it was supportive vs neutral, and in the 16 remaining cases, one of the reviewers rated the article either supportive or critical and the other was undecided between the same rating and neutral). All but 4 of these minor

	alternatives; criticizes authors emphasizing safety/efficacy.	discrepancies were resolved by having both raters reread the articles. The articles then were submitted to a third rater (D.H.) who had no prior contact with either the articles or the other raters' ratings. The articles were sent to this rater with all indications of authors' affiliations removed. In the undisputed cases, the latter ratings agreed with the original 2 raters in all but 5 cases; in those cases, the original ratings were determinant. In the 4 originally disputed cases, the third rater agreed with one or the other of the original raters, and her ratings were accepted as final.
Massougbodji, 2014	For each review included in the analysis, we extracted the final statement on the association between SSB consumption and obesity/weight gain. These final conclusions were anonymously compiled into a booklet; each page contained the statement with a Likert scale ranging from 0 = no evidence of a causal relation to 5 = strong evidence of a causal relation.	We selected a convenience sample of 11 readers among professionals and graduate students working in the field of obesity research at the Quebec Heart and Lung Institute Research Center. These readers were invited to blindly score their understanding of study conclusions and an average position score was calculated for each review.
Mugambi, 2013	The authors' overall study conclusion and conclusions on reported clinical outcomes were evaluated and categorized as: 1. Positive: The author's conclusion preferred the sponsor's products over control/placebo. Interpretation of data supported the sponsor's products over control. 2. Negative: The sponsors' products were not preferred over control / placebo. Interpretation of data did NOT support the sponsors' products. 3. Neutral: The author's conclusion was neutral to the sponsor's products. 4. No clear conclusion was offered by author.	Two reviewers (MM, ML) independently extracted data using a pretested data extraction form that was designed for this review. The reviewers (MM, ML) cross checked data and resolved any differences through discussion. Unresolved disagreements were resolved by a third party (RB)
Nkansah, 2009	The following categories were coded: (xviii) authors' conclusion (whether the authors recommended Ca supplementation, did not recommend Ca supplementation or had a neutral conclusion).	Articles meeting inclusion criteria were examined individually by three reviewers (study investigators: H.I., T.N. and N.N.) and subsequently coded using a standard instrument. Each reviewer extracted details from the articles independently. After independent

		review, all three reviewers met to reconcile the results of the coding, and discrepancies were resolved by reviewing the original article and establishing consensus.
Wilde, 2012	The article was determined to be favorable if the results suggested beneficial health effects or an absence of expected adverse health effects; the article was determined to be unfavorable if the conclusions suggested adverse health effects; and the paper was determined to be neutral if the conclusions were neither favorable nor unfavorable or null findings of the expected beneficial health effects.	Each article's title and abstract was read by the two article classifiers, who made independent determinations about whether the article was relevant to dairy and obesity, and, if so, whether the findings were favorable, unfavorable, neutral, or undeterminable to the dairy Industry. After classification, the two article classifiers met to reconcile and corroborate their determinations. For each Principal Investigator–article pair, the reviewers determined whether their independent classifications of relevancy and outcome were unanimous or discrepant. Those articles for which the relevancy was discrepant were revisited and either a consensus or divergence of opinion was established. Relevant articles were reviewed further for outcome. For those in which the outcome was discrepant, the reviewers revisited the abstracts and established either a consensus or a divergence of opinion.

MANUSCRIPT TWO

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. 2019;9(5):e022912. doi: 10.1136/bmjopen-2018-022912)

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

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

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

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

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

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

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

Corresponding author: Prof. Lisa Bero, lisa.bero@sydney.edu.au

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

Abstract

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

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

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

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

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

Conclusions: We did not establish that the presence of food industry sponsorship or authors with a COI with the food industry was associated with results or conclusions that favour industry sponsors. The association of food industry sponsorship or authors with a COI with the food industry and favourable results or conclusions is uncertain. However, our analysis was hindered by the low level of COI disclosure in the included studies. Our findings support international reforms to improve the disclosure and management of conflicts of interest in nutrition research. Without such disclosures, it

will not be possible to determine if the results of nutrition research are free of food industry influences and potential biases.

Systematic review registration: PROSPERO ID CRD42017055841

Strengths and limitations of this study

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

BACKGROUND

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

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

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

questions they ask (research agenda), how they design and conduct a study, the selection of results they report and through 'spin' on conclusions. [16-19]

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

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

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

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

The secondary objectives of this review are to determine whether:

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

METHODS

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

Literature search strategy

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

Eligibility Criteria

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

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

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

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

Types of Outcome Measures

Primary Outcomes

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

1. Statistical significance of results favourable to the sponsor

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

2. Effect size of results

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

3. Conclusions

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

Secondary Outcomes

We assessed two secondary outcomes:

1. The risk of bias of the included studies

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

2. Concordance between study results and conclusions

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

Selection of studies

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

Data Collection and analysis

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

From each study we extracted:

- Year of publication

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

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

Classification of industry sponsorship and author conflicts of interest

Sponsorship was categorized as 1) industry or 2) non-industry. We defined industry sponsored studies as those declaring any sponsorship from the food industry, including if the study received 'mixed funding' from the food industry, non-profit organizations or other industries (i.e. pharmaceutical). Any study with an author with any disclosed financial tie to the food industry was classified as having a conflict of interest (COI). Author COI were categorized as 1) presence of a COI

with the food industry or 2) no COI. Any studies that did not contain an author COI disclosure statement were classified as no COI. We contacted the authors of one paper [24] for clarification on their disclosure of funding source.

Assessment of risk of bias in included studies

We used an adapted version of the Cochrane Collaboration's 'Risk of Bias in Non-Randomized Studies-of Interventions' (ROBINS-I)[25] tool to measure the risk of bias of included observational studies. The tool assesses bias across seven domains. Each domain is assessed at a low, moderate, serious or critical risk of bias, or no information. The domain rating with the highest risk of bias determines the overall risk of bias rating for the study. For example, if a study is rated as being at a serious risk of bias in one domain, the overall risk of bias rating is 'serious.'

Analysis

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

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

We used meta-analysis to examine whether food industry sponsorship and / or authors with COI with the food industry modified the magnitude of association between whole grains and

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

Protocol Registration

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

Patient Involvement

No patients were involved in the completion of this review.

RESULTS

Search results

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

Characteristics of included Studies

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

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

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

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

		Funding Source, n (%[1])		
Characteristic	Category	Total N = 22	Industry/COI N = 9	Non-Industry/No COI N = 13
Sex	Male	4 (18)	4 (44)	0 (0)
	Female	6 (27)	1 (11)	5 (38)
	Both	12 (55)	4 (44)	8 (62)
Sample Size, quartiles	<5000	6 (27)	2 (22)	4 (31)
	5000-50,000	9 (41)	4 (44)	5 (38)
	>50,000	7 (32)	3 (33)	4 (31)
Length of Follow up	N/A*	3 (14)	1 (11)	2 (15)
	<10 years	1 (5)	1 (11)	0 (0)
	10-15 years	12 (55)	4 (44)	8 (62)
	>15	6 (27)	3 (33)	3 (23)
Percent Wholegrain	Not defined	12 (55)	3 (33)	9 (69)
	>25%**	10 (45)	6 (67)	4 (31)
Type of Wholegrain	Only Wholegrain Intake	15 (68)	5 (56)	10 (77)
	Individual Wholegrain Food***	7 (32)	4 (44)	3 (23)
Primary Outcome	Favourable to Wholegrains	16 (73)	8 (89)	8 (62)
	Unfavourable to Wholegrains	6 (27)	1 (11)	5 (38)

Conclusions	Favourable to Wholegrains	16 (73)	8 (89)	8 (62)
	Unfavourable to Wholegrains	6 (27)	1 (11)	5 (38)
Risk of Bias Assessment				
	Serious/Critical Bias due to confounding	21 (95)	9 (100)	12 (92)
	Serious/Critical Bias in selection of participants into the study	3 (14)	1 (11)	2 (15)
	Serious/Critical Bias in classification of exposures	16 (73)	5 (56)	11 (85)
	Serious/Critical Bias due to deviations from exposures	7 (32)	3 (33)	4 (31)
	Serious/Critical Bias due to missing data	0 (0)	0 (0)	0 (0)
	Serious/Critical Bias in measurement of outcomes	1 (5)	1 (11)	0 (0)
	Serious/Critical Bias in selection of reported results	0 (0)	0 (0)	0 (0)
	Serious/Critical overall risk of bias	21 (95)	9 (100)	12 (92)

[1] Percentages may not add to 100 due to rounding
* Case control studies were not followed up
**Any wholegrain foods defined as >25%
***Individual foods included wholegrain cereal, breakfast cereal, bread & brown rice

Risk of bias in included studies

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

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

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

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

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

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

Favourable conclusions: Industry sponsored versus non-industry sponsored

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

Risk of Bias Assessment by Industry Ties

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

DISCUSSION

Observational studies examining the effect of wholegrain consumption on cardiovascular disease outcomes that were sponsored by the food industry and / or had authors with a COI with the food industry more often had favourable results than research not tied to the food industry. However, this finding was inconclusive with respect to the association between industry ties and favorable results, as the relative risk could be as high as 2.35 or as low as 0.88. We found no evidence of a difference in the magnitude of effect between industry sponsored and non-industry sponsored studies. It is difficult to detect differences in effect size by sponsorship as many study design features, such as dose and duration of exposures, and specific cardiovascular disease outcomes, vary across studies and may influence the effect size. In previous assessments of drug studies that have demonstrated that industry funded studies are more likely to have results that favour the study

sponsors, there was no statistically significant difference found in effect sizes between industry and non-industry sponsored studies. [13]

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

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

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

Strengths and limitations of this review

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

of risk of bias in the included studies was based on a tool that is under development, but changes to the tool are unlikely to affect the risk of bias ratings.[25]

Agreements and disagreements with other studies or reviews

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

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

Implications for clinicians, policy makers and future research

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

that we observed between industry and non-industry studies, the differences are unlikely to be explained by methodological risks of bias in these studies.

There are ways that study sponsorship can influence outcomes other than through the design of research. Bias may also be introduced in the way industry sponsored studies code events and analyse data, [35 36] through the selective reporting of study outcomes and through publication bias. [37] It has been demonstrated in other areas of medical research that there is a greater propensity to publish studies with statistically significant results. [38] Therefore, selective publication of study results or studies in their entirety, may limit the availability of all relevant nutrition data and can skew results that are used in dietary guideline development.[39] Publication bias could be minimized with the introduction of study registries for nutrition research, as has been established in pharmaceutical research. [40] The association of food industry sponsorship with the reporting of nutrition research still needs to be assessed.

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

Conclusion

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

association of food industry sponsorship or authors with a COI with the food industry and favourable results or conclusions is uncertain. However, our analysis was hindered by the low level of COI disclosure in the included studies. This research further strengthens calls for stricter policies relating to the disclosure and management of conflicts of interest in nutrition research. Without such disclosures, it will not be possible to determine if the results of nutrition research are free of food industry influences and potential biases.

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

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Ethical Approval: Not required

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

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

Figure 1. Study Flow Diagram

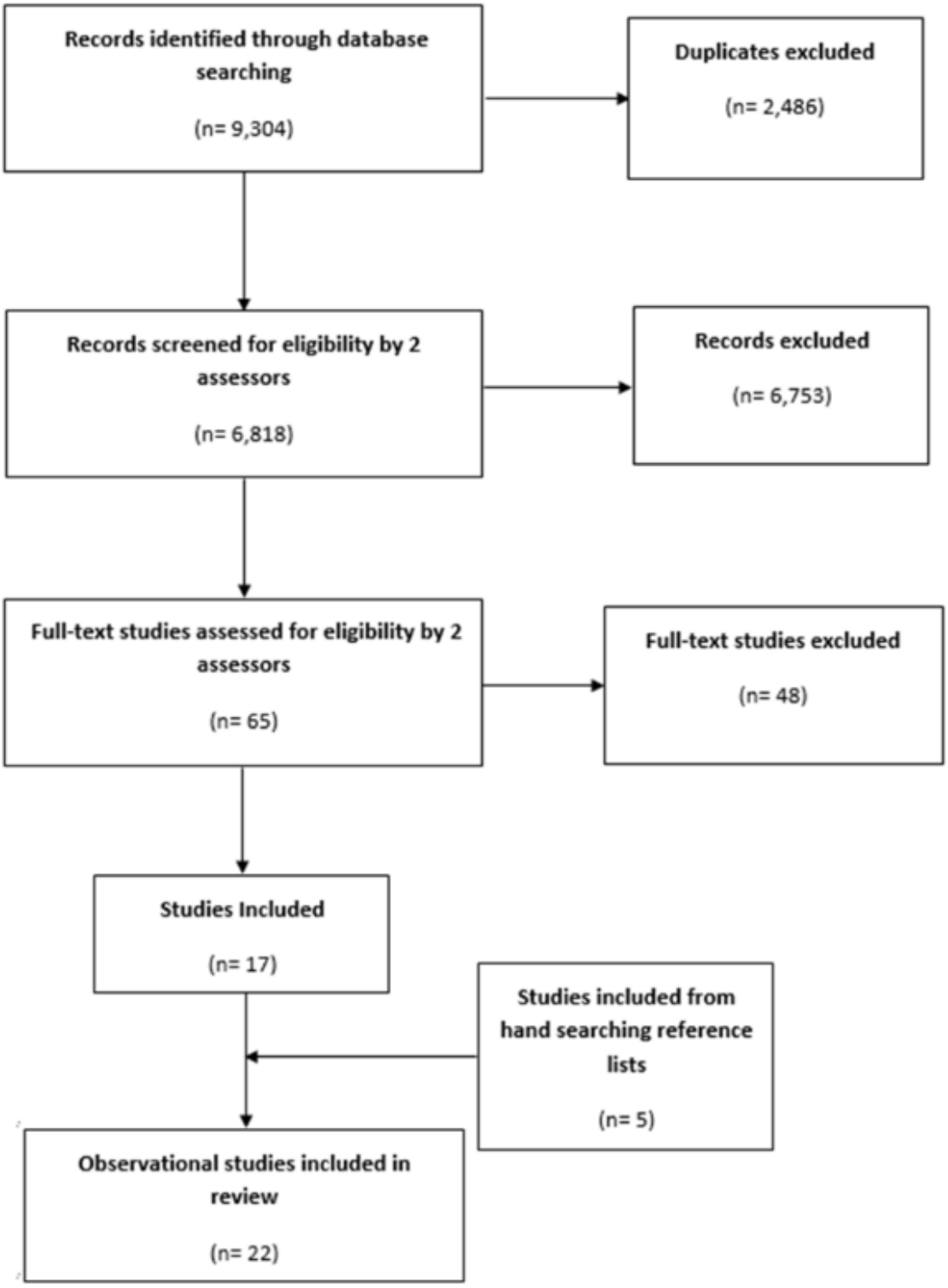


Figure 2. Risk of Bias of Included Studies

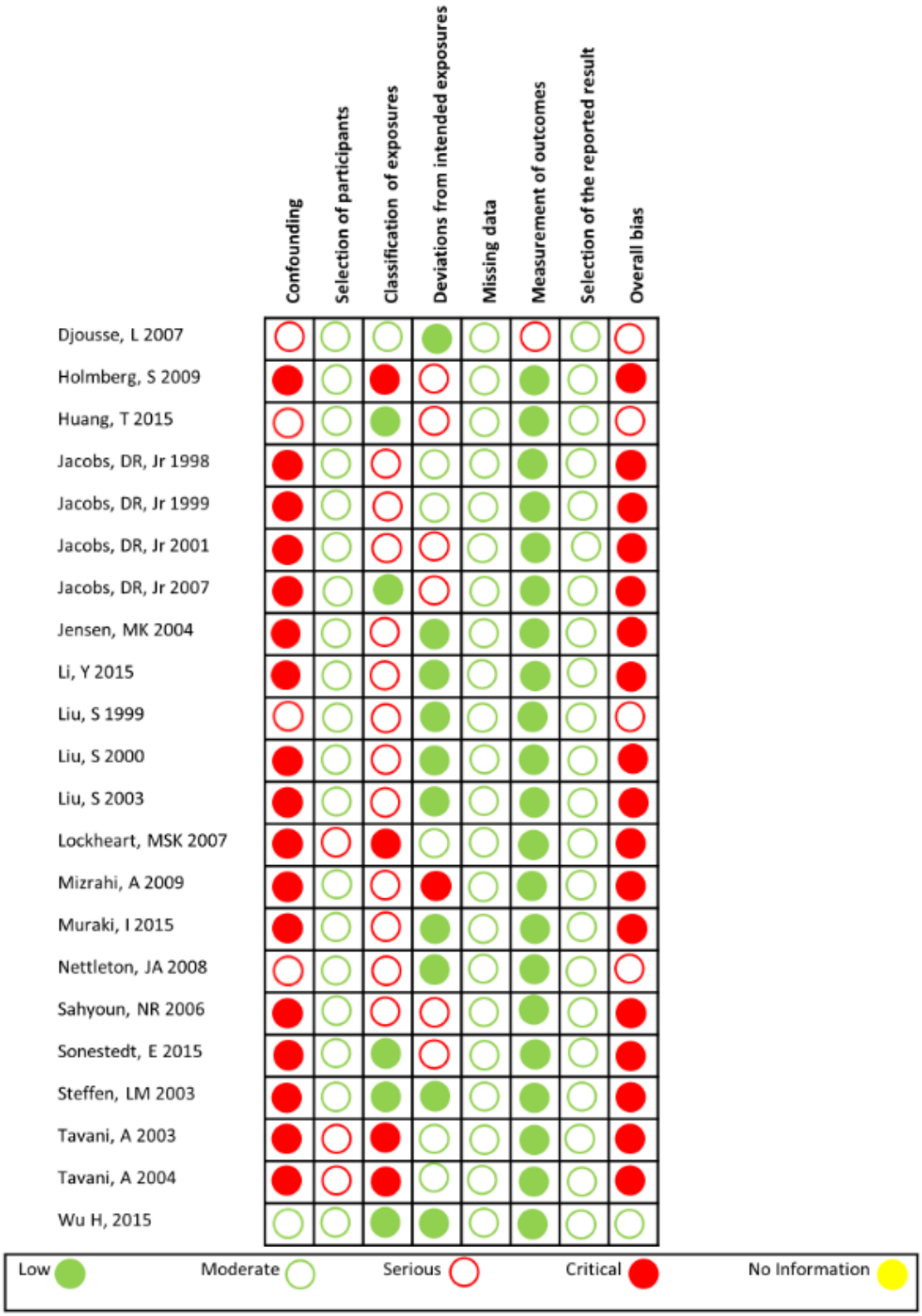


Figure 3: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Risk Ratio

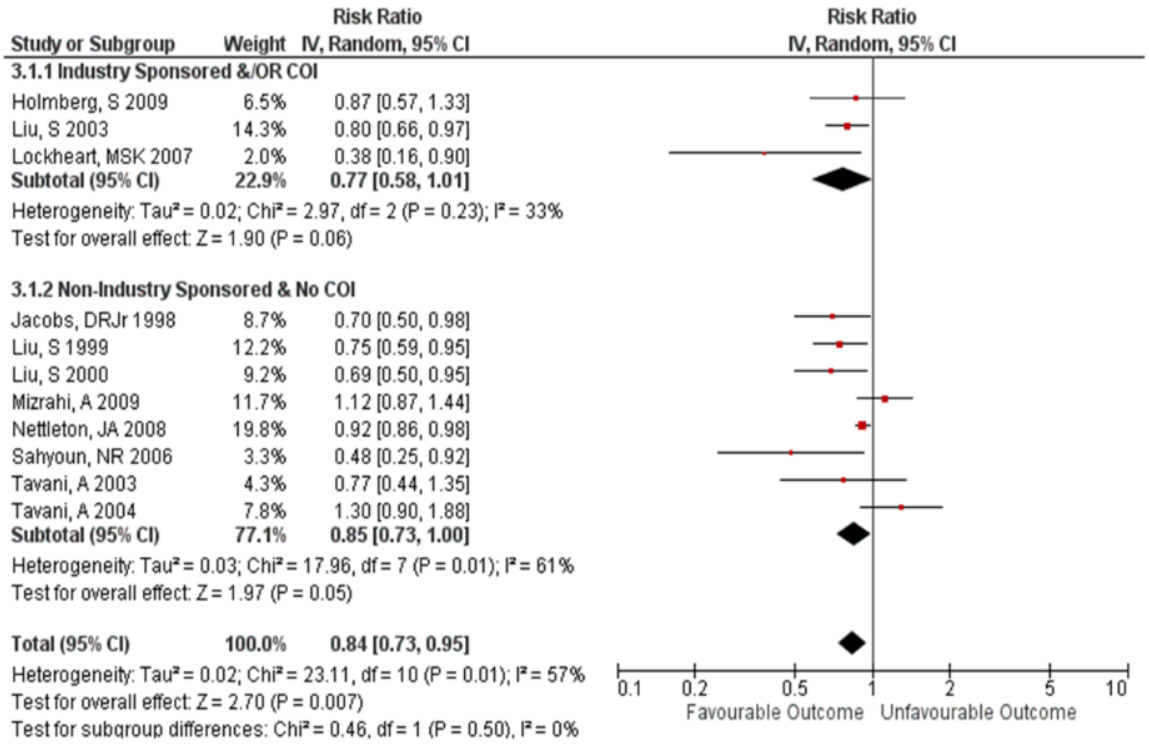
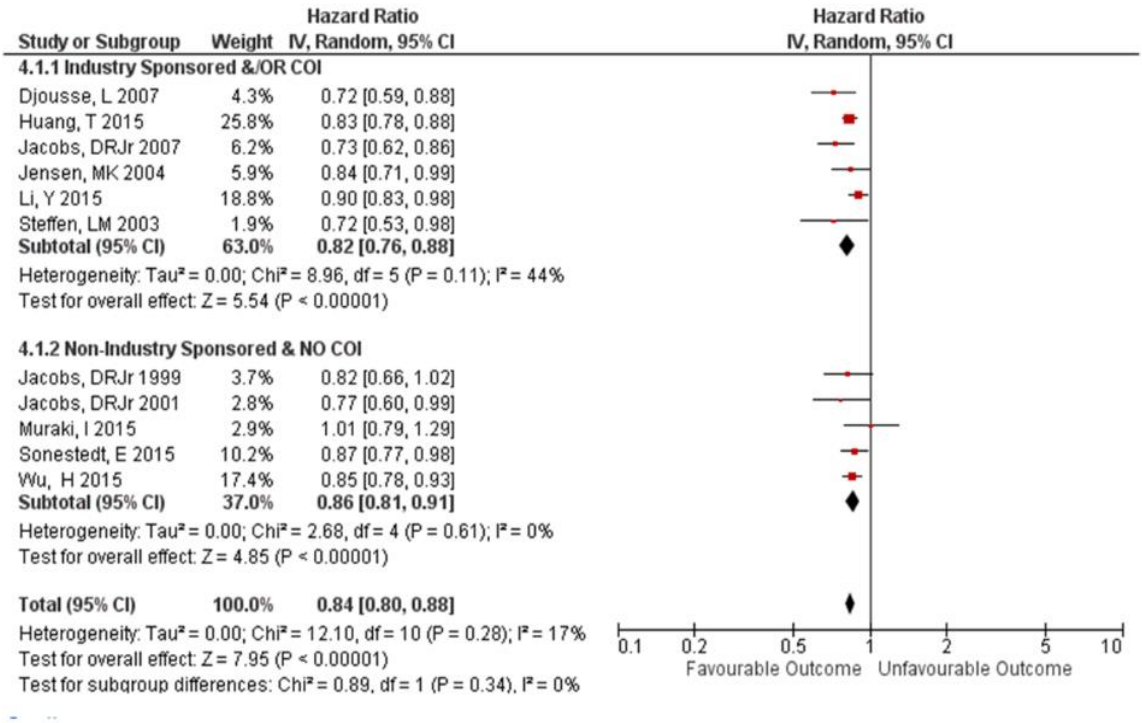


Figure 4: Effect Size - Industry sponsored &/OR author COI versus non-industry sponsored & no author COI studies, Hazard Ratio



Supplementary File 1: Search Strategy OVID Medline: Wholegrain & CVD

1. Randomized controlled trial*.sh.

2. experimental design.tw.

3. intervention*.tw.

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

5. random* control* trial*.tw.

6. clinical trial*.sh.

7. field trial*.tw.

8. community trial*.tw.

9. controlled clinical trial*.tw.

10. pragmatic trial*.tw.

11. observational study.sh.

12. cohort study.tw.

13. prospective cohort*.tw.

14. retrospective cohort*.tw.

15. case control*.sh.

16. ecological study.tw.

17. time series analys?s.tw.

18. before-after study.tw.

19. pre-post study.tw.

20. follow up stud*.sh.

21. comparative stud*.sh.

22. evaluation stud*.sh.

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

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

25. grain*.tw.

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

27. whole grain*.tw.

28. partially processed grains.tw.

29. whole wheat.tw.

30. wholemeal.tw.

31. rice*.tw.

32. oat*.tw.

33. barley*.tw.

34. wheat*.tw.

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

36. amaranth.tw.

37. Millets/me [Metabolism]

38. millet*.tw.

39. Sorghum/me [Metabolism]

40. sorghum*.tw.

41. maize*.tw.

42. spelt*.tw.

43. buckwheat*.tw.

44. Triticale/me [Metabolism]

45. triticale*.tw.

46. fonio*.tw.

47. emmer.tw.

48. einkorn*.tw.

49. kamut*.tw.

50. canary seed*.tw.

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

52. bread*.tw.

53. breakfast cereal*.tw.

54. pasta*.tw.

55. noodle*.tw.

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

57. flour*.tw.

58. polenta*.tw.

59. semolina*.tw.

60. bran.tw.

61. corn.tw.

62. wheat germ*.tw.

63. corn cake*.tw.

64. scone*.tw.

65. couscous.tw.

66. crumpet*.tw.

67. dietary fiber.tw.

68. dietary carbohydrate*.tw.

69. glycemic index.tw.

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

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

72. cardiovascular disease*.tw.

73. coronary*.tw.

74. heart*.tw.

75. cardia*.tw.

76. myocard*.tw.

77. isch?em*.tw.

78. angina*.tw.

79. ventric*.tw.

80. tachycardi*.tw.

81. pericard*.tw.

82. endocardi*.tw.

83. atrial fibrillat*.tw.

84. arrhythmi*.tw.

85. athero*.tw.

86. arterio*.tw.

87. HDL.tw.

88. LDL.tw.

89. VLDL.tw.

90. lipid*.tw.

91. lipoprotein*.tw.

92. triacylglycerol*.tw.

93. hyperlipid*.tw.

94. hypercholesterol*.tw.

95. hypercholester?emia*.tw.

96. hypertriglycerid?emia*.tw.

97. Cholesterol/

98. Stroke/

99. Cerebrovascular Disorders/

100. vascular accident*.tw.

101. TIA.tw.

102. Thrombosis/

103. thrombosis.tw.

104. Embolism/ or Pulmonary Embolism/

105. apoplexy.tw.

106. (brain adj2 accident*).tw.

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

108. Blood Pressure/ or Hypertension/

109. systolic blood pressure.tw.

110. diastolic blood pressure.tw.

111. Peripheral Vascular Diseases/ or Peripheral Arterial Disease/

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

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

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

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

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

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

118. Mortality/

119. mortality.tw.

120. Diabetes Mellitus, Type 2/

121. Hyperglycemia/

122. hyperglycemi*.tw.

123. (glucose adj2 intoleran*).tw.

124. Insulin Resistance/

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

126. metabolic cardiovascular syndrome.tw.

127. dysmetabolic syndrome x.tw.

128. HbA1c.tw.

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

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

131. 23 and 70 and 130

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

Supplementary File 2.

The protocol is published in PROSPERO, ID CRD42017055841, Available from:

http://www.crd.york.ac.uk/PROSPERO/.

Due to the length of the supplementary file it has not been included in the current thesis.

Supplementary File 3. List of Excluded Studies and Reasons for Exclusions

Available from: https://bmjopen.bmj.com/content/9/5/e022912

Due to the length of the supplementary file it has not been included in the current thesis.

Supplementary File 4: Characteristics of Included Studies

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

Li, Y 2015	2 Cohorts	30 years & 24 years	127,536	NHS 30-55 years HPFS 40-75 years	Wholegrain 4.6 % of total Energy Intake	Wholegrain 0.4 % of total Energy Intake	Coronary Heart Disease Death or Event (non-fatal MI & CHD deaths)	Non-Industry[9]	Yes[e]
Liu, S 1999	Cohort	10 years	75,521	38-63 years	Wholegrain 2.70 servings/day (median)	Wholegrain 0.13 servings/day (median)	Coronary Heart Disease Death or Event (non-fatal MI & fatal CHD)	Non-Industry[10]	No disclosure
Liu, S 2000	Cohort	12 years	75,521	38-63 years	Wholegrain 2.70 servings/day (median)	Wholegrain 0.13 servings/day (median)	Ischemic Stroke Death or Event	Non-Industry[11]	No disclosure
Liu, S 2003	Cohort	5.5 years (average)	86,190	40–84 years	Wholegrain Breakfast Cereal 1 servings/day	Rarely	Cardiovascular Disease Deaths	Non-Industry[12]	Yes[f]
Lockheart, MSK 2007	Case Control		211	Case 62·5 ± 7·7 Control 62·2 5 ± 7·7	Wholegrain Breakfast Cereal 36 g/day (median) & Wholegrain breads 240 g/day (median)	0 94 g/day	Myocardial Infarction (first MI)	Industry[13]	No Disclosure
Mizrahi, A 2009	Cohort	24 years	3,932	40–74 years	Wholegrain Men 280–1321 g/day (range) Women 195–963 g/day (range)	Wholegrain Men 0–139 g/day (range) Women 0–89 g/day (range)	Cerebrovascular Disease Death or Event (total strokes, including all acute strokes, subarachnoidal haemorrhages and other, undefined strokes; ischaemic stroke and intracerebral haemorrhage)	Non-Industry[14]	No[g]

Muraki I, 2015	3 Cohorts	26 years, 20 years & 24 years	207,556	Not available	Brown Rice ≥ 5 servings/week	Brown Rice < 1 servings/week	Cardiovascular Disease Death or Event (nonfatal MI, fatal CAD, and stroke (nonfatal or fatal))	Non-Industry[15]	No[h]
Nettleton, JA 2008	Cohort	13.3 years (average)	14,153	45-64 years	Wholegrain 1.3 ± 0.01 servings/day	Wholegrain 1.1 ± 0.04 servings/day	Heart Failure Death or Event	Non-Industry[16]	No[i]
Sahyoun, NR 2006	Cohort	Baseline 1981-84, followed through to 1995	535	60–98 years	Wholegrain >1.94 servings/day	Wholegrain ≤0.56 servings/day	Cardiovascular Disease Death	Non-Indusry[17]	No[j]
Sonestedt, E 2015	Cohort	14 year (average)	26,445	44–74 years	Wholegrain 2.5 portions/day	Wholegrain 0 portions/day	Cardiovascular Disease Death or Event (Incident CVD events, Stroke events, CHD (fatal or non-fatal myocardial infarction or death due to ischemic heart disease), Ischemic stroke).	Non-Industry[18]	No Disclosure
Steffen, L M 2003	Cohort	11 years	11,940	45–64 years	Wholegrain 3.0 servings/day	Wholegrain 0.1 servings/day	Coronary Artery Disease Death or Event (the first definite or probable MI, silent MI by electrocardiography, definite CAD death, or coronary revascularization) & Ischemic Stroke Death or Event (first	Non-Industry[19]	Yes[k]

							definite or probable cardioembolic or thrombotic brain infarction)		
Tavani, A 2003	Case Control		881	25–79 years	Wholegrain Bread Consumers	Wholegrain Bread Non-Consumers	Myocardial Infarction (first acute)	Non-Industry[20]	No Disclosure
Tavani, A 2004	3 Case Controls		1,602	17–79 years	Wholegrain >2 portions/per week	Wholegrain <2 portions/per week	Myocardial Infarction (first acute)	Non-Industry[21]	No Disclosure
Wu, H 2015	2 Cohort	26 years & 24 years	118,085	NHS 30-55 years HPFS 32-87 years	Wholegrain NHS 33 g/day (median) HPFS 47.8 g/day (median)	Wholegrain NHS 4.2 g/day (median) HPFS 5.9 g/day (median)	Cardiovascular Disease Death	Non-Industry[22]	No[l]

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

Description of Funding Source (Verbatim)

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3. This study is funded by an unrestricted research fund from NutraSource.Dr. Qi was supported by grants from the National Heart, Lung, and Blood Institute (HL071981), the National Institute of Diabetes and Digestive and Kidney Diseases (DK091718), the Boston Obesity Nutrition Research Center (DK46200), and United States–Israel Binational Science Foundation Grant 2011036. Dr. Qi was a recipient of the American Heart Association Scientist Development Award (0730094 N). Funding from NutraSource. There were no other relationships or activities that could appear to have influenced the submitted work
4. Supported by the National Institutes of Health (research grant CA-39742)
5. This research was supported by grant CA-39742 from the National Institutes of Health
6. Institute for Nutrition Research, University of Oslo and National Health Screening Service, Oslo, Norway
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19. Supported by the National Heart, Lung, and Blood Institute (contract nos. N01-HC-55015, N01-HC-55016, HC-55018, N01-HC-55019, HC-55020,N01-HC-55021, and N01-HC-55022)
20. This study was partly supported by "Ministero della Salute" (contract No 177, RF 2001).
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b) A Lee NutraSource (AWL), Royal Oak, MI 48073, USA. S Cho NutraSource (SSC), Clarksville, MD 21029, USA
c) None of the authors had a conflict of interest
d) None of the authors had any conflicts of interest
e) Dr. Hu has received honoraria from the Hass Avocado Board for participating in an academic symposium; and grant support from Metagenics and the California Walnut Commission
f) In 2001 SL received honoraria from General Mills Co for a presentation unrelated to this article
g) None of the authors had any personal or financial conflict of interest.
h) All authors reported no conflicts of interest related to the study.

i) The authors have no conflicts of interest to report

j) None of the authors had a conflict of interest

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

l) None reported

MANUSCRIPT THREE

The association of industry sponsorship with findings of randomised controlled trials examining the effect of wholegrain foods on cardiovascular disease outcomes, Systematic review and Meta-analysis

(Under Review)

Nicholas Chartres, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, New South Wales, 2006, Australia

Sally McDonald, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, New South Wales, 2006, Australia

Jessica Turton, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, New South Wales, 2006, Australia

Margaret Allman-Farinelli, The University of Sydney, D17, The Hub, 4th floor, Charles Perkins Centre, The University of Sydney, New South Wales, 2006, Australia

Joanne E McKenzie, Monash University, 553 St Kilda Road, Melbourne, Victoria, 3004, Australia

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

Corresponding author: Prof. Lisa Bero, lisa.bero@sydney.edu.au

Abstract

Objective: To investigate whether randomised controlled trials (RCTs) measuring the effect of wholegrain consumption and cardiovascular disease (CVD) outcomes with food industry sponsorship/and or authors with a conflict of interest (COI) are more likely to report favorable outcomes than those with no industry ties.

Data sources & extraction: We searched 8 databases from 1997-2018 for RCTs conducted in healthy adults or children.

Data synthesis: We used meta-analysis to test for differences in effect sizes.

Results: Twenty-four trials were included in the review. Trials with industry sponsorship were more likely to report favourable results RR =1.96 (95% CI 0.87, 4.41) and conclusions, RR= 1.60 (95% CI 0.87, 2.94) than trials with no industry sponsorship. The association was reversed for trials with a COI. There was uncertainty in all these relationships. We did not find a difference in effect sizes between studies with or without industry ties.

Conclusions: The effect of food industry sponsorship on the findings of RCTs examining the association of wholegrains and CVD was uncertain. More disclosure of study funding and author COI in all journals is needed to improve transparency and further examine this relationship.

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

BACKGROUND

Dietary Guidelines are essential in informing public health policies, clinical advice and helping consumers make informed decisions on what to eat to promote wellbeing and reduce the risk of non-communicable diseases. While recent recommendations have been made on how to redesign and optimise the process for developing dietary guidelines,[1,2] unless the primary studies that are included in these guidelines are designed and conducted to minimise bias, then the public's health may be at risk and confusion may arise about what constitutes a healthy diet.[3]

The beneficial effects of wholegrain foods on reducing cardiovascular disease (CVD) remains uncertain. Evidence from recent systematic reviews and meta-analyses of observational studies[4-6] support the summaries of evidence in various dietary guidelines that there is a probable association between wholegrain consumption and a reduced risk of cardiovascular disease.[7-9] However, these effects have not been observed in randomised controlled trials (RCTs) examining CVD risk factors, including blood lipids and blood pressure.[10,11]

Although dietary guidelines assess bias in primary studies using various methods,[12] they do not assess one important potential bias, industry sponsorship or author conflicts of interest. Empirical investigations of pharmaceutical, tobacco and chemical research have demonstrated that industry sponsorship is associated with findings that favour the study sponsor, even when controlling for other methodological biases.[13-21] It has been proposed that other mechanisms may explain this funding bias, including systematic differences in a study's design, conduct, and reporting of results.[22] Food manufacturers may have a financial interest in the findings of wholegrain RCTs, because wholegrain products (such as breakfast cereals) may be used to support health claims and market their products.

Studies sponsored by the food industry are more likely to have favorable conclusions, than studies with no industry sponsorship.[23] We recently examined the association of industry ties (industry sponsorship and author conflict of interest) with the results from observational studies measuring the effect of wholegrain foods on cardiovascular disease and mortality.[24] We found that studies with industry ties more often have favourable results and conclusions compared to those with no industry ties, but the association was uncertain. To date, there has been no such examination in RCTs.

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

- RCTs estimating the effects of wholegrain foods on cardiovascular disease with food industry sponsorship and / or authors with a conflict of interest with the food industry, are more likely to have results and/ or conclusions favourable to industry than those with no industry ties.

The secondary objectives of this review are to determine whether RCTs with food industry sponsorship and/or authors with a conflict of interest with the food industry:

I. differ in their risk of bias compared with trials with no industry ties;
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 RCTs examining the effect of wholegrain consumption on cardiovascular disease outcomes. The protocol is published in PROSPERO [25] ID CRD42017055841.

Literature search strategy

The search included terms to locate both RCTs and observational studies, the latter of which were included in a separate systematic review.[24] The search strategy was developed according to the Process Manual used in the formation of the 2013 Australian Dietary Guidelines[26] and the assistance of an information specialist. We searched the following databases from January 1997-November 2018: MEDLINE; CINAHL; PubMed; PreMEDLINE; Cochrane Library; PsycINFO; Science Direct; and ERIC. The search strategy we used for Ovid MEDLINE is shown in Supplementary file 1. We adapted this strategy for the other databases. We also hand searched the references lists of identified trials and reviews

Eligibility Criteria

We included RCTs that estimated the effects of wholegrain consumption on cardiovascular disease outcomes in healthy children and/or adults.

We included RCTs that defined wholegrains in anyway, as defined by the author. We included trials that compared wholegrain food to control, to other foods or compared different types of wholegrains (e.g. sorghum vs. wheat) to each other.

We included RCTs that measured a surrogate outcome of cardiovascular disease. We restricted our inclusion to trials that measured surrogate outcomes because long term clinical outcomes (e.g. mortality) are rarely measured in RCTs. The specific surrogate outcomes included were: low-density lipoprotein (LDL) cholesterol, systolic blood pressure (BP), diastolic BP and glycated hemoglobin (HbA1c). Outcomes were standardized to the same units when measured using different units across the trials (e.g. LDL cholesterol in mmol/L or mg/dl).

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

Types of Outcome Measures

Primary Outcomes

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

3. Statistical significance of results favourable to the study sponsor

Favourable results were defined as results that were favourable to the sponsor's product(s), indicating a statistically significant decreased cardiovascular disease risk factor versus the comparator. Favourable results were defined as those that were statistically significant at the 0.05 level (two tailed). Otherwise, results were classified as unfavourable. In the circumstance where a trial reported multiple results (e.g. systolic BP and diastolic BP), only one result needed to be 'favourable' for the trial to be classified as 'favourable'.

4. Effect size of results

Effect size was defined as the difference in means (or mean difference [MD]) between wholegrain tested versus comparator on the cardiovascular disease outcome.

5. Conclusions

Conclusions that suggested that the wholegrain intervention being investigated was beneficial to health were coded favourable to the study sponsor. Otherwise, the conclusions were considered unfavourable. In the circumstance where a trial reported multiple results (e.g. systolic BP and diastolic BP), the trial only had to report favourably for on one of the results for the conclusions to be classified as favourable.

Secondary Outcomes

We assessed two secondary outcomes:

3. The risk of bias of the included trials

We used the Cochrane Cochrane Collaboration's tool for assessing risk of bias in randomised trials for the included trials. [27] The tool assesses bias across seven domains ('Random sequence generation', 'Allocation concealment', 'Blinding of participants and personnel', 'Blinding of outcomes assessment', 'Incomplete outcome data', 'Selective reporting' and 'Other sources of bias'), with each domain assessed as having a low, unclear or high risk of bias. In the circumstance where a trial reported multiple results (e.g. systolic BP and diastolic BP), the risk of bias was only assessed for one randomly selected outcome.

4. Concordance between study results and conclusions

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

Selection of trials

Three reviewers (NC, SMc & JT, working in pairs) independently screened the titles and abstracts of all retrieved records for exclusions. Both reviewers had to exclude the study for the full text not to be retrieved. The full text of potentially eligible RCTs were then retrieved, and the three reviewers (NC, SMc & JT) assessed these against the inclusion criteria. Agreement amongst the reviewers was reached by consensus. If agreement could not be reached, a third reviewer (LB) determined the decision.

Data Collection

From each RCT we extracted:

- Year of publication
- Study design (individual crossover or individual parallel)
- Sample size of trial at randomization
- Average age of participants (combined or if reported, separately)
- Length of trial up to the final follow up time reported in the study
- How the trial defined wholegrain (verbatim)
- Disclosure of funding source (no disclosure, yes and there is a sponsor, no, the authors state they received no funding for their work)
- Name of the funders of the study (verbatim)
- Disclosed 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 conflict of interest (no disclosure, yes and there is a conflict, no, the authors state they had no conflicts of interest)
- Authors conflict of interest statement (verbatim)
- Outcomes assessed in the study (LDL cholesterol, systolic BP, diastolic BP and HbA1c)

- The numerical results of the study (e.g. mean of each intervention group, mean difference, standard deviation(s)(SD), standard error(s) (SE), 95% confidence interval(s) (CI) and p value(s)).

Extracted data were stored in REDcap, a secure web-based application for data collection and management.[28] Two reviewers (NC & JT) independently extracted the data. Any disagreements in the data extraction were resolved by consensus. If agreement could not be reached, a third reviewer (LB) determined the decision.

We contacted all authors for missing data and a total of four responded. For a particular outcome (e.g. LDL cholesterol) within a study, if there were multiple measurements reported at different timepoints, we selected the last follow up measure.

Classification of industry sponsorship and author conflicts of interest

We categorised sponsorship as 1) industry or 2) non-industry. Any study that did not contain a funding disclosure statement was classified as non-industry. We classified industry sponsored trials as those that declared any food industry sponsorship, this included if the study received 'mixed funding' that involved funding from food industry, other industries (i.e. pharmaceutical) or sectors such as government or non-profit. Author conflict of interests were categorised as 1) conflict of interest or 2) no conflict of interest. Trials with at least one author with any disclosed financial tie to the food industry were categorised as having a conflict of interest. Any study that did not contain an author conflict of interest disclosure statement was classified as 'no conflict of interest'.

Analysis methods

We report the frequencies and percentages of the study characteristics across all included RCTs, and separately by funding source and author conflict of interest. We depict visually the percentage of trials at a low, high, and unclear risk of bias for each domain.

To quantify the association between food industry sponsorship and/or authors with a conflict of interest with the food industry and (i) favourable results, (ii) favourable conclusions, (iii) risk of bias across domains, and (iv) level of concordance, we calculated risk ratios (and 95% confidence intervals).

Meta-analysis methods

Measures of treatment effect

As all outcomes were continuous and measured on, or could be converted to, the same scale, we estimated the intervention effect using the mean difference (i.e. wholegrain mean minus comparator group mean) with 95% confidence interval for each study. The factor used to convert LDL cholesterol measured in mg/dL to mmo/L was 38.67.[29]

Dealing with different study designs

We included both crossover and parallel RCTs. In order to meta-analyse results from these study designs, we required an estimate of the mean difference and its standard error. For the crossover design, (when available) we extracted the mean difference and the corresponding standard deviation of differences, from which we calculated the standard error. For the parallel design, (when available) we extracted the means and standard deviations of each group. We then calculated the pooled standard deviation across groups, from which we calculated the standard error. When estimates of standard deviations were not directly reported, we attempted to calculate these through algebraic manipulation of available statistics (e.g. exact p-values, 95% confidence limits).[30]

We included one multi-arm randomized trial.[31] For this three-arm trial, we combined the summary statistics of the two relevant experimental intervention groups to create a single pairwise comparison.[30]

Dealing with missing data

For trials that did not report the results in sufficient detail to be included in a meta-analysis, we sought data from the authors. If we did not receive the required data from the authors, we assessed if imputation of missing values was appropriate. In trials that only reported medians, we used the methods described by Hozo et al.[32] to estimate the means from the reported medians, range and sample size.

Synthesis

To examine whether RCTs with food industry sponsorship and/or authors with a conflict of interest with the food industry modified the magnitude of effect of wholegrains on cardiovascular disease outcomes we used meta-analysis. For each outcome, we combined mean differences 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 undertook a fixed-effects test for subgroup differences (defined by industry sponsorship / authors conflict of interest) using the Chi2 test and calculated the difference in mean differences along with 95% confidence intervals. Analyses were undertaken in Review Manager 5.3.[33] As trials reported a mix of post intervention and change-from-baseline summary statistics, we combined effects calculated from these statistics in the meta-analysis. Combining post intervention and change-from-baseline values in a meta-analysis when using MD is appropriate as they can be usually assumed to be addressing exactly the same underlying intervention effects.[34]

We were unable to examine whether industry sponsorship and/ or author COI modified the magnitude of effect between wholegrains and HbA1c% since all trials had either industry sponsorship or authors with a COI.

Sensitivity analysis

We conducted sensitivity analyses to investigate if our findings were robust to our classification of trials with no disclosure statement as 'no conflict of interest'. In the sensitivity analysis, we re-classified these trials as having a 'conflict of interest'. We also planned to use sensitivity analysis to assess the influence of risk of bias by restricting the analysis to trials at a 'low risk of bias' across all domains. However, as risk of bias was unclear for most domains across all trials, this was not undertaken.

RESULTS

Search results

We identified 8, 295 references for screening, from which, 24 trials met the inclusion criteria (Figure 1). See Supplementary file 2 for 'List of excluded trials and reasons for exclusion'.

Characteristics of included Trials

All included trials were published between 2001 and 2018. Ten trials disclosed food industry sponsorship related to wholegrains, but only one study described the role of the sponsor in the study. Five trials did not contain an author conflict of interest statement. Twelve trials contained an author with a conflict of interest with the food industry. Sixteen trials either had food industry sponsorship or an author with a conflict of interest with the food industry (industry ties).

Overall, the study characteristics between industry and non-industry sponsored trials were similar (Table 1). Food industry sponsored trials (50%) were more often used a parallel design as compared with trials with no industry sponsorship (36%). A larger percentage of industry sponsored trials (30%) had sample sizes >50, compared with trials with no industry sponsorship (7%).

Trials with authors with a conflict of interest with the food industry (83%) more often analysed both males and females, compared with trials with no author conflict of interest (58%). A greater percentage of trials with author conflict of interest (33%) had sample sizes >50 than those trials with no author conflict of interest (0%). Trials with an author with a conflict of interest with the food industry also more often analysed any type of wholegrain food (75%), rather than a specific type of wholegrain, compared with those without an author with a conflict of interest with the food industry (25%).

Details of each included trial are in Supplementary file 3.

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

Risk of bias in included trials

The reporting of methods was commonly incomplete, which led to a risk of bias rating of 'unclear' for the majority of trials for the domains: 'random sequence generation', 'allocation concealment' and 'selective reporting' (Figure 2). Conversely, the domains of 'blinding of outcome assessment', 'incomplete data' and 'other sources of bias' were rated as a low risk of bias in the majority of the trials (Table 1)

Favourable results - Statistical significance: Industry sponsored vs non-industry sponsored and conflict of interest vs no conflict of interest

The risk of reporting favourable results was 96% higher in industry sponsored trials (7/10) than in non-industry sponsored trials (5/14) RR =1.96 (95% CI 0.87, 4.41; n= 24). Although, the confidence interval was wide and included the possibility of no, or an unimportant, difference in risks. When we assessed trials with a conflict of interest with food industry (5/12) compared to those with no conflict of interest with the food industry (7/12), the risk was reversed RR= 0.71 (95% CI 0.31, 1.63; n = 24 trials), although again the association was uncertain.

Effect size: Industry sponsored vs non-industry sponsored, and conflict of interest vs no conflict of interest

LDL cholesterol

We found no important difference in the magnitude of the MD (difference in means between wholegrains and comparator) for LDL cholesterol in trials with industry sponsorship (MD = -0.12; n = 8 trials) compared with those without industry funding (MD = -0.09; n = 10 trials) (difference in MDs -0.03 (95%CI -0.17, 0.11)); p = 0.710 (Figure 3).

We found no important difference in the magnitude of the MD for LDL cholesterol in trials with an author with a conflict of interest with the food industry (MD = -0.07; n = 10 trials) compared with trials with no author conflict of interest with the food industry (MD = -0.15; n = 8 trials) (difference in MDs 0.08 (95%CI -0.06, 0.22)); P=0.25 (Figure 4).

Systolic blood pressure

We found no important difference in the magnitude of the MD for systolic blood pressure in trials with industry sponsorship (MD = -1.53; n =3 trials) compared with trials with no industry sponsorship (MD = -0.54; n =7 trials) (difference in MDs -0.99 (95%CI -4.51, 2.53)); P=0.58 (Figure 5).

We found no important difference in the magnitude of the MD for systolic blood pressure between trials with an author with a conflict of interest with the food industry (MD = -0.13; n = 7 trials) and trials with no author with a conflict of interest with the food industry (MD = -2.07; n = 3 trials) (difference in MDs 1.94 (95%CI -0.96, 4.84)); P=0.19 (Figure 6).

Diastolic blood pressure

We found no important difference in the magnitude of the MD for diastolic blood pressure in trials with industry sponsorship (MD = -0.02; n = 4 trials) and those trials with no industry sponsorship (MD = 0.42; n = 5 trials) (difference in MDs -0.44 (95%CI -2.47, 1.59)) P=0.67 (Figure 7).

We found no important difference in the magnitude of the MD for diastolic blood pressure between trials with an author with a conflict of interest with the food industry (MD = 0.14; n = 7 trials) and trials with no author with a conflict of interest with the food industry (MD = -0.66; n = 2 trials) (difference in MDs 0.8 (95%CI -2.36, 3.96)); P=0.62 (Figure 8).

Favourable conclusions: Industry sponsored versus non-industry sponsored and conflict of interest vs no conflict of interest

The risk of reporting favourable conclusions was 60% higher in industry sponsored trials (8/10) than in than trials with no industry sponsorship (7/14) RR= 1.60 (95% CI 0.87, 2.94; n= 24), although the confidence interval was wide and included the possibility of no, or an unimportant, difference. When we

compared trials with a conflict of interest with the food (8/12) industry to those with no conflict of interest (9/12), the risk was lower RR = 0.89 (95% CI 0.53, 1.49; n = 24), however there was uncertainty in the association.

Risk of Bias Assessment

Risk ratios for a high risk of bias rating (for each domain) in industry funded or trials with an author with a conflict of interest versus no industry funding or no conflict of interest trials are presented in Table 2. There was little consistency in the direction of risk ratios across the risk of bias domains, with some indicating an increased risk of a high risk of bias rating with industry funding or a conflict of interest, while other indicated a decreased risk. The confidence intervals were wide providing little certainty in these estimates.

Concordance between study results and conclusions

Five trials that all had unfavorable results, overemphasized the benefits of wholegrains or highlighted p values that were inappropriate (highlighting change from baseline within groups, not between groups).

Industry sponsored trials (2/10) were 7% less likely to have discordant results and conclusions than non-industry sponsored trials (3/14) RR = 0.93 (95% CI 0.19, 4.60; n = 24 trials), however the confidence interval was wide. Trials with an author conflict of interest with the food industry (3/12) were 50% more likely to have discordance than those with no conflict of interest with the food industry (2/12) RR = 1.50 (95% CI 0.30, 7.43; n = 24 trials).

Sensitivity Analysis

We reanalysed trials that did not report a conflict of interest disclosure and categorised them as a 'conflict of interest'. The results from our original analysis were robust and our conclusions did not change. The results from our original risk of bias ratings were also robust and there was also no change in the risk of bias ratings across each domain. Results of the sensitivity analyses are available in supplementary file 4.

DISCUSSION

The association between trials with food industry sponsorship and/ or authors with a COI and the reporting of favorable results and conclusions compared with trials without industry ties was uncertain. Although studies with industry sponsorship were more likely and studies with a COI less likely, to report more favorably on these outcomes.

We did not find any evidence of a clinically important difference in the magnitude of effect between trials with industry sponsorship and those with no industry sponsorship for all outcomes. Similarly, we did not find a clinically important difference in the magnitude of effect between trials with a COI and those with no COI with the food industry. However, our ability to classify trials as having industry funding and COI was compromised given the lack of statements or variability in funding. In addition, the risk of bias could not be determined or was high for most domains across all trials.

We did not find an association between trials sponsored by the food industry and discordant results, although industry sponsored trials were less likely to have discordant results and conclusions, compared with trials with no industry funding. Although again uncertain, we found studies with a COI with the food industry more likely to have discordant results and conclusions, compared with trials with no industry

funding. Even when study results are reported as non-significant, 'spin' on the conclusions can occur. Although conclusions are not used in the development of dietary guidelines, they still may be used to inform health practitioners and consumers on what constitutes a healthy diet. Spin in biomedical research has been shown to be cause for concern.[35,36]

Agreements and disagreements with other trials or reviews

Although there was uncertainty in the association between trials with food industry sponsorship and the statistical significance of the results and conclusions, similar findings showing studies with industry ties are more likely to report favourable outcomes have been identified in observational studies examining the effects of wholegrain foods and cardiovascular disease outcomes and in a review of a broad range of nutrition research we previously conducted.[23,24] Similar findings have also been found in empirical investigations of pharmaceutical, tobacco and chemical research have demonstrated that industry sponsorship is associated with outcomes that favour the study sponsor, even when controlling for other methodological biases.[13-21]

The association of favourable outcomes with author conflicts of interest has been less studied; some have identified an association,[37-41] while others have found no association.[42-44] One reason for the lack of research on author conflict of interest may be that disclosure of author conflict of interest is less complete compared with funding sources.[45] More than a quarter of trials did not have conflict of interest disclosure statement. Therefore, a third of the trials we classified as 'no conflict of interest' with the food industry were trials with no disclosure. Lack of compliance with author conflict of interest disclosure policies is now well established in numerous fields of research. [36,45-49] Although various solutions have been discussed to improve rates of disclosure including mandatory disclosure

requirements in all journals and the use of penalties for those who fail to comply, [23,40] this remains an issue in nutrition research.

Incomplete reporting of methods is consistent with previous systematic reviews of RCTs examining the effect of wholegrain foods on cardiovascular disease outcomes.[10] There was little to no difference found in the risk of bias ratings across each bias domain in trials with industry sponsorship and / or authors with a conflict of interest with the food industry and those without industry ties. Previous examinations of pharmaceutical, tobacco and nutrition research that has demonstrated that studies with the presence of industry sponsorship are of equal or better internal validity than those without the presence of sponsorship.[18,21,23,24,35,40]

It has been proposed that mechanisms other than those assessed in risk of bias tools may explain funding bias, including systematic differences in a study's design, conduct, and reporting of results. [22] [50,51] [52] On average both industry and non-industry sponsored trials reported on 18 outcomes in all trials, making selective reporting of outcomes based on their direction, magnitude, or statistical significance, possible. The extent of selective reporting is difficult to assess without the registration of protocols and reporting of all outcomes, a priori. Such reporting may skew the results that are used in the development of dietary guideline and lead to biased recommendations.[53]

In order to make reliable and trustworthy guidelines, bias in the primary studies that are used in their development, must be minimised. Therefore, until the possible influence of food industry sponsorship and food industry ties in primary nutrition studies of wholegrain foods can be further examined with larger samples of trials, this bias, if it is present, may be unaccounted for in dietary guidelines.

Strengths and limitations of this review

We examined the association of both study sponsorship and author conflicts of interest independently, the latter of which has been less studied. We prospectively registered our review in PROSPERO.[25] We used well defined inclusion and exclusion criteria, conducted a comprehensive search across multiple database and hand searched the references lists of included trials. We contacted all authors for missing data on methods or outcomes. We did not contact the authors of trials lacking a sponsorship or author conflict of interest disclosure statements and therefore may underestimating the number of RCTs with industry ties.

Conclusions: The association between trials with food industry sponsorship and/ or authors with a COI and the reporting of favorable results and conclusions compared with trials without industry ties was uncertain. Participation in trial registries and mandatory disclosure requirements of study funding and author conflicts of interests in all journals are necessary to improve the transparency of nutrition research so that all biases can be assessed.

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Table 1. Characteristics of the included trials by sponsorship, author conflict of interest and industry ties[#]

		Total	Industry		COI		Industry Ties	
			Funding Source, n (%[1])					
Characteristic	Category	Total N = 24	Industry N=10	Non-Industry N=14	COI N =12	No COI N=12	Industry/ COI N = 16	Non-Industry/ No COI N = 8
Study Design	Crossover	14 (58)	5 (50)	9 (64)	6 (50)	8 (66)	8 (50)	6 (75)
	Parallel	10 (42)	5 (50)	5 (36)	6 (50)	4 (33)	8 (50)	2 (25)
Sex	Male	2 (8)	1 (10)	1 (7)	0 (0)	2 (17)	1 (6)	1 (13)
	Female	5 (21)	3 (30)	2 (14)	2 (17)	3 (25)	3 (19)	2 (25)
	Both	17 (71)	6 (60)	11 (79)	10 (83)	7 (58)	12 (75)	5 (63)
Sample Size	<25	8 (33)	3 (30)	5 (36)	4 (33)	4 (33)	6 (38)	2 (25)
	25-50	12 (50)	4 (40)	8 (57)	4 (33)	8 (66)	6 (38)	6 (75)
	>50	4 (17)	3 (30)	1 (7)	4 (33)	0 (0)	4 (25)	0 (0)
Length of Follow up	<6 weeks	2 (8)	(0)	2 (14)	1 (8)	1 (8)	1 (6)	1 (13)
	6-12 weeks	18 (75)	8 (80)	10 (71)	9 (75)	9 (75)	12 (75)	6 (75)
	>12 weeks	4 (17)	2 (20)	2 (14)	2 (17)	2 (17)	3 (19)	1 (13)
Type of Wholegrain*	Any Wholegrain food	12 (50)	5 (50)	7 (50)	9 (75)	3 (25)	9 (56)	3 (38)
	Individual Wholegrains	12 (50)	5 (50)	7 (50)	3 (25)	9 (75)	7 (44)	5 (63)
Type of Comparator **	'No' or 'low'	17 (71)	7 (70)	10 (71)	9 (75)	8 (66)	11 (69)	6 (75)
	'Equivalent'	7 (29)	3 (30)	4 (29)	3 (25)	4 (33)	5 (31)	2 (25)
Risk of Bias Assessment								

		Total	Industry		COI		Industry Ties	
Characteristic	Category	Total N = 24	Industry N=10	Non-Industry N=14	COI N =12	No COI N=12	Industry/ COI N = 16	Non-Industry/ No COI N = 8
	High Risk of Bias in random sequence generation	0 (0)	0 (0)	0(0)	0 (0)	(0)	0 (0)	0 (0)
	High Risk of Bias in allocation concealment	1 (4)	0 (0)	1 (7)	1 (8)	(0)	1 (6)	0 (0)
	High Risk of Bias in blinding of participants and personnel	16 (66)	8 (80)	8 (57)	8 (66)	8 (66)	11 (69)	5 (63)
	High Risk of Bias in blinding of outcome assessment	0 (0)	(0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	High Risk of Bias in incomplete outcome data	4 (17)	0 (0)	4 (29)	3 (25)	1 (8)	3 (19)	1 (13)
	High Risk of Bias in selective reporting	0 (0)	(0)	(0)	0 (0)	0 (0)	0 (0)	0 (0)

		Total	Industry		COI		Industry Ties	
Characteristic	Category	Total N = 24	Industry N=10	Non-Industry N=14	COI N =12	No COI N=12	Industry/ COI N = 16	Non-Industry/ No COI N = 8
	High Risk of Bias due to other sources of bias	3 (13)	2 (20)	1 (7)	1 (8)	2 (17)	2 (13)	1 (13)

[#] An industry tie is defined as a study with industry sponsorship and / or an author with a conflict of interest

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

* Individual types of wholegrains e.g. oats, quinoa, barley etc

** 'Equivalent' are trials that had compared similar levels of wholegrains e.g. sorghum vs. wheat

Table 2. High risk of bias rating, Industry sponsored vs non-industry sponsored, and conflict of interest vs no conflict of interest

Risk of Bias Domain	Industry	COI
Random sequence generation	*	*
Allocation concealment	*	*
Blinding of participants and personnel	RR = 1.40 (95% CI 0.81,2.43)	RR = 1.00 (95% CI 0.57, 1.76)
Blinding of outcome assessment	*	*
Incomplete outcome data	*	RR = 3.00 (95% CI 0.36, 24.92)
Selective reporting	*	*
Other bias	RR = 2.80 (95% CI 0.29, 26.81)	RR = 0.50 (95% CI 0.05, 4.81)

*RR could not be calculated as there were no studies rated as high risk of bias for the domain

Figure 1. Study Flow Diagram of Included Trials

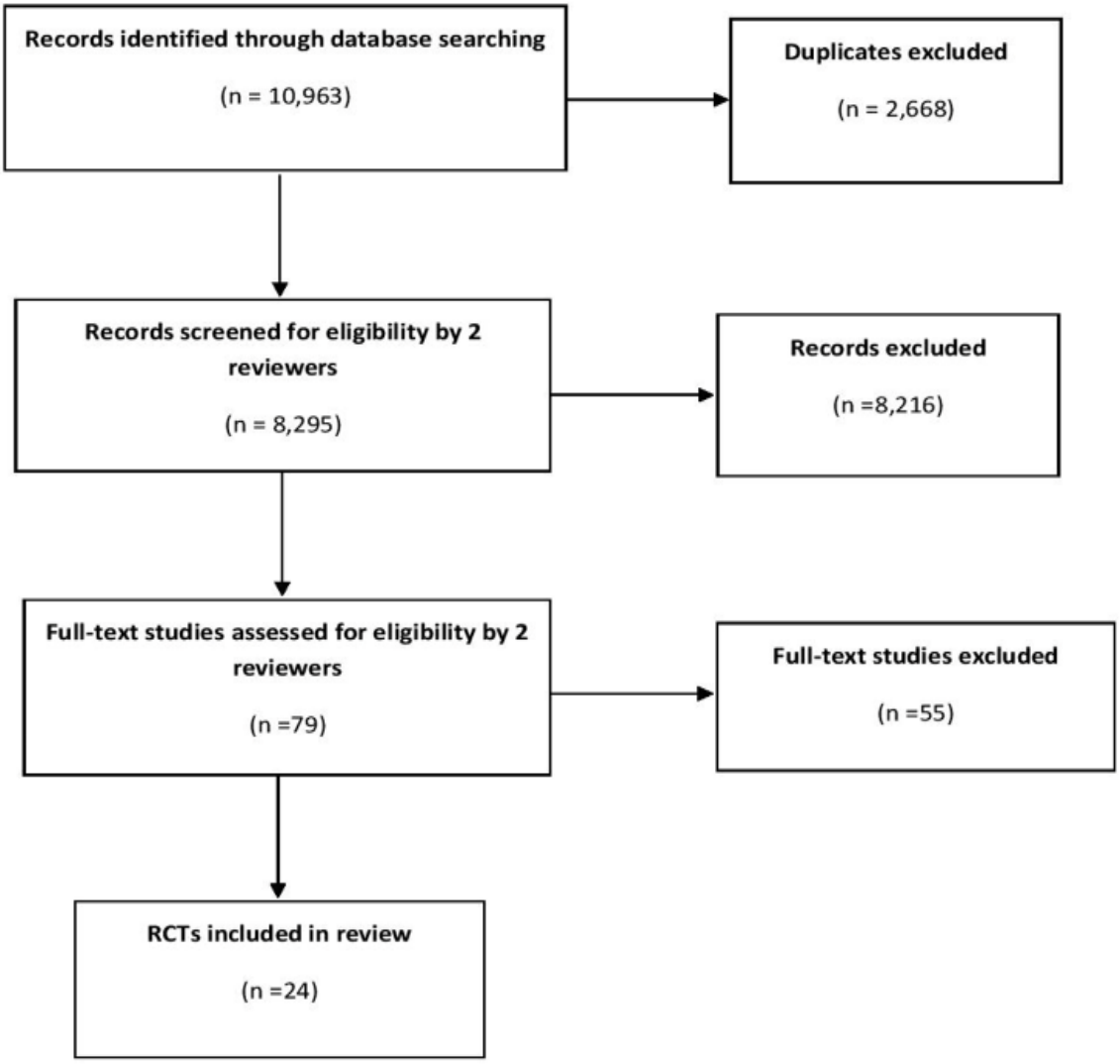


Figure 2. Risk of Bias as Percentages Across All Included Trials

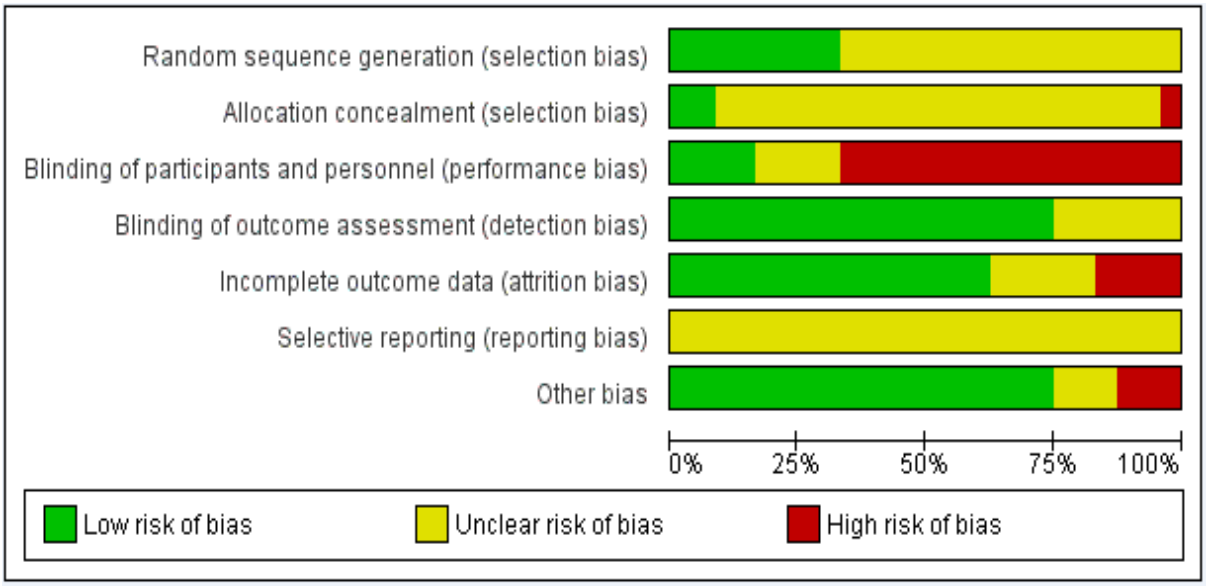


Figure 3. Effect Size - LDL cholesterol (mmol/L), Industry sponsored vs non-industry sponsored

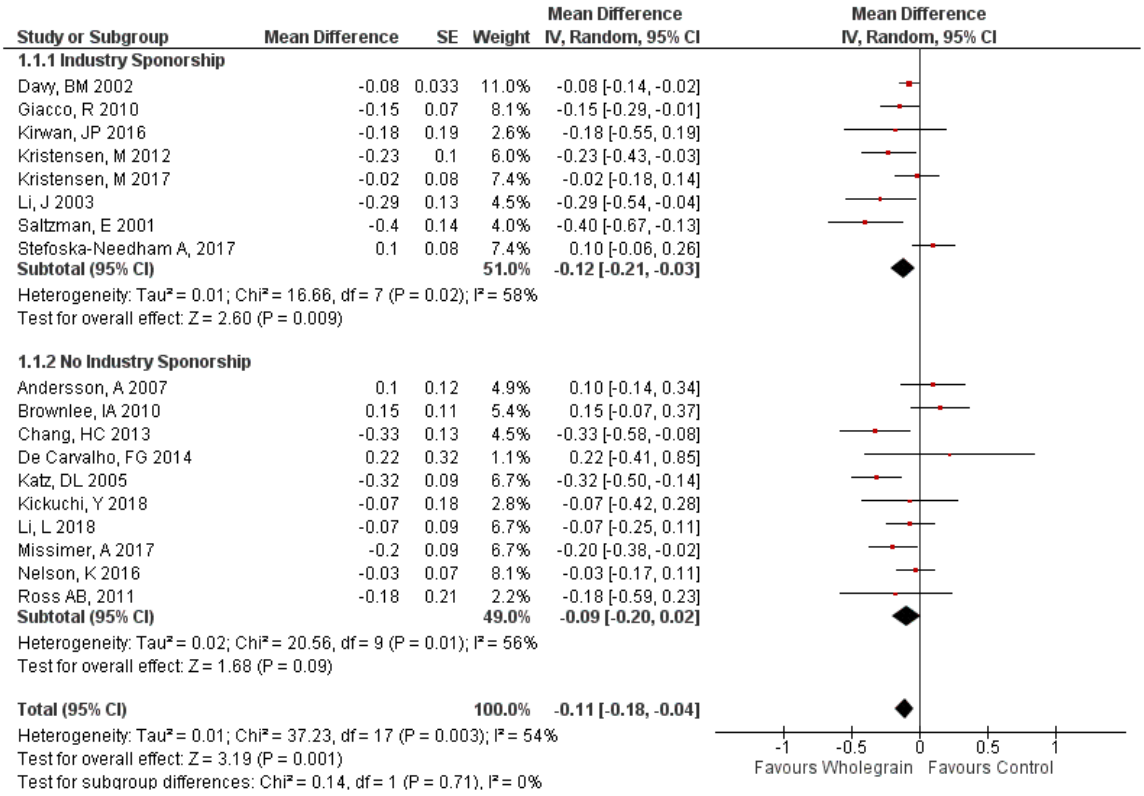


Figure 4. Effect Size - LDL cholesterol (mmol/L), Conflict of interest vs no conflict of interest

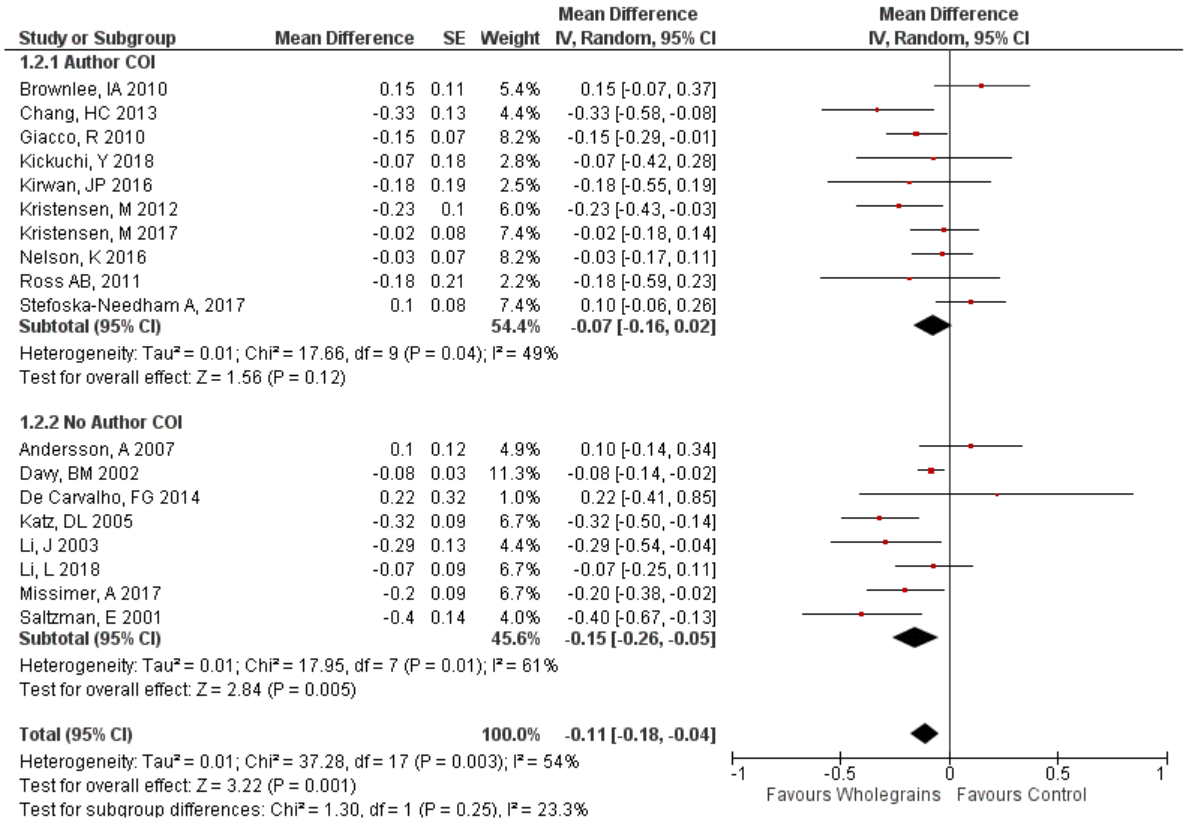


Figure 5. Effect Size – Systolic Blood Pressure (mm/Hg), Industry sponsored vs non-industry sponsored and conflict of interest vs no conflict of interest

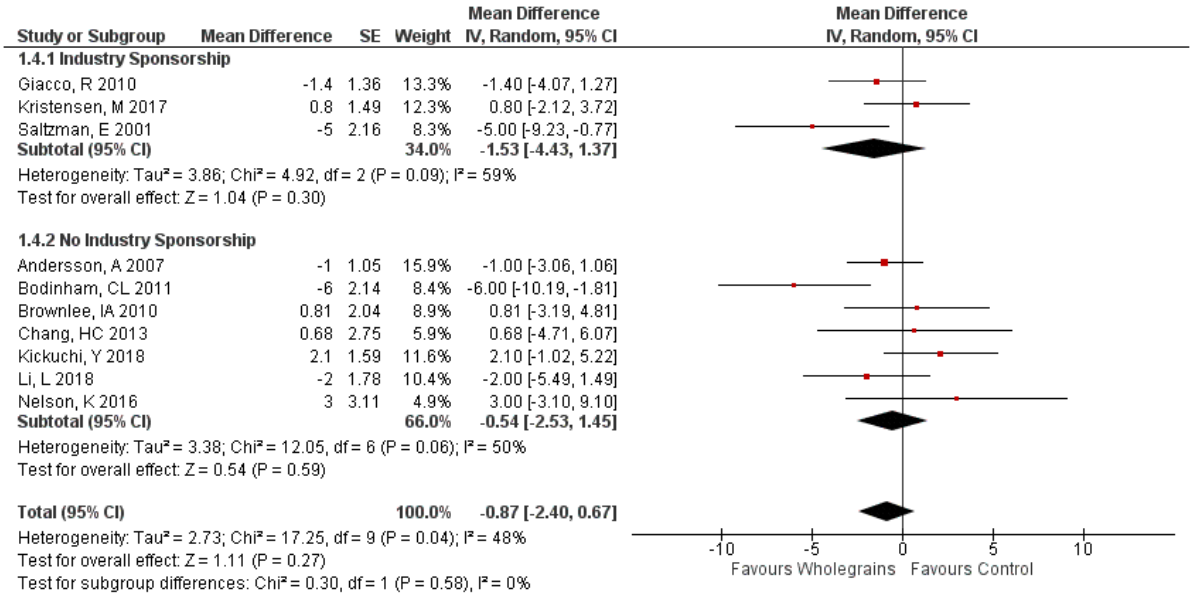


Figure 6. Effect Size – Systolic Blood Pressure (mm/Hg), Conflict of interest vs no conflict of interest

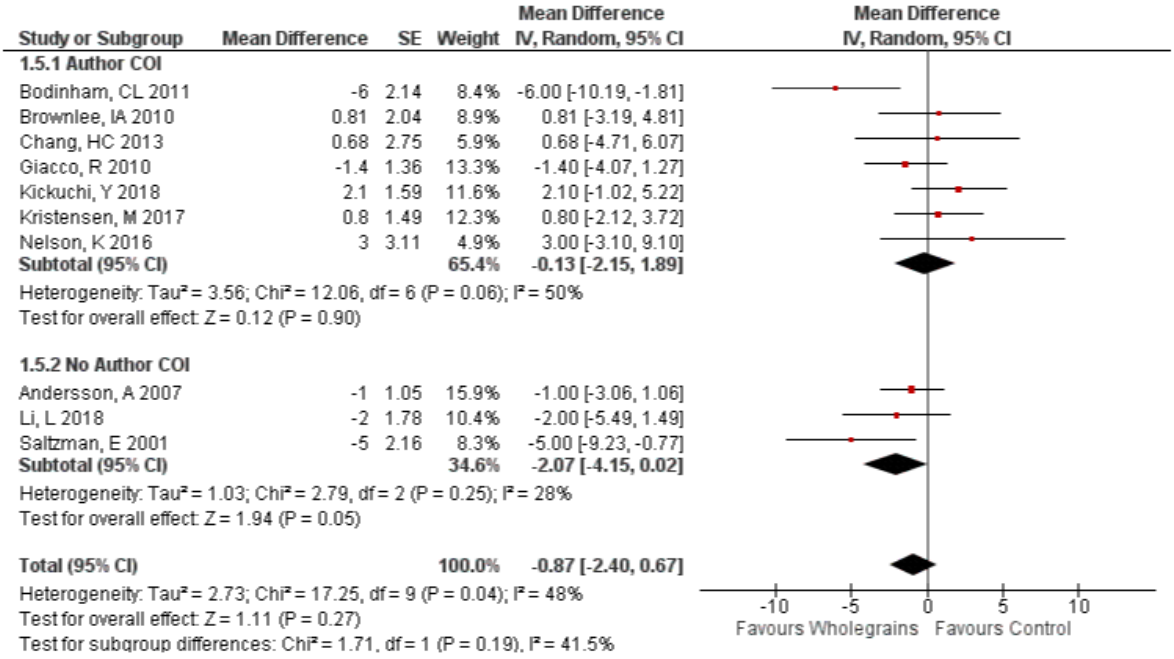


Figure 7. Effect Size - Diastolic Blood Pressure (mm/Hg), Industry sponsored vs non-industry sponsored

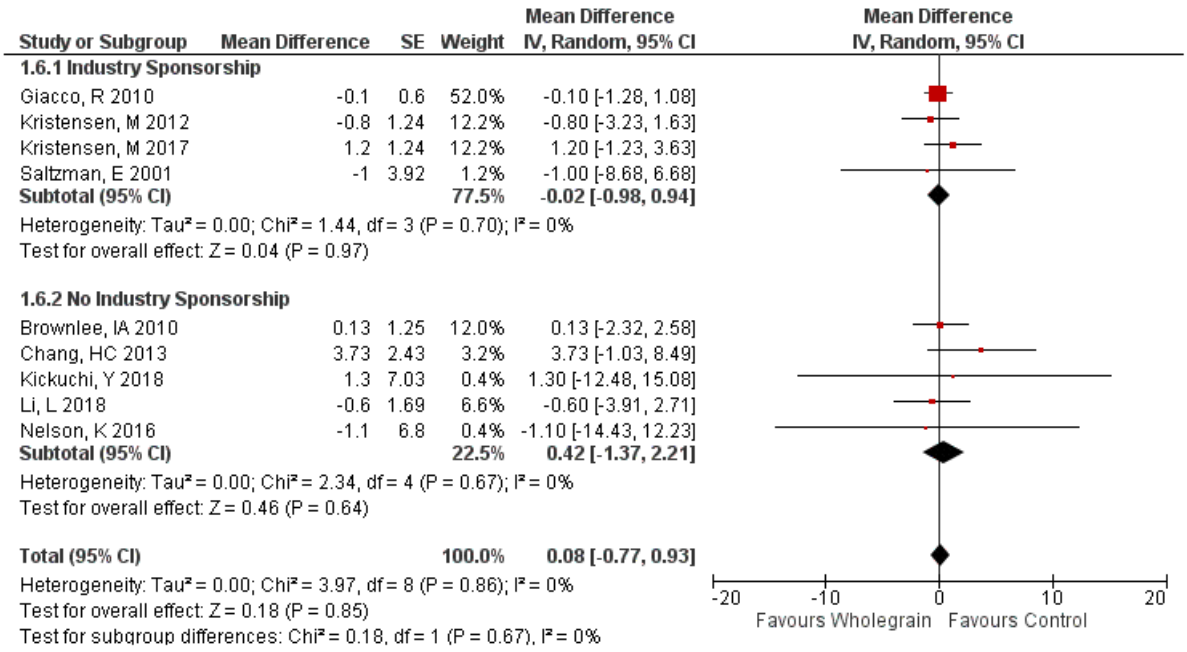
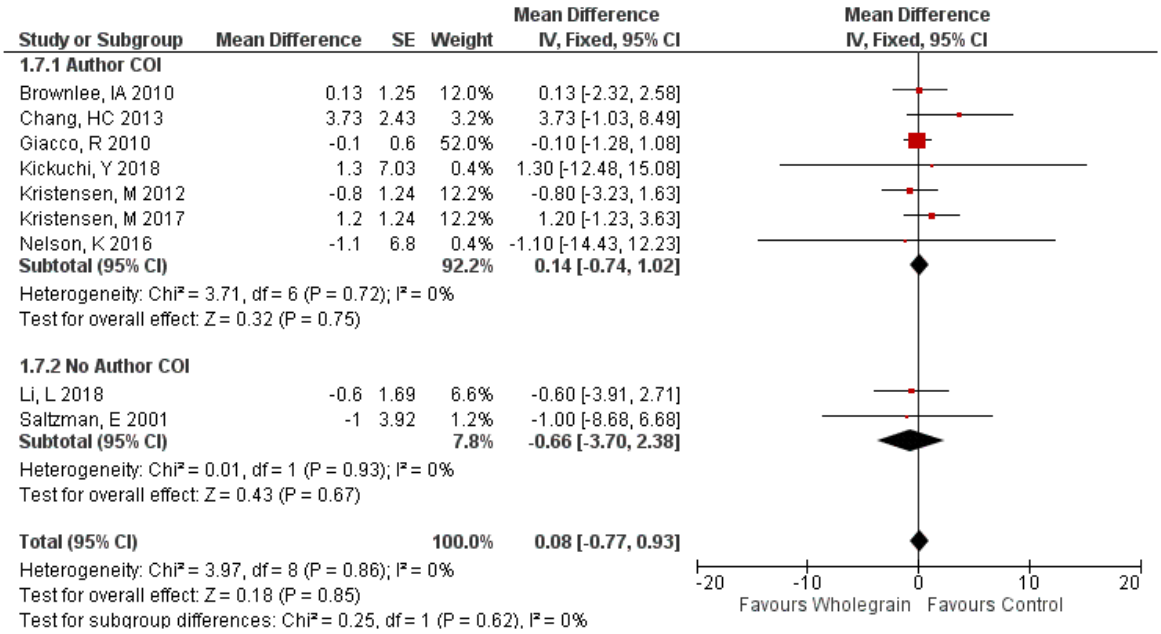


Figure 8. Effect Size - Diastolic Blood Pressure (mm/Hg), Conflict of interest vs no conflict of interest



Supplementary File 1: Search Strategy OVID Medline: wholegrain & CVD

1. Randomized controlled trial*.sh.

2. experimental design.tw.

3. intervention*.tw.

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

5. random* control* trial*.tw.

6. clinical trial*.sh.

7. field trial*.tw.

8. community trial*.tw.

9. controlled clinical trial*.tw.

10. pragmatic trial*.tw.

11. observational study.sh.

12. cohort study.tw.

13. prospective cohort*.tw.

14. retrospective cohort*.tw.

15. case control*.sh.

16. ecological study.tw.

17. time series analys?s.tw.

18. before-after study.tw.

19. pre-post study.tw.

20. follow up stud*.sh.

21. comparative stud*.sh.

22. evaluation stud*.sh.

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

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

25. grain*.tw.

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

27. whole grain*.tw.

28. partially processed grains.tw.

29. whole wheat.tw.

30. wholemeal.tw.

31. rice*.tw.

32. oat*.tw.

33. barley*.tw.

34. wheat*.tw.

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

36. amaranth.tw.

37. Millets/me [Metabolism]

38. millet*.tw.

39. Sorghum/me [Metabolism]

40. sorghum*.tw.

41. maize*.tw.

42. spelt*.tw.

43. buckwheat*.tw.

44. Triticale/me [Metabolism]

45. triticale*.tw.

46. fonio*.tw.

47. emmer.tw.

48. einkorn*.tw.

49. kamut*.tw.

50. canary seed*.tw.

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

52. bread*.tw.

53. breakfast cereal*.tw.

54. pasta*.tw.

55. noodle*.tw.

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

57. flour*.tw.

58. polenta*.tw.

59. semolina*.tw.

60. bran.tw.

61. corn.tw.

62. wheat germ*.tw.

63. corn cake*.tw.

64. scone*.tw.

65. couscous.tw.

66. crumpet*.tw.

67. dietary fiber.tw.

68. dietary carbohydrate*.tw.

69. glycemic index.tw.

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

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

72. cardiovascular disease*.tw.

73. coronary*.tw.

74. heart*.tw.

75. cardia*.tw.

76. myocard*.tw.

77. isch?em*.tw.

78. angina*.tw.

79. ventric*.tw.

80. tachycardi*.tw.

81. pericard*.tw.

82. endocardi*.tw.

83. atrial fibrillat*.tw.

84. arrhythmi*.tw.

85. athero*.tw.

86. arterio*.tw.

87. HDL.tw.

88. LDL.tw.

89. VLDL.tw.

90. lipid*.tw.

91. lipoprotein*.tw.

92. triacylglycerol*.tw.

93. hyperlipid*.tw.

94. hypercholesterol*.tw.

95. hypercholester?emia*.tw.

96. hypertriglycerid?emia*.tw.

97. Cholesterol/

98. Stroke/

99. Cerebrovascular Disorders/

100. vascular accident*.tw.

101. TIA.tw.

102. Thrombosis/

103. thrombosis.tw.

104. Embolism/ or Pulmonary Embolism/

105. apoplexy.tw.

106. (brain adj2 accident*).tw.

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

108. Blood Pressure/ or Hypertension/

109. systolic blood pressure.tw.

110. diastolic blood pressure.tw.

111. Peripheral Vascular Diseases/ or Peripheral Arterial Disease/

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

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

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

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

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

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

118. Mortality/

119. mortality.tw.

120. Diabetes Mellitus, Type 2/

121. Hyperglycemia/

122. hyperglycemi*.tw.

123. (glucose adj2 intoleran*).tw.

124. Insulin Resistance/

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

126. metabolic cardiovascular syndrome.tw.

127. dysmetabolic syndrome x.tw.

128. HbA1c.tw.

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

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

131. 23 and 70 and 130

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

Supplementary File 2: List of Excluded Trials and Reasons for Exclusion

Year: Author	Title	Reason for exclusion
Abellan Ruiz, MS 2017[1]	Effect of quinua (Chenopodium quinoa) consumption as a coadjuvant in nutritional intervention in prediabetic subjects	Participants did not meet inclusion criteria
Ahuja, KD 2012[2]	Postprandial platelet aggregation: effects of different meals and glycemic index	The intervention measured the effect of glycemic index. No separate analysis of wholegrains
Albertson, AM 2009[3]	The relationship of ready-to-eat cereal consumption to nutrient intake, blood lipids, and body mass index of children as they age through adolescence	Measurement was of ready to eat cereals, which included refined grains
Aldana, SG 2006[4]	The behavioral and clinical effects of therapeutic lifestyle change on middle-aged adults	Study measured effect of a mixed lifestyle intervention. No separate analysis of wholegrains
Aller, R 2004[5]	Effect of soluble fiber intake in lipid and glucose levels in healthy subjects: a randomized clinical trial	The intervention group consumed foods supplemented with dietary fiber, not wholegrains
Ard, JD 2000[6]	Culturally-sensitive weight loss program produces significant reduction in weight, blood pressure and cholesterol in eight weeks	The intervention did not include wholegrains
Arts J, 2016[7]	A Nutrition Intervention to Increase Whole Grain Intake in College Students	Not an RCT
Bajerska J, 2015[8]	Effects of Rye Bread Enriched with Green Tea Extract on Weight Maintenance and the Characteristics of Metabolic Syndrome Following Weight Loss: A Pilot Study	Participants did not meet inclusion criteria
Beck, EJ 2010[9]	Oat beta-glucan supplementation does not enhance the effectiveness of an energy-restricted diet in overweight women	The intervention group consumed foods supplemented with beta-glucan, not wholegrains
Bergeron N, 2016[10]	Diets high in resistant starch increase plasma levels of trimethylamine-N-oxide, a gut microbiome metabolite associated with CVD risk.	The intervention did not include wholegrains
Bloedon, LT 2008[11]	Flaxseed and cardiovascular risk factors: results from a double blind, randomized, controlled clinical trial	Participants did not meet inclusion criteria
Bourdon, I 1999[12]	Postprandial lipid, glucose, insulin, and cholecystokinin responses in men fed barley pasta enriched with beta-glucan	No relevant outcomes were measured
Brighenti, F 1999[13]	Effect of consumption of a ready-to-eat breakfast cereal containing inulin on the intestinal milieu and blood lipids in healthy male volunteers	The intervention group consumed foods supplemented with inulin, not wholegrains

Year: Author	Title	Reason for exclusion
Brufau, G 2004[14]	Evaluation of lipid oxidation after ingestion of bakery products enriched with phytosterols, beta-carotene and alpha-tocopherol	The intervention group consumed foods supplemented with sterol esters, a-tocopherol and b-carotene, not wholegrains
Carvalho-Wells AL,2010	Determination of the in vivo prebiotic potential of a maize-based whole grain breakfast cereal: a human feeding study	No data available on relevant outcomes
Charlton, KE 2012[15]	Effect of 6 weeks' consumption of beta-glucan-rich oat products on cholesterol levels in mildly hypercholesterolaemic overweight adults	Participants did not meet inclusion criteria
Chen J, 2006[16]	A randomized controlled trial of dietary fiber intake on serum lipids	The intervention group consumed foods supplemented with oat bran concentrate, not wholegrains
Cherbut, C 1997[17]	Digestive and metabolic effects of potato and maize fibres in human subjects	The intervention group consumed foods supplemented with fibre, not wholegrains
Cioffi I, 2016[18]	Whole-grain pasta reduces appetite and meal-induced thermogenesis acutely: a pilot study	Not an RCT
Clifton, PM 2004[19]	Cholesterol-lowering effects of plant sterol esters differ in milk, yoghurt, bread and cereal	Participants did not meet inclusion criteria
Costabile, G 2018[20]	Subjective satiety and plasma PYY concentration after wholemeal pasta	No relevant outcomes were measured
Dainty SA, 2016[21]	Resistant Starch Bagels Reduce Fasting and Postprandial Insulin in Adults at Risk of Type 2 Diabetes	The intervention group consumed foods with resistant starch, not whole grains
de Rougemont, A 2007[22]	Beneficial effects of a 5-week low-glycaemic index regimen on weight control and cardiovascular risk factors in overweight non-diabetic subjects	The intervention measured the effect of glycemic index. No separate analysis of wholegrains
Dinu, M 2017[23]	Consumption of buckwheat products and cardiovascular risk profile: a randomized single-blinded crossover trial	Participants did not meet inclusion criteria
Fatahi, S 2018[24]	Impact of Diets Rich in Whole Grains and Fruits and Vegetables on Cardiovascular Risk Factors in Overweight and Obese Women: a Randomized Clinical Feeding Trial	Participants did not meet inclusion criteria
Gonzalez-Ortiz, M 2004[25]	Effect of a high fat or high carbohydrate breakfast on postprandial lipid profile in healthy subjects with or without family history of type 2 diabetes mellitus	The intervention group consumed high carbohydrate breakfast foods, not wholegrains

Year: Author	Title	Reason for exclusion
Guess N, 2016[26]	The effect of dietary changes on distinct components of the metabolic syndrome in a young Sri Lankan population at high risk of CVD	Not an RCT
Hu X, 2013[27]	Soy fiber improves weight loss and lipid profile in overweight and obese adults: a randomized controlled trial	The intervention group consumed foods supplemented with soy fibre, not whole grains
Ibrugger, S 2013[28]	Extracted oat and barley beta-glucans do not affect cholesterol metabolism in young healthy adults	The intervention group consumed foods supplemented with different beta-glucans, not wholegrains
Jalil, A 2016[29]	Acute effects of breads prepared with beta-glucan and black tea on glucose and insulin responses in healthy volunteers	Conference abstract only. No full text could be found
Karl, JP 2017[30]	Substituting whole grains for refined grains in a 6-wk randomized trial favorably affects energy-balance metrics in healthy men and postmenopausal women	No relevant outcomes were measured
Karmally, W 2005[31]	Cholesterol-lowering benefits of oat-containing cereal in Hispanic Americans	The intervention group consumed foods supplemented with oat bran, not wholegrains
Kleemola, P 1999[32]	The effect of breakfast cereal on diet and serum cholesterol: a randomized trial in North Karelia, Finland	The intervention group consumed ready to eat cereals, not specifically wholegrains
Kristensen M, 2011[33]	A diet rich in oat bran improves blood lipids and hemostatic factors, and reduces apparent energy digestibility in young healthy volunteers	The intervention group consumed foods supplemented with oat bran, not wholegrains
Kristensen M, 2015[34]	Effect of wholegrain emmer wheat on serum folate and homocysteine-a pilot human intervention study	Conference abstract only. No full text could be found
Lee, KW 2006[35]	The effects of Goami No. 2 rice, a natural fiber-rich rice, on body weight and lipid metabolism	The intervention group consumed high fibre rice, not wholegrain rice
Leinonen, KS 2000[36]	Rye bread decreases serum total and LDL cholesterol in men with moderately elevated serum cholesterol	No combined outcome data available. Males and females analysed separately
Maki, KC 2010[37]	Whole-grain ready-to-eat oat cereal, as part of a dietary program for weight loss, reduces low-density lipoprotein cholesterol in adults with overweight and obesity more than a dietary program including low-fiber control foods	Participants did not meet inclusion criteria
Malin SK, 2018[38]	A whole-grain diet reduces peripheral insulin resistance and improves glucose kinetics in obese adults: a randomized-controlled trial.	No relevant outcomes were measured

Year: Author	Title	Reason for exclusion
Martinez, I 2013[39]	Gut microbiome composition is linked to whole grain-induced immunological improvements	No relevant outcomes were measured
Meydani, M 2016[40]	Short term consumption of whole grain foods independent of weight loss does not affect surrogate markers of cvd	Conference abstract only. No full text could be found
Mills, LM 2015[41]	Increased oats' consumption does not reduce cardiovascular disease risk markers in middle-aged healthy volunteers	Conference abstract only. No full text could be found
Pomeroy, S 2001[42]	Oat ß-glucan lowers total and LDL-cholesterol	The intervention group consumed foods supplemented with beta-glucan, not wholegrains
Poppitt, SD 2007[43]	Supplementation of a high-carbohydrate breakfast with barley beta-glucan improves postprandial glycaemic response for meals but not beverages	The intervention group consumed foods supplemented with beta-glucan, not wholegrains
Price, RK 2010[44]	Consumption of wheat aleurone-rich foods increases fasting plasma betaine and modestly decreases fasting homocysteine and LDL-cholesterol in adults	The intervention group consumed foods enriched with wheat aleurone, not wholegrains
Ridges, L 2001[45]	Cholesterol lowering benefits of soy and linseed enriched foods	Participants did not meet inclusion criteria
Roager HM, 2018[46]	Whole grain-rich diet reduces body weight and systemic low-grade inflammation without inducing major changes of the gut microbiome: a randomised cross-over trial.	Participants did not meet inclusion criteria
Robitaille, J 2005[47]	Effect of an oat bran-rich supplement on the metabolic profile of overweight premenopausal women	The intervention group consumed foods supplemented with oat bran, not wholegrains
Rosado, JL 2008[48]	An increase of cereal intake as an approach to weight reduction in children is effective only when accompanied by nutrition education: a randomized controlled trial	Measurement was of ready to eat breakfast foods, not wholegrains specifically
Sandberg JC, 2016[49]	Rye-Based Evening Meals Favorably Affected Glucose Regulation and Appetite Variables at the Following Breakfast; A Randomized Controlled Study in Healthy Subjects	No relevant outcomes were measured
Sandberg JC, 2017[50]	Effects of whole grain rye, with and without resistant starch type 2 supplementation, on glucose tolerance, gut hormones, inflammation and appetite regulation in an 11-14.5 hour perspective; a randomized controlled study in healthy subjects.	No relevant outcomes were measured
Sereni, A 2017[51]	Cardiovascular benefits from ancient grain bread consumption: findings from a double-blinded randomized crossover intervention trial	Intervention groups consumed 'ancient' and 'modern' grains, not wholegrains

Year: Author	Title	Reason for exclusion
Soderholm, PP 2012[52]	Rye bread intake improves oxidation resistance of LDL in healthy humans	No relevant outcomes were measured
Tighe, P 2010[53]	Effect of increased consumption of whole-grain foods on blood pressure and other cardiovascular risk markers in healthy middle-aged persons: a randomized controlled trial	Participants did not meet the inclusion criteria
Tighe, P 2013[54]	Effects of wheat and oat-based whole grain foods on serum lipoprotein size and distribution in overweight middle aged people: a randomised controlled trial	Participants did not meet the inclusion criteria

References

1. Abellan Ruiz MS, Barnuevo Espinosa MD, Garcia Santamaria C, et al. [Effect of quinua (Chenopodium quinoa)consumption as a coadjuvant in nutritional intervention in prediabetic subjects]. *Nutricion Hospitalaria* 2017;34(5):1163-69.
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Supplementary File 3: Characteristics of Included Trials

Trial ID	Trial Deign	Length of Intervention	Number of Participants	Age (mean years)	Intervention	Control	Outcomes Measured	Funding Source	Disclosed author conflicts of interest
Ampatzoglou, A 2015[1]	Crossover Trial	12 weeks (2 x 6 week periods, with a 4 week washout period)	33 men & women	48.8 y	Wholegrain foods (>80 g/d)	Refined grain diet (<16 g/d of wholegrains)	1. LDL cholesterol, mmol/L 2. Systolic BP, mm Hg 3. Diastolic BP, mm Hg	Industry[1]	Yes[a]
Andersson, A 2007[2]	Crossover Trial	12 weeks (2 x 6 week periods, with a 6-8 week washout period)	30 men & women	59 ± 5 y	Wholegrain foods (112 g/d (3 bread slices, 2 crisp bread slices, 1 portion muesli, and 1 portion pasta))	Refined grain diet (3 bread slices, 2 crisp bread slices, 1 portion muesli, and 1 portion pasta)	1. LDL cholesterol, mmol/L 2. Systolic BP, mm Hg 3. Diastolic BP, mm Hg	Non-Industry[2]	No[b]
Bodinham, CL 2011[3]	Crossover Trial	6 weeks (2 x 3 week periods, with a 3 week washout period)	14 men & women	26 ± 1.4 y	2 wholegrain rolls/d (48 g/d)	2 refined grain rolls/d	1. Systolic BP, mm Hg 2. Diastolic BP, mm Hg	No Disclosure	Yes[c]
Brownlee, IA 2010[4]	3 Arm Parallel design	16 weeks	316 (266 analysed) men & women	18-65 y (median 46)	*Intervention group 1:* wholegrain foods (60 g/d x 16 weeks)	Normal diet	1. LDL cholesterol, mmol/L 2. Systolic BP, mm Hg	Non-Industry[3]	Yes[d]

Trial ID	Trial Deign	Length of Intervention	Number of Participants	Age (mean years)	Intervention	Control	Outcomes Measured	Funding Source	Disclosed author conflicts of interest
					Intervention group 2: wholegrain foods (60 g/d x 8 weeks, 120 g/day x 8 weeks)		3. Diastolic BP, mm Hg		
Chang, HC 2013[5]	Parallel design	12 weeks	34 men & women	18-65 y (control, 37.67±10.59, oat, 39.44±11.69)	2 x oats cereal with beta-glucan/d (37.5 g/pack)	2 x oats cereal without beta-glucan/d (37.5 g/pack)	1. LDL cholesterol, mg/dl) 2. Systolic BP, mm Hg 3. Diastolic BP, mm Hg	No Disclosure	Yes[e]
Cooper DN, 2017[6]	Parallel design	6 weeks	46 (45 analysed) men & women	25.8 ± 0.9 y	Wholegrain foods (number of grain servings per week) were determined based on the caloric needs of the subjects, determined using the Harris-Benedict equation) *	Refined grain foods	1. LDL cholesterol (no units given)	Non Industry[4]	No[f]

Trial ID	Trial Deign	Length of Intervention	Number of Participants	Age (mean years)	Intervention	Control	Outcomes Measured	Funding Source	Disclosed author conflicts of interest
Davy, BM 2002[7]	Parallel design	12 weeks	36 (35 analysed) men	50–75 y (control, 61±2, WG , 57±2)	60 g Quaker Oatmeal/d and 76 g Quaker Oat Bran ready-to-eat cold cereal/d	60 g Mother's Whole Wheat Hot Natural Cereal/d and 81 g Frosted Mini-Wheats/d	1. LDL cholesterol, mmol/L	Industry[5]	No Disclosure
De Carvalho, FG 2014[8]	Parallel design	4 weeks	35 women	61±7 y	25 g of quinoa flakes/d	25 g of corn flakes/d	1. LDL cholesterol, mg/dl	Non Industry[6]	No[g]
Durazzo, A 2014[9]	Crossover Trial	8 weeks (2 x 4 week periods, with a 2 week washout period)	20 (13 analysed) women	52.8±1.0 y	Wholegrain foods (30 g/d breakfast cereals or biscuits, etc., 80 g/d wholegrain pasta)	Refined grain foods	1. Systolic BP, mm Hg 2. Diastolic BP, mm Hg	Non Industry[7]	No[h]
Ghiselli L, 2013[10]	Crossover Trial	20 weeks (2 x 10 week periods, with a 2 week washout period)	20 men & women	35 y (median)	70 g/d Senatore Cappelli pasta	Commercially available pasta obtained from a modern wheat variety	1. LDL cholesterol, mg/dl	Non Industry[8]	No Disclosure
Giacco, R, 2010[11]	Crossover Trial	6 weeks (2 x 3 week period, no washout period)	15 men & women	54.5 +- 7.6 y	Wholemeal wheat bread, pasta, rusks	Refined wheat bread, pasta, rusks and crackers (cereal fiber 9.8 g/d)	1. LDL cholesterol, mg/dl 2. Systolic BP, mm Hg	Industry[9]	Yes[i]

Trial ID	Trial Deign	Length of Intervention	Number of Participants	Age (mean years)	Intervention	Control	Outcomes Measured	Funding Source	Disclosed author conflicts of interest
					and crackers (cereal fiber 23.1 g/d)		3. Diastolic BP, mm Hg		
Katz, DL 2005[12]	Crossover Trial	12 weeks (2 x 6 week periods, with a 4 week washout period)	49 men & women	55.7 y	Uncooked whole oats (60 g/d) (C)**	Two eggs/d (I)**	1. LDL cholesterol, mg/dl 3. Systolic BP, mm Hg 2. Diastolic BP, mm Hg	Non Industry[10*,**]	No Disclosure
Kickuchi Y, 2018[13]	Parallel design	12 weeks	50 (49 analysed) men and women	20–64 y (control, 47.0 ± 1.7 WG, 48.1 ± 1.6)	2 loaves of two loaves of wholegrain wheat bread/d (100 g (88 g on dry base) whole grain wheat/d)	2 loaves of two loaves of refined wheat bread/d	1. LDL cholesterol, mg/dl 2. Systolic BP, mm Hg 3. Diastolic BP, mm Hg	Non Industry[11]	Yes[j]
Kirwan JP, 2016[14]	Crossover Trial	16 weeks (2 x 8 week periods, with a 10 week washout period)	40 (33 analysed) men and women	39±7 y	Wholegrains (50 g/1000 kcal).	Refined grains (50 g/1000 kcal).	1. LDL cholesterol, mg/dl 2. Systolic BP, mm Hg 3. Diastolic BP, mm Hg 4. HbA1c, %	Industry[12]	Yes[k]

Trial ID	Trial Deign	Length of Intervention	Number of Participants	Age (mean years)	Intervention	Control	Outcomes Measured	Funding Source	Disclosed author conflicts of interest
Kristensen, M 2012[15]	Parallel design	12 weeks	79 (72 analysed) women	45-70 y (control, (60.3 ± 5.3 y, WG, 59.1± 5.6 y)	Wholegrain wheat foods: 62 g of bread, 60 g pasta and 28 g biscuits/d (105 g of whole grains/d)	Refined wheat foods: 62 g of bread, 60 g pasta and 28 g biscuits/d	1. LDL cholesterol, mmol/L 2. Systolic BP, mm Hg 3. Diastolic BP, mm Hg 4. HbA1c, %	Industry[13*,***]	Yes[l]
Kristensen, M 2017[16]	Parallel design	12 weeks	179 (169 anlaysed) women	20-50 y (control 35.3±8.7, WG 36.2±10.1)	Wholegrain diet: bread, breakfast cereal, pasta, rice, couscous, and muesli bars (80 g/d)	Refined grain diet	1. LDL cholesterol, mmol/L 2. Systolic BP, mm Hg 3. Diastolic BP, mm Hg 4. HbA1c, %	Industry[14]	Yes[m]
Li, J 2003[17]	Crossover Trial	8 weeks (2 x 4 week periods, with a 4 week washout period)	10 women	20.4 +-1.3 y	Wholegrain barley diet: replacing 30% of the carbohydrates in the standard diet with barley.	Standard diet	1. LDL cholesterol, mg/dl 2. HbA1c, %	Industry[15]	No Disclosure
Li, L 2018[18]	Crossover Trial	8 weeks (2 x 4 week periods, with a 4 week	37 (28 analysed) men	51.54 y	One quinoa roll/d (20 g quinoa flour)	Placebo bread (100% refined wheat flour)	1. LDL cholesterol, mmol/L 2. Systolic BP, mm Hg	Non Industry[16]	No[n]

Trial ID	Trial Deign	Length of Intervention	Number of Participants	Age (mean years)	Intervention	Control	Outcomes Measured	Funding Source	Disclosed author conflicts of interest
		washout period)					3. Diastolic BP, mm Hg		
Missimer, A 2017[19]	Crossover Trial	8 weeks (2 x 4 week periods, with a 3 week washout period)	50 (48 analysed) men & women	23.3 ± 3.1 y	One packet of oatmeal/d (C)*****	2 eggs per/d (I) *****	1. LDL cholesterol, mmol/L 2. Systolic BP, mm Hg 3. Diastolic BP, mm Hg	Non Industry[17]	No[o]
Nelson, K 2016[20]	Crossover Trial	8 weeks (2 x 4 week periods, with a 2 week washout period)	10 men & women (8 cholesterol)	30-60 y (43.8 ± 8.4 males, 50.8 ± 8.1, female)	Malted wheat breakfast biscuits (the breakfast meal comprised breakfast biscuits and low fat (1.3%) milk, calculated based on each participant's individual percentage of maintaining daily energy requirements (DER). Goals for breakfast meals including milk	White wheat breakfast biscuits	1. LDL cholesterol, mmol/L 2. Systolic BP, mm Hg 3. Diastolic BP, mm Hg	No Disclosure	Yes[p]

Trial ID	Trial Deign	Length of Intervention	Number of Participants	Age (mean years)	Intervention	Control	Outcomes Measured	Funding Source	Disclosed author conflicts of interest
					were <30% individual DER with the breakfast biscuit component calculated at 10% DER)				
Ross AB, 2011[21]	Crossover Trial	4 weeks (2 x 2 week periods, with a 5-7 week washout period)	22 (17 analysed) men & women	20 - 50 y (men 36.5 y & Women 34.1 y)	Wholegrain diet (150 g/d on a dry weight basis)	Refined grain diet	1. LDL cholesterol, mmol/L	Non Indsutry[18]	Yes[q]
Saltzman, E 2001[22]	Parallel design	6 weeks	43 men & women	18-75 y (control, 44.1 ± 21.3; Oat, 45.1 ± 22.7)	Diet containing oats (oats, 45 g/4.2 MJ daily energy)	Control diet	1. LDL cholesterol, mmol/L 2. Systolic BP, mm Hg 3. Diastolic BP, mm Hg	Industry[19]	No Disclosure
Sofi, F 2013[23]	Crossover Trial	16 weeks (2 x 8 week periods, with a 8 week washout period)	22 men & women	50.5± 11.8 y	Grain products made from Kamut (500g/wk of pasta, 150g/d of bread, 500g/mo of crackers and 1kg/mo of	Grain products made from semi-whole-grain wheat durum and soft wheat varieties (500g/wk of pasta, 150g/d of bread, 500g/mo of	1. LDL cholesterol, mg/dl	Industry[20]	No[r]

Trial ID	Trial Deign	Length of Intervention	Number of Participants	Age (mean years)	Intervention	Control	Outcomes Measured	Funding Source	Disclosed author conflicts of interest
					biscuits for a period of 8 wks)	crackers and 1kg/mo of biscuits for a period of 8 wks)			
Stefoska-Needham A, 2017[24]	Parallel design	12 weeks	60 (56 analysed) men & women	18-65 y (control, mean 48.6 ± 11.4 sorghum, 48.1 ± 10.3)	45 g of flaked Sorghum cereal biscuits/d	45 g of flaked white wheat cereal biscuits/d	1. LDL cholesterol, mmol/L 2. HbA1c, % 3. HbA1c, mmol/L	Industry[21*] *****	Yes[s]

* A subject with an estimated energy expenditure of 1960 kcals would be provided a 2000 kcal per day basket and would receive six servings of grains per day, and a total of 42 servings of grains in their weekly market basket

** In the study, oats were the comparator and eggs were the intervention

***Funding for this study was provided by the American Egg Board*Egg Nutrition Centre/ U.S. Department of Agriculture and therefore considered non-industry

**** European Commission in the Communities 6th Framework Programme, Project HEALTHGRAIN, partnered with food industry members and is therefore considered industry

*****In the study, oat meal was the comparator and eggs were the intervention

****** Australian Health and Nutrition Association, also known as Sanitarium Health & Wellbeing Company

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Description of Author Disclosure Statement (Verbatim)

a) AB Ross was an employee of Nestle at the time of this research, and F Thielecke and SS Jonnalagadda are employees of Cereal Partners Worldwide and General Mills, respectively
b) A. Andersson, S. Tengblad, B. Karlstro¨m, A. Kamal-Eldin, R. Landberg, S. Basu, P. A˚ man, and B. Vessby, no conflicts of interest
c) C. L. B. was supported by an educational fellowship from Premier Foods

d) Peter Ashby - Cereal Partners Worldwide. David P. Richardson -DPRNutrition, Group Chief Scientist and Head of Nutrition Science and Communication at Nestlé UK Ltd.

e) S.J. Wang - Division of Research and Development, STANDARD Foods Co.,Taipei, Taiwan

f) The authors declare no conflict of interest

g) The authors declare no competing financial interests exist

h) The authors report no conflict of interest

i) M.A. Bianchi and R. Ciati - R&D, Barilla G&R F.lli. SpA, Parma, Italy

j) Authors KY, NS,MM, YS, and FS are employees of Nisshin Seifun Group Inc

k) J-P Godin, S Kochhar, and AB Ross are employed by the Nestle Research Center

l) M.Petronio and G. Riboldi are employed by Barilla, and A.B.Ross is employed by Nestle´ both companies that produce whole-grain foods

m) M.K. and A.B.R. have performed consulting work for Cereal Partners Worldwide. F.T. was an employee of Cereal Partners Worldwide and A.B.R. was an employee of Nestec SA at the time this study was conducted

n) The authors declare no conflict of interest

o) The authors declare no conflict of interest

p) J. Ashton is employed by SanitariumTM who supplied the test cereal and provided for biological assays via a commercial laboratory for lipids, insulin, hs-CRP and MDA

q) All authors are employees of Nestle SA, a part of a food company that produces a range of WG cereal products

r) The authors declare no conflict of interest

s) John Ashton- Sanitarium Development and Innovation, Cooranbong, New South Wales, Australia

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Supplementary File 4: Sensitivity Analysis, Conflict of Interest vs No Conflict of Interest

Results

Result	Original Analysis	Sensitivity Analysis
Favourable results - Statistical significance	RR= 0.71 (95% CI 0.31, 1.63; n = 24 trials)	RR =1.24 (95% CI 0.47, 3.24; n= 24 trials)
Effect size: LDL cholesterol	difference in MDs 0.08 (95%CI -0.06, 0.22)); P=0.25	difference in MDs -0.08 (95%CI -0.17, 0.01)); P=0.35
Favourable conclusions:	RR = 0.89 (95% CI 0.53, 1.49; n = 24 trials)	RR = 1.24 (95% CI 0.61, 2.52; n = 24 trials)
Concordance	RR = 1.50 (95% CI 0.30, 7.43; n = 24 trials)	RR = 0.62 (95% CI 0.13, 2.93; n = 24 trials)

Risk of Bias Assessment

Risk of Bias Domain	Original Analysis	Sensitivity Analysis
Random sequence generation	*	*
Allocation concealment	*	*
Blinding of participants and personnel	RR = 1.00 (95% CI 0.57, 1.76)	RR = 1.23 (95% CI 0.61, 2.52)
Blinding of outcome assessment	*	*
Incomplete outcome data	RR = 3.00 (95% CI 0.36, 24.92)	RR = 1.24 (95% CI 0.15, 9.94)
Selective reporting	*	*
Other bias	RR = 0.50 (95% CI 0.05, 4.81)	RR = 0.82 (95% CI 0.09, 7.68)

*RR could not be calculated as there were no studies rated as high risk of bias for the domain

MANUSCRIPT FOUR

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

(Under Review)

Authors: Nicholas Chartres[1], Alice Fabbri[1], Sally McDonald[1], Joanna Diong[2], Joanne Mckenzie[3], Lisa Bero[1]

1. The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, New South Wales, 2006, Australia
2. The University of Sydney, School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney, New South Wales, 2006, Australia
3. Monash University, 553 St Kilda Road, Melbourne, Victoria, 3004, Australia

Corresponding author: Lisa Bero, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, New South Wales, 2006, Australia, email lisa.bero@sydney.edu.au; Telephone +612 8627

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Conflict of Interest: None

Authorship: NC, AF, MA-F 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.

Ethical Standards Disclosure: All data was publicly available.

Abstract

Objective: To determine if observational studies measuring the effect of dairy foods and cardiovascular disease outcomes with food industry ties (sponsorship and / or author conflict of interest) are more likely to report favourable results and/ or conclusions than 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.

Results: Studies with industry ties were less likely to report favourable results RR= 0.26 (95% CI 0.04, 1.87) and conclusions RR= 0.75 (95% CI 0.29, 1.95) than studies with no industry ties, but there was uncertainty in these relationships. 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) were more likely to show a statistically significant decreased risk in CVD outcomes vs. no industry sponsorship, (HR=0.97; n=18) (difference in HRs -0.19 (95%CI -0.34, - 0.07)); P=0.03.

Conclusions: The association between studies with food industry ties and the reporting of favourable results and conclusions compared with studies without industry ties was uncertain. The statistically significant decreased risk in CVD outcomes identified in industry sponsored studies compared to non-industry sponsored studies, however, is important in quantifying the magnitude and effect of industry influence on studies included in dietary guidelines. Further, typical risk of bias tools do not account for the funding bias that we have established in this study.

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

Introduction

The beneficial effect of dairy foods on reducing 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.[1-4] The effects on 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 have led to a significant reduction in the recommended daily intake of dairy foods.[7]

Industry sponsors may bias research by influencing the research agenda, design and conduct of the study and the reporting of the results.[8-11] Prior examinations of pharmaceutical and tobacco research have identified that even when accounting 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] Studies with food industry sponsorship are more likely to have favorable conclusions, than studies with no sponsorship, but the effects of food industry sponsorship 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 is uncertain.[16] Only one study has demonstrated an association of food industry sponsorship with effect size of studies.[17] Food industry sponsored studies reported significantly smaller effect estimates than those with no food industry sponsorship when measuring the association between soft drink consumption and various adverse health outcomes.

It remains unclear how dietary guideline committees account for industry sponsorship when assessing bias in primary nutrition studies.[18] Industry sponsorship and authors with a conflict of interest (COI) with the food industry may be a risk of bias in studies of dairy consumption as industry sponsors may benefit from studies establishing that dairy products have health benefits. The association of industry sponsorship and the outcomes of dairy studies is unclear.[19] A recent dairy industry funded meta-analysis of observational studies found that studies without food industry sponsorship demonstrated that dairy consumption was associated with a statistically significant decreased risk of developing CVD and Type 2 (T2D) diabetes, while food industry funded studies did not report these effects.[20] There has been no assessment, however, of the association of food industry sponsorship and/or author COI and the statistical significance of results, effect sizes, conclusions and risk of bias of observational studies examining the cardiovascular health benefits of dairy foods.

The primary objective of this review is to determine whether studies of observational design examining the effects of dairy foods on CVD with food industry sponsorship and / or authors with COI with the food industry are more likely to have results and/ or conclusions that are favourable to industry than those with no industry ties. We focused on cohort and case control studies as these designs are often used to assess the association of diet with long term health outcomes.

The secondary objectives of this review are to determine whether observational studies with food industry ties differ in their risk of bias compared with studies with no industry ties; and whether studies with food industry ties 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 with CVD. We attempted to register our protocol with Prospero,[21] ID 129659, but it is yet to be accepted.

Literature Search Strategy

The search included terms to locate observational studies and randomised control trials, the latter of which were included in a separate systematic review. (Chartres, under 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.[22] We 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 is shown in Supplementary file 1. We adapted this strategy for the other databases. We hand searched references lists of the identified studies and reviews.

Eligibility Criteria

We included observational studies of cohort or case control designs that estimated the effects of dairy consumption on CVD outcomes in healthy adults.

We included observational studies that defined dairy in anyway, as defined by the author of the included study. We included studies that compared dairy food 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 blood pressure.

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

Types of Outcome Measures

Primary Outcomes

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

1. Statistical significance of results favourable to the sponsor

Favourable results were defined as results that were favourable to the sponsor's product(s), indicating a statistically significant decreased risk of CVD than the comparator. Favourable results were defined as those that were statistically significant at the 0.05 level (two tailed). Otherwise, results were classified as unfavourable. In the circumstance where a trial reported multiple results (e.g. first myocardial infarction and total stroke), only one result needed to be 'favourable' for the trial 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 tested versus comparator on the CVD outcome.

3. Conclusions

Conclusions that suggested that the dairy intervention being studied was beneficial to health by decreasing CVD incidence were considered favourable to the study sponsor. Otherwise, the conclusions were considered unfavourable.

Secondary Outcomes

We assessed two secondary outcomes:

1. The risk of bias of the included studies

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,[23] the ROBINS-E[24]. Bias is assessed across seven domains by the tool ('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 at a low, moderate, serious or 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.'

2. Concordance between study results and conclusions

Results unfavorable 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 in pairs) independently screened the titles and abstracts of all records for obvious exclusions. Both investigators had to exclude the study for the full text not to be retrieved. The full text of potentially eligible studies was then retrieved, and three investigators (NC, SMc & AF) assessed these against the inclusion criteria. Agreement between the

investigators was reached by consensus. If agreement could not be reached, a fourth investigator (LB) determined the decision.

Selection of results from included studies

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 compared 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). If our pre-specified rules for selecting results did not allow us to uniquely identify one exposure in the meta-analysis, 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 blood pressure as our outcome. If a study assessed subgroups of CVD deaths and events (e.g., intracerebral haemorrhages, ischaemic stroke) and assessed them collectively (e.g., cerebrovascular diseases), we took the result that had assessed them collectively. If our pre-specified rules for selecting results did not allow us to uniquely identify one outcome for inclusion in the meta-analysis, 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)
- The numerical results of the study (eg., 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.[25] Five investigators (NC, SMc, AF, AL & JD) working 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) determined the outcome.

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). Industry sponsored studies were also defined as those with 'mixed

funding' from the food industry, non-profit organizations or other industries (i.e. pharmaceutical) for the study. 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'.

Studies classified as industry funded and / or having an author COI were classified as having an industry tie. 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 funding source, 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 food industry sponsorship and/or authors with a conflict of interest with the food industry and (i) favourable results, (ii) favourable conclusions, (iii) overall risk of bias across, 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 sponsorship and/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 either RR and OR or HR 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.[26] 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 difference in RR and OR or HR along with 95% confidence intervals. Analyses were undertaken in Review Manager 5.3. [27]

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. However, as the overall risk of bias was high across all studies, this was not undertaken.

Results

As shown in Figure 1,1858 studies were screened for inclusion and 43 studies were included (3 case controls, 40 cohorts). See Supplementary file 2 for 'List of excluded studies and reasons for exclusion'

Characteristics of included Studies

All studies were published between 2001 and 2019. All but one study 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, containing 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%). Studies with industry sponsorship were also more likely to have sample sizes <5000 (75%) than non-industry sponsored studies (37%). 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 3.

Risk of bias in included studies

Every study was assessed as having an overall high risk of bias, 10 as having a serious risk of bias and 33 as having a critical risk of bias (Figure 2). Most studies had a critical risk of bias rating for the domain 'Bias due to confounding'. For example, a confounder was fruit and vegetable intake. If these 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 were likely to have a serious or critical risk of bias rating for 'Bias in classification of exposures'. For all other domains the risk of bias classifications was similarly distributed across studies with industry ties vs no industry ties (Table 1).

Favourable results - Statistical significance: Industry ties versus no industry ties

The risk of reporting favourable results was 74% less in studies with industry ties (1/14) than those with no industry ties (8/29), RR= 0.26 (95% CI 0.04, 1.87; n=43 studies). However, the confidence interval was wide and included the possibility of no, or an unimportant, difference in risks**.** When

comparing studies with industry sponsorship (1/8) with those with no industry sponsorship (8/35), the risk was similar, RR = 0.55 (95% CI 0.08, 3.77; n=43 studies).

Favourable results - Effect Size, Cardiovascular Disease: Industry ties v no industry ties, and industry sponsorship vs no sponsorship

We found no important difference in the magnitude of the RRs (measuring the association between dairy and comparator) for CVD outcomes 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) (difference in RRs -0.1 (95% CI -0.28,0.08)); P=0.27, (Figure 3), as every study was unfavorable. For studies that had quantified the association using HRs, we again 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) (difference in HRs 0.01 (95% CI -0.10, 0.12)); P=0.86 (Figure 4).

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 (difference in RRs -0.14 (95% CI -0.73, 0.45)); P=0.65. 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 (difference in HRs -0.19 (95%CI -0.34, -0.04)); P=0.03 (Figure 5).

Favourable results - Effect Size, Blood Pressure: Industry ties v no industry ties

We were only able to analyse blood pressure in studies that had measured the outcome using HRs. We found no important difference in the magnitude of the HRs (measuring the association between dairy and comparator) for blood pressure in studies with industry ties, (HR = 0.89; n =2) and those

studies with no industry ties, (HR = 0.78; n= 5) (difference in HRs 0.11 (95%CI -0.10, 0.32)); P=0.32 (Figure 6).

The same studies that had industry ties, also had industry sponsorship. Therefore, we again found no important difference in the magnitude of the HRs for blood pressure in studies with industry sponsorship, (HR = 0.89; n =2) and those studies with no industry sponsorship, (HR = 0.78; n= 5) (difference in HRs 0.11 (95%CI -0.10, 0.32)); P=0.32

Favourable conclusions: Industry ties versus no industry ties

The risk of reporting more favourable conclusions was 25% less in 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), although the confidence interval was wide and included the possibility of no, or an unimportant, difference. When we compared studies only by industry sponsorship the risk was reversed, with industry sponsored studies (3/8), more likely to report favorable conclusions compared to studies with no sponsorship (12/35), RR = 1.09 (95% CI 0.40, 2.99; n=43).

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 risk of bias between studies with industry ties or industry sponsorship and those without industry ties or sponsorship.

Concordance between study results and conclusions

Six studies, all with unfavorable results, overemphasized the benefits of the dairy exposure in their conclusions and thus were coded as ‘favourable’ conclusions.

Studies with industry ties (3/14) were more likely to have discordant results and conclusions than those with no industry ties (3/29), RR = 2.07 (95% CI 0.48, 8.99; n=43), however the confidence interval was wide. When comparing studies with industry sponsorship (2/8) to those with no industry sponsorship (4/35), the risk was similar, RR = 2.19 (95% CI 0.48-9.94).

Discussion

The association between observational studies with food industry ties and the reporting of favorable results and conclusions compared with studies without industry ties was uncertain. Although, studies with industry ties were less likely to report more favorably on these outcomes. However, 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 heterogenous group of sponsors. Unlike in drug studies, [28]the funders in the studies included in this review were extremely diverse, with Big Food and trade association jointly sponsoring several studies.

We found evidence of a clinically important difference in the magnitude of effect (measuring the association between dairy and comparator) for CVD outcomes between studies with industry sponsorship and those with no industry sponsorship when HR were measured. Those with industry sponsorship were more likely to show a statistically significant decreased risk in CVD outcomes than those without industry sponsorship. Such results may drive the recommendations made in dietary guidelines regarding dairy consumption. We found no evidence of a clinically important difference in the magnitude of effect between studies with industry ties compared to those with no industry ties for other outcomes.

When comparing studies by sponsorship only, we found studies funded by the food industry were more likely to have favorable conclusions, than those with no industry sponsorship. However, there was uncertainty in this association.

The overall risk of bias in every study, was classified as high (meaning either serious or critical) due to the ROBINS-E tool rating studies overall risk of bias based on the domain with the highest rating. This therefore does not allow for differentiation between studies that may have a high risk of bias in one domain and those that may have a high risk of bias across several domains.

We found that 'spin,' a lack of concordance between results and conclusions, with the conclusions being more favourable towards dairy foods, was more likely to be present in studies with both industry ties and industry sponsorship only. Although, there was again uncertainty found in these associations. Spin on conclusions can influence the interpretation and the credibility of research[10,29] and has been identified as a tactic used by industry in other areas of health research.[14,29]

Agreements and disagreements with other studies or reviews

The statistically significant decreased risk in CVD outcomes that was demonstrated in industry sponsored studies compared to non-industry sponsored studies is consistent with previous research that 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-industry sponsored studies were associated with a statistically significant decreased risk of developing CVD and Type 2 diabetes, while industry sponsored studies reported non-significant results.[20] The differences in the results of our current review and this previous review can be attributed to a

number of important factors in how the studies were conducted, including how the exposures were classified and the outcomes selected for the meta-analyses. For the exposures, our study included yogurt and cheese, as well as 'total dairy' and milk, whereas the Dairy Board study included only 'total dairy' and milk as exposures. While for outcomes, we included all outcomes related to CVD, and the Dairy Board review included only CVD and stroke, as well as type two diabetes.

Although there was uncertainty in the association we found between studies with food industry sponsorship having more favorable conclusions than those with no sponsorship, it is consistent with a previous systematic review of methodological studies[15] and in an examination of the association of industry ties in studies that measured the effect of wholegrain foods on CVD outcomes.[16] While it is the results of studies that are used in the development of dietary guidelines, conclusions may guide dietary choices of consumers and the advice health practitioners offer to the public.[30]

The lack of difference in the overall risk of bias and across each domain in 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.[12,15,28,31,32]

Industry sponsors may however bias research via different mechanisms, including the design and conduct of a study, the selective reporting of results and by spinning conclusions. [33] It can also be biased through the questions they ask. It has been suggested that the dairy industry may only fund research on topics which will provide them with more favourable outcomes.[19] The influence of the food industry on the research agenda has been demonstrated in an examination of research topics covered by a 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]

Strengths and limitations of this review

Our review was submitted prospectively in PROSPERO and is still waiting registration.[21] 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.[24] We did not analyse low and full fat dairy results separately, rather we took 'total dairy' when it was available. Further analysis between low and full fat dairy may provide different results on the effects of dairy consumption and CVD risk.

This study adds to recent empirical work assessing the relationship between food industry sponsors and/ or authors with a conflict of interest with the food industry and the results, conclusions and risk of bias in primary nutrition studies. As dietary guidelines depend on an evidence base that should be as free of bias as it is rigorous and systematic, the statistically significant decreased risk in CVD outcomes we identified in industry sponsored studies compared to non-industry sponsored studies is therefore important in quantifying the magnitude and effect of industry influence of the included

studies in dietary guidelines. Further, as studies with industry ties have been shown again to have the same risk of bias or internal validity as those with no industry ties, this study further highlights the need for dietary guideline committees to account for industry sponsorship when assessing bias in primary nutrition studies. Current risk of bias tools will not account for the funding bias we have established in this study.

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

			Funding Source, n (%[1])					
			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)
Risk of Bias Assessment								
	Serious/Critical Bias due to confounding	43 (100)	8 (100)	35 (100)	10 (100)	33 (100)	14 (100)	29 (100)

			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
	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)

[#] An industry tie is defined as a study with industry sponsorship and / or an author with a conflict of interest

[1] 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

Figure 1. Study Flow Diagram of Included Studies

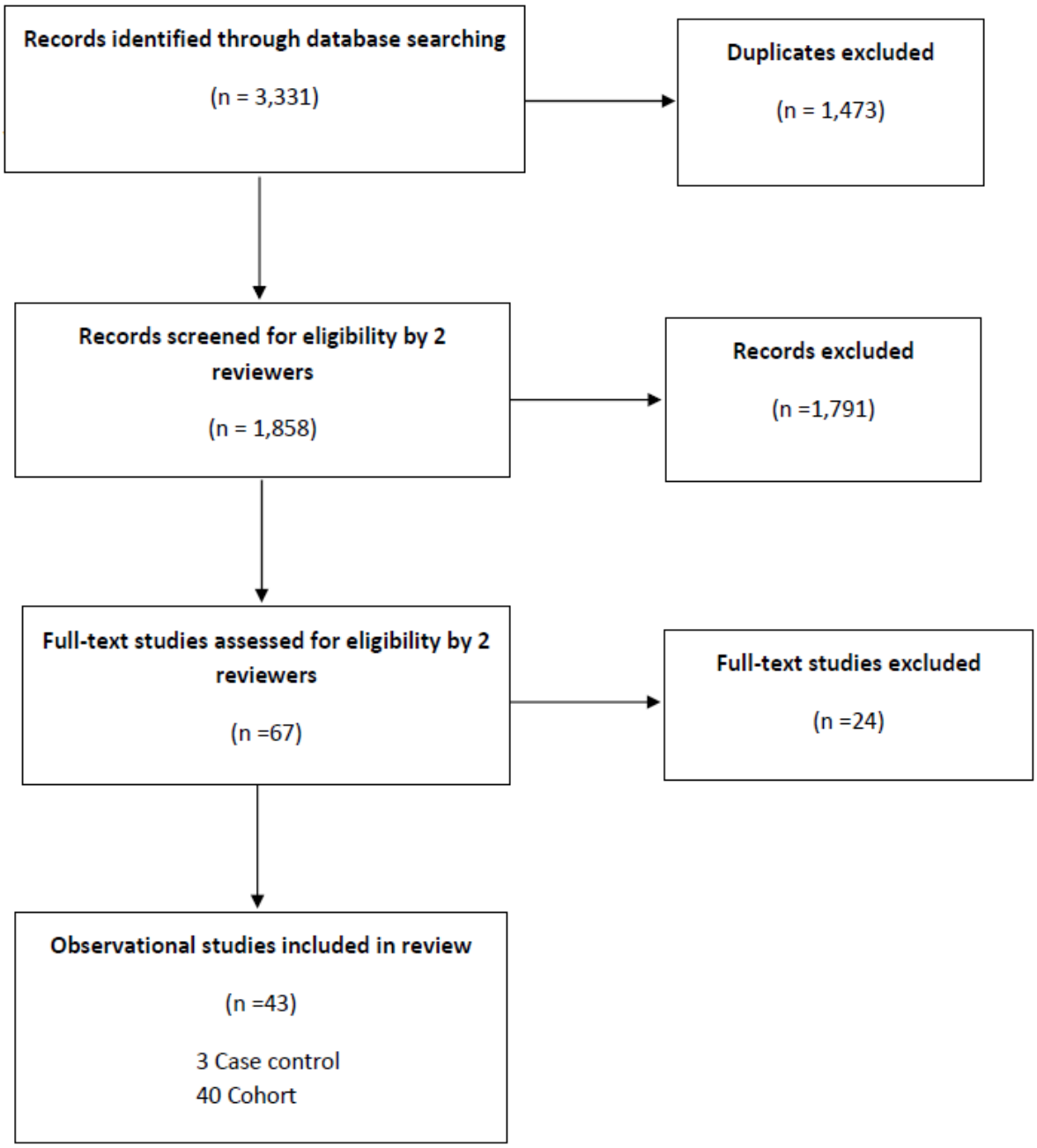
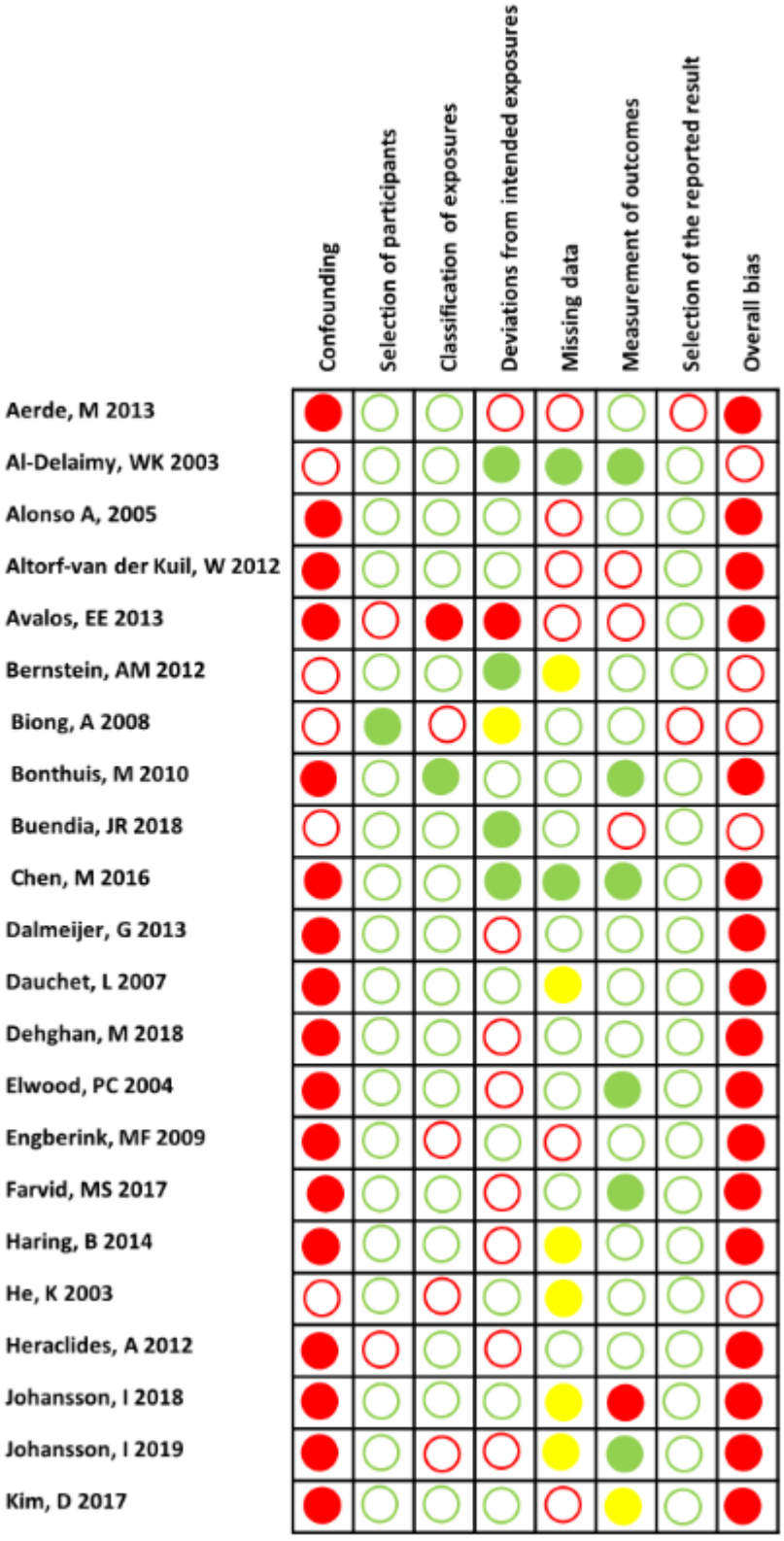


Figure 2. Risk of bias in included studies



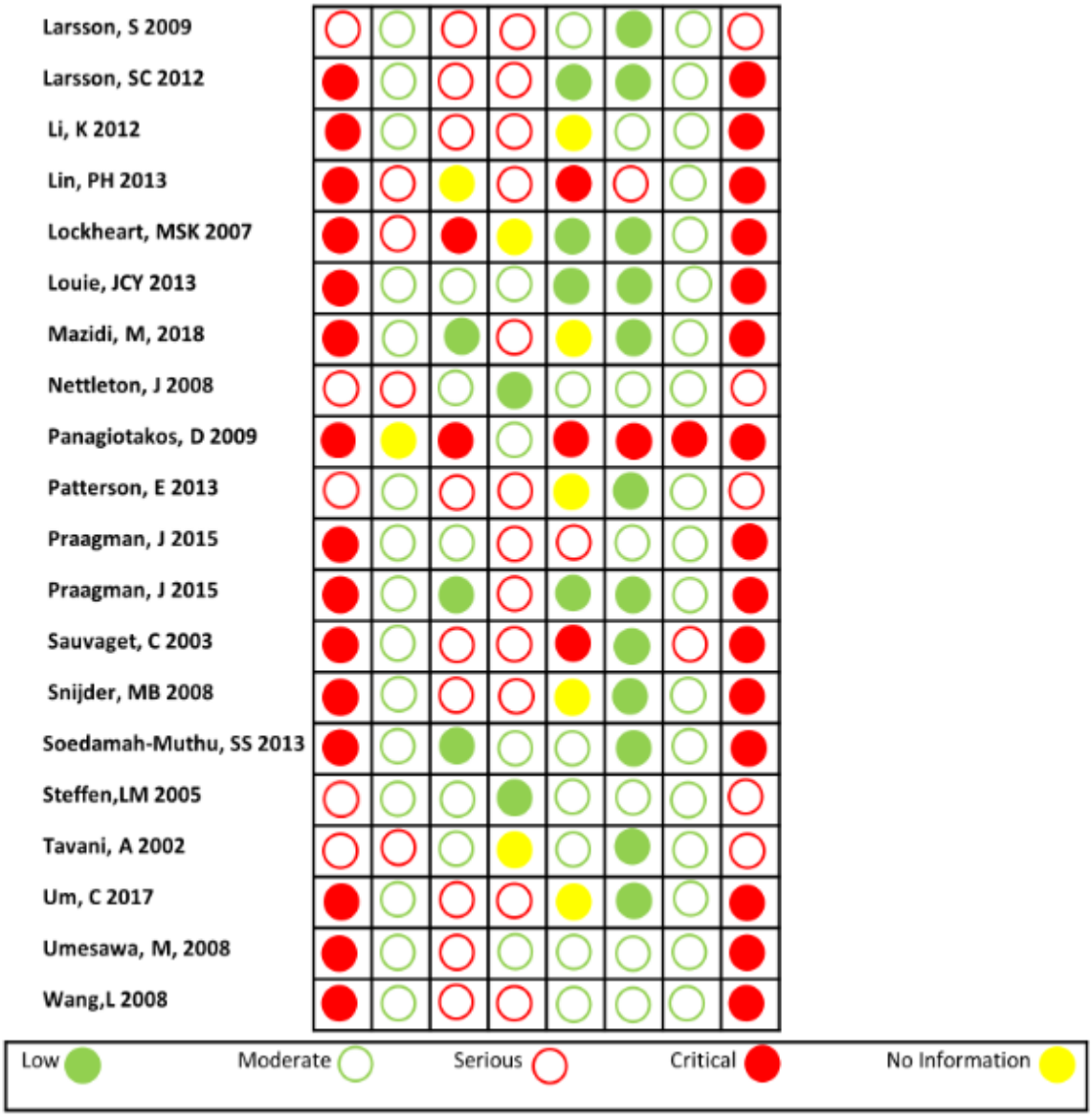

Larsson, S 2009
Larsson, SC 2012
Li, K 2012
Lin, PH 2013
Lockheart, MSK 2007
Louie, JCY 2013
Mazidi, M, 2018
Nettleton, J 2008
Panagiotakos, D 2009
Patterson, E 2013
Praagman, J 2015
Praagman, J 2015
Sauvaget, C 2003
Snijder, MB 2008
Soedamah-Muthu, SS 2013
Steffen,LM 2005
Tavani, A 2002
Um, C 2017
Umesawa, M, 2008
Wang,L 2008
Low
Moderate
Serious
Critical
No Information

Figure 3. Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Risk Ratios

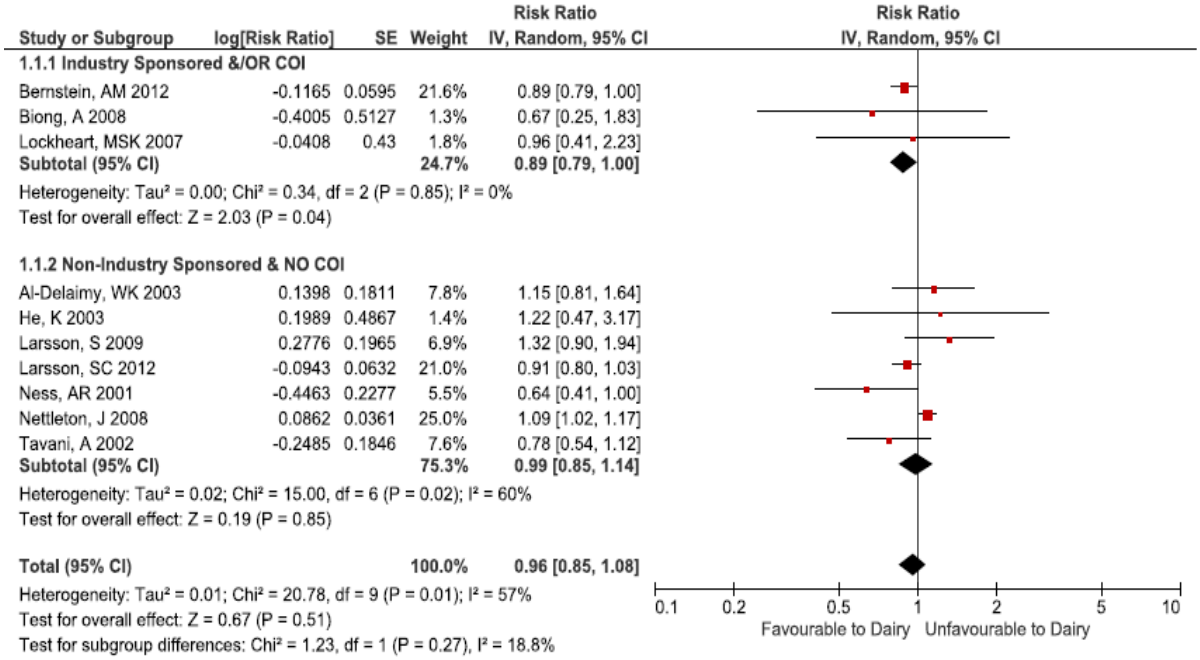


Figure 4. Effect Size, Cardiovascular Disease: Industry ties v no industry ties, Hazard Ratios

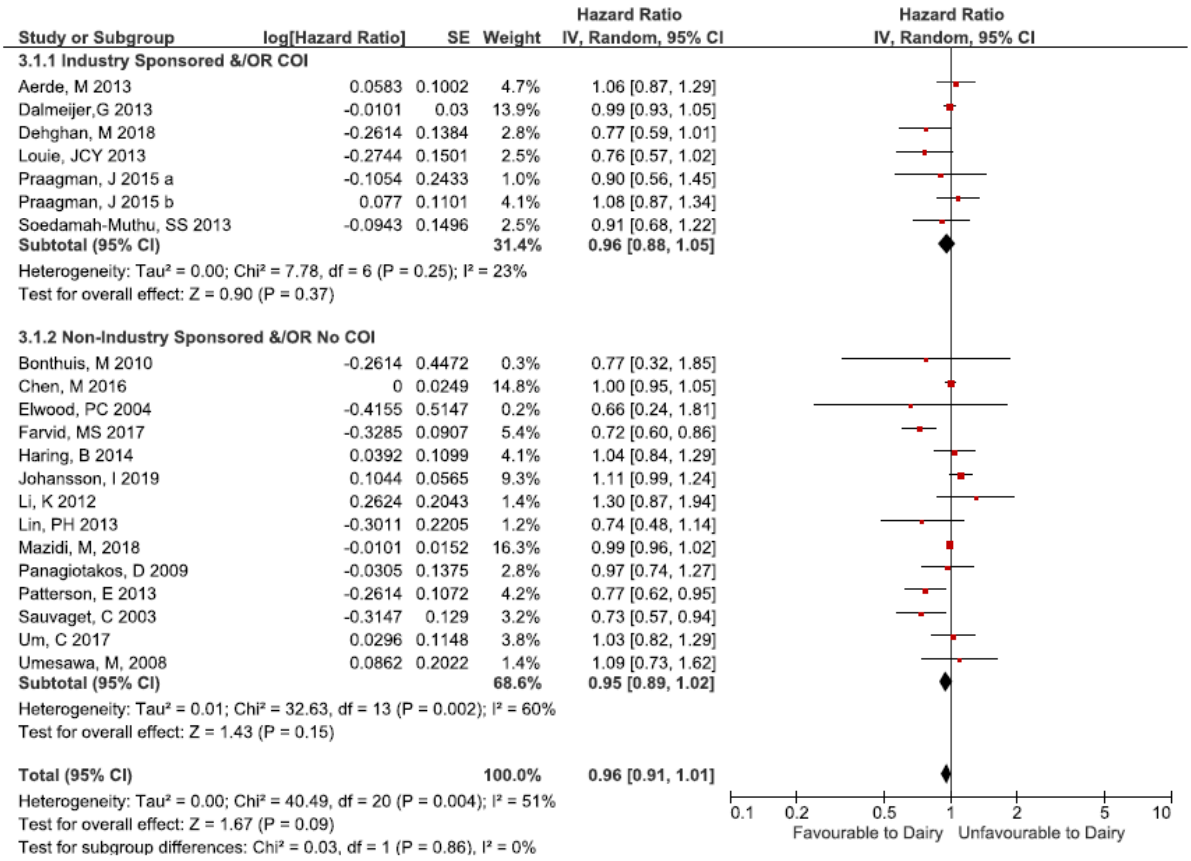


Figure 5. Effect Size, Cardiovascular Disease: Industry sponsorship vs no sponsorship, Hazard Ratios

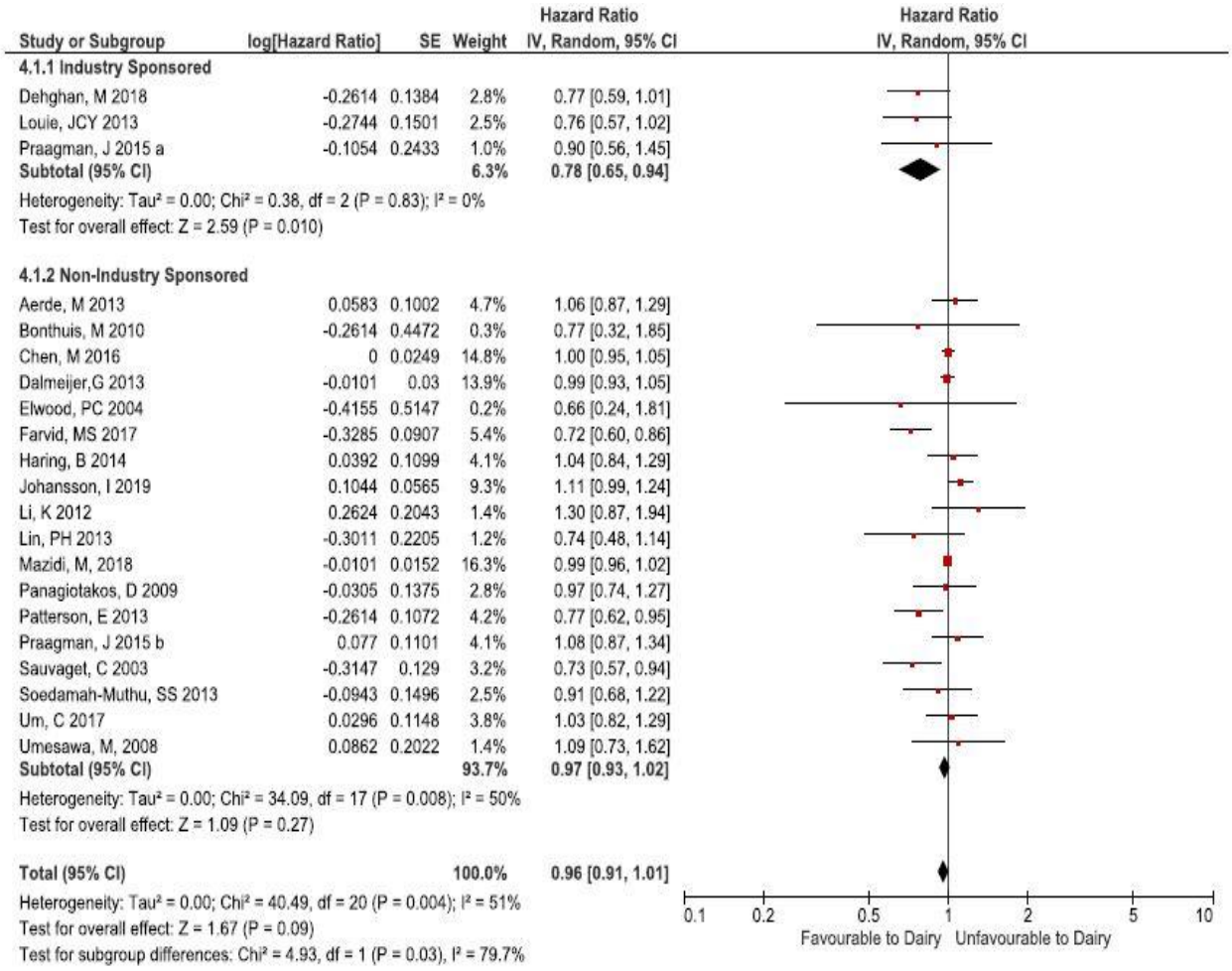
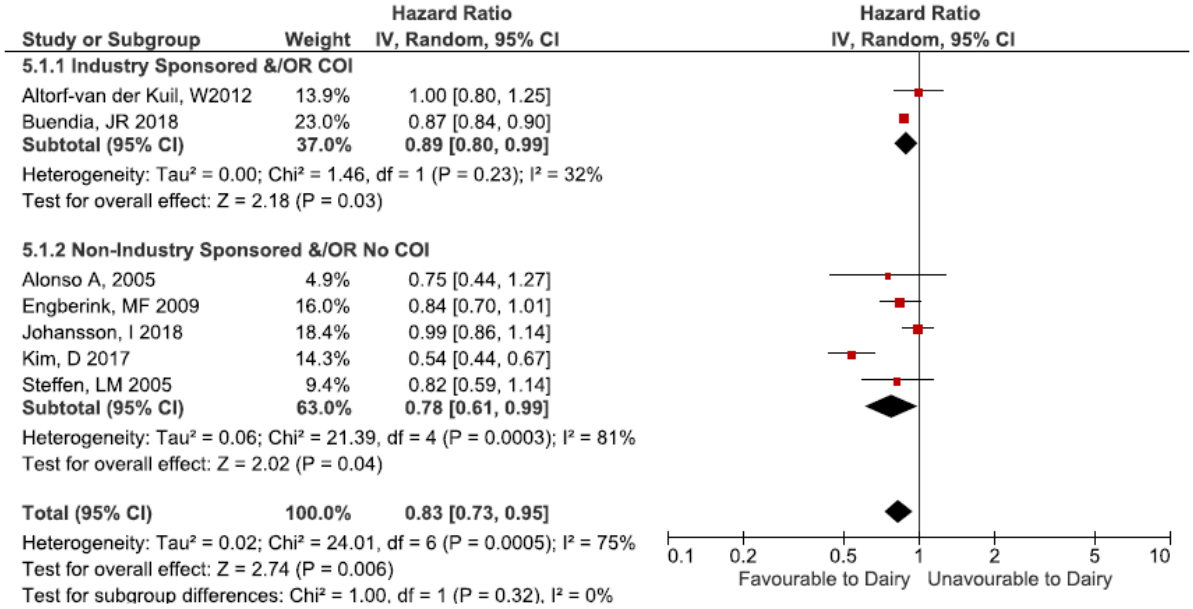


Figure 6. Effect Size, Blood Pressure: Industry ties v no industry ties, Hazard Ratios



Supplementary File 1. 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 2. 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 making outcome assessment not possible
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 in middle-aged men from the MONICA/KORA	Dietary patterns only were assessed, not dairy foods

	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. Not full study
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 3. 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 (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	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
					cheese wedges, soft unripened cheese, other cheese, custard, and ice cream)				
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	Milk, Yogurt & Cheese Sometimes/often, daily, 4–6 times/week, 1–3 times/week and 1–3 times/month (Whole milk (non-fat milk, cheese, yogurt)	Rarely/never, never & 1–11 times/year	Incident CHD	Non-industry[5]	No[e]

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
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. dairy (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 whole-fat (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 0.11 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	Dairy T3, 628 g/day ('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, 163 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, <6 serves/day to >3 serves/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 serves/day	High Blood Pressure	Industry[9]	No[i]

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
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]
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]

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
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]
Dehghan, M 2018[13]	Cohort	9.1 yrs	136,384 men & women	50·1 years	Dairy Q4, >2 servings/ day (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]

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
Farvid, MS 2017[16]	Cohort	8 years	42,403 men & women	51.6 years	Total Dairy Q5, 2.4 serves/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, 0.35 serves/day (median)	Cardiovascular Disease Mortality	Non-Industry[15]	No[o]
Haring, B 2014[17]	Cohort	22 years (median)	12,066 men & women	45-64 calculated	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 serves/week	Q 1, <1 serves/week	Blood Pressure	Non-Industry [21]	No[u]

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,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
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]

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
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 serves/day (median) (included all dairy foods)	T1, 0.6 serves/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]
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]

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
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 (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]

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 (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]
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

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
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[jj]

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

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d) Altorf-van der Kuil W, Engberink MF, Geleijnse JM - Top Institute Food and Nutrition, PO Box 557, 6700 AN, Wageningen, The Netherlands.

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h) The authors declare no conflict of interest.

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m) We declare no competing interests.

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Chapter Two

Examining Biases in Methods Used for Public Health Guideline Development

Publication details

This chapter contains the following manuscript:

1. **Chartres N**, Bero LA, Norris SL. A review of methods used for hazard identification and risk assessment of environmental hazards. *Environ Int.* 2019;123:231-239.

Overview

While quantifying the potential bias in the evidence base used in the development of public health guidelines is vital to ensuring the credibility of the recommendations that are made, there are several other critical steps that are required to ensure that bias is minimised in the entire guideline development process.

In recent years, there has been a focus by several organisations throughout the world to ensure that the methods used in clinical practice guidelines are rigorous and credible. One such organisation is the World Health Organisation (WHO) that sets norms, standards and guidance for how guidelines should be developed.[1] During my PhD work, I was privileged with the opportunity to spend ten weeks at the World Health Organization to work on a program of work to assess the methods and processes that are currently being used by various national and international organisations that conduct hazard identification and / or risk assessment of environmental exposures. On the surface, this topic may have seemed unrelated to nutrition and the development of dietary guidelines. However, when I first discussed it with the Guidelines Committee Secretariat, Dr Susan Norris, I soon learned that the harms that are assessed in these environmental studies are measured with same study designs and methods as the studies included in dietary guidelines. The processes for selecting, evaluating and synthesising the body of evidence in these public health guideline areas was in fact the same. In addition, my dissertation supervisor, Professor Lisa Bero, had made me aware of the National Health and Medical Research Council (NHMRC) efforts to develop modules for the 'Guidelines for Guidelines' that were specific to public health guidelines.[2] NHMRC's definition of public health guidelines includes both environmental and dietary guidelines. Thus, the collaborative project with WHO was highly relevant to my dissertation and could be used to inform NHMRC methods.

The complexities of these assessments of hazardous exposures due to the types of evidence that are used in their development, coupled with the limited empirical evaluation of the methods that are employed in developing public health guidelines, led to the development of the manuscript presented here in Chapter Two. This manuscript aimed to compare and assess these current practices and identify any knowledge gaps to reduce potential biases, and therefore improve the quality and credibility of the recommendations that are made in these assessments.

We showed that there is an urgent need in this area of public health to develop and implement explicit processes and to adopt empirically-based tools and methods to evaluate and synthesise the evidence used in formulating conclusions in these assessments across all organisations throughout the world. This work is transferable to the processes and methods that are required in other public health areas, including the development of dietary guidelines. Such improvements to both the tools and methods will lead to greater transparency, comparability and validity of all public health guideline recommendations.

In the next Chapter of this dissertation, Chapter Three, I will discuss one final influence that may impact the credibility of public health guidelines and the recommendations that are made from them, that is the social processes that take place between the guideline development working committees and those groups responsible for conducting the systematic reviews of the evidence. Using qualitative research methods, I aimed to understand these processes, as they may differ from what is described in guideline handbooks and cannot necessarily be quantified as they are lived, real life experiences of those that took part in their development.

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MANUSCRIPT FIVE

A review of methods used for hazard identification and risk assessment of environmental hazards

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Authors:

Nicholas Chartres[a]

The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, NSW, 2006, Australia, nicholas.chartres@sydney.edu.au

Lisa A Bero[b]

The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, NSW, 2006, Australia, lisa.bero@sydney.edu.au

Susan L. Norris[c]

Department of Innovation, Evidence and Research, World Health Organization, norriss@who.int, Av. Appia 20 CH-1211 Geneva 27 Switzerland, norriss@who.int

Corresponding author:

Lisa A Bero[b]

The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, NSW, 2006, Australia, lisa.bero@sydney.edu.au

Abstract

Background: Approximately one quarter of all deaths globally are attributed to living or working in an unhealthy environment, with household and ambient air pollution, along with exposures to ultraviolet radiation and chemicals amongst the leading causes. At present there are no international standards for assessing the risks of these environmental hazards. The use of heterogeneous methods to identify health risks from environmental hazards may reduce the level of confidence the public has in the conclusions that are made.

Objectives: To describe and compare the processes and methods used by national and international organisations that conduct hazard identification and/or risk assessment (HI/RA) of environmental hazards and to identify knowledge gaps to inform the development of future methods.

Methods: We searched the websites of 19 organisations (ten national, five international and four World Health Organization (WHO) units) and extracted data from all relevant, publicly available resources which described the processes and methods used in HI/RA of environmental hazards. We contacted each organisation for any additional information.

Results: Five organisations were excluded from further analysis: three made recommendations but did not conduct HI/RA; one used heterogenous methods across their reviews for HI; and one WHO unit did not have any published guidelines. Of the 14 organisations analysed, five (36%) describe the process for establishing the questions to be answered in the assessments. Only one (7%) organisation uses systematic review methods, although five (36%) state that they use such methods. Ten (71%) assess the scientific quality of the included studies, however only three (21%) use explicit criteria. Only three (21%) organisations assess the quality of the body of evidence using explicit criteria. Four (29%) organisations describe the process for making the final HI conclusions and three (38%) the final RA conclusions. Eight (57%) have a conflict of interest policy and seven (50%) organisations describe a process for managing them. The US Office of Health Assessment and Translation and the World Health Organisation meet the most criteria for describing their processes and methods.

Conclusions: The processes and methods used by organisations conducting HI/RA of environmental hazards are inconsistent. There is a need for empirically based tools and methods to be adopted for the evaluation and synthesis of evidence, and the formulation of conclusions across all organisations that conduct HI or RA. These tools and methods will lead to increased transparency, comparability and validity of the assessments.

Keywords: Environmental Health, Environmental Hazards, Hazard Identification, Risk Assessment, Methods, Review

Abbreviations: HI, Hazard Identification; HC, Hazard Characterisation; RA, Risk Assessment; WHO, World Health Organization

1. Introduction

Approximately one quarter of all deaths globally are attributed to living or working in an unhealthy environment, with household and ambient air pollution, along with exposures to ultraviolet radiation and chemicals amongst the leading causative risk factors.[1] While it is estimated that there are approximately 85,000 chemicals in use, the majority of these have not been assessed for toxicity.[2,3]

A hazard is any natural or man-made substance, chemical, physical or biological agent, that is capable of causing an adverse health outcome in certain circumstances. Risk is an estimate of the effect of an adverse health outcome when exposed to a hazard.[4] Risk assessment is a multi-step process, which includes: hazard identification (can a substance lead to an adverse health outcome in any circumstance?); hazard characterisation (what is the probability of an adverse health outcome at various exposure levels?); exposure assessment (what is the extent of exposure of a substance in a population?); and finally risk characterisation (the integration of both hazard characterisation and exposure assessment to estimate the level of risk of an adverse health outcome in the most sensitive populations). Risk assessment informs the development of risk management options for environmental hazards.

There are a number of challenges in conducting hazard identification (HI) and risk assessment (RA) of environmental hazards that are distinct from assessments of the effectiveness of clinical interventions. The causal chain linking harmful substances with adverse outcomes is complex, with various interactions and often considerable time periods between exposure and effects. Hazardous substances may be comprised of many toxic components, with various interactions among them, making it difficult to identify the precise toxic component that causes an adverse health outcome. There is no one single measurement to assess the association of a harmful substance and an adverse outcome. For example, in assessing the toxicity of triclosan in non-human mammalian evidence, over 100 unique outcome measures were identified.[5] Several factors must be considered when assessing

the risk of a hazard, including populations that are most susceptible (due to intrinsic biological factors), vulnerable (due to environmental factors), and sensitive (both susceptible and vulnerable).[6] Data required for HI and RA are rarely derived from randomized, controlled trials and usually come from human observational, animal and mechanistic studies, making assessments and synthesis of the evidence challenging. Confounding and selection bias in observational studies make establishing causal links between exposure and effect difficult. Finally, the methods to assess the quality of the evidence from these studies are not well established.[7-9]

At present there are no international standards for conducting HI or RA. Use of heterogeneous methods to identify health risks posed by environmental hazards may reduce the level of confidence the public has in the assessments and hinder the decision-making process. Different pronouncements on the harms of environmental hazards, such as those surrounding glyphosate[10,11] and bisphenol-A (BPA)[12,13] by national and international organisations, leave both the public and policy-makers confused.

Several groups have begun developing methods and frameworks to address environmental health questions, including the assessment of environmental exposures and human health, by extending methods from clinical medicine.[14,15] It has been proposed that well-structured, flexible approaches that are not too prescriptive and account for scientific issues in the design, conduct and analysis of environmental epidemiological and animal toxicology studies may increase transparency and prevent the introduction of a systematic bias when drawing conclusions on environmental hazards.[7] The use of scientifically robust and transparent methods to evaluate the evidence also allows the reasons for conflicting conclusions and opinions to be readily identified.[16]

The objectives of this study were to:

- describe the processes and methods used by national and international organisations, including World Health Organization (WHO) technical units that conduct HI and/or RA of environmental hazards;
- compare these processes and methods; and
- identify knowledge gaps to inform the development of standardised tools and processes for the evaluation and synthesis of evidence and the formulation of conclusions in HI/RA.

2. METHODS

We conducted a cross-sectional content analyses of all publicly available relevant resources of selected national and international organisations that perform HI and/or RA of environmental hazards. We use the term 'organisation' to refer to each organisation, agency, office, unit or department included in our study.

2.1. Selection of organisations

We included organisations that assessed environmental hazards that were categorized as:

- chemical agents, both organic (made with carbon and hydrogen) and inorganic (without carbon);
- radioactive agents, including ionizing and non-ionizing radiation and waste products from the production of nuclear weapons and energy; and
- complex exposures, which include multiple hazardous agents.

If an organisation performed HI/RA for a mixture of agents, including biological and physical, we included the organisation. If a WHO unit had conducted any stage of the HI/RA process in forming a guideline, we included it. Included organisations had to have published at least one assessment or guideline in English.

We excluded organisations that assessed environmental hazards that were categorized as physical agents (including noise, force and light), or biological agents (including mould, bacteria and pollen), even if they were part of complex exposures, such as water quality and air pollution. We excluded voluntary exposures including medications, diet and active smoking. Chemicals ingested through food sources, such as pesticides and food additives were considered involuntary. We also excluded organisations that published conclusions based on assessments provided by other organisations, but did not perform their own HI or RA.

We categorised each included organisation based on the assessments they performed, defined as: *Hazard Identification* -whether a substance may lead to key adverse health outcomes at any level of exposure; *Hazard Characterisation (HC)* - a quantitative assessment of the dose/exposure-response relationship between a hazardous substance and an adverse health outcome; *Exposure Assessment* - the measurement of the magnitude, frequency and duration of exposure to a hazardous substance in the environment on a specified population; *Risk Characterisation* - the approximation of the incidence and severity of health outcomes, following exposure to the hazardous substance(s); and *Risk Assessment* – the process of completing each of the previous steps.

We initially identified five key organisations that produce HI and/or RA of environmental hazards of the types of interest to us, then consulted those organisations and other experts to identify other organisations for potential inclusion.

2.2. Data sources

Between May and September 2017, we conducted an initial search of the web-sites of identified organisations for publicly available resources which described the processes and methods used in HI and RA of environmental hazards. We also contacted organisation officials via email for guidance on relevant resources.

We examined written guidance documents, assessments, guidelines and websites that described the processes and methods used by an organisation in HI/RA of environmental hazards on any health outcome. If guidance documents were not available, we tried to identify the most recent assessments or guidelines produced by the organisation to identify the processes and methods used in HI/RA.

If a unit or office within an organisation referenced general guidance documents used by the organisation for various stages of the HI/RA process but did not clearly describe how this guidance was applied for a particular HI or RA, we did not include it in our extraction. We excluded hazard safety cards, facts sheets and safety guides, as well as documents and web-sites that were not written in English.

2.3. Data collection and analysis

A data extraction sheet was developed to characterise the processes and methods used in HI/RA by the included organisations. One author (NC) performed data extraction independently and data were then tabulated and coded in MS Excel (Microsoft, Redmond WA, USA, 2016 MSO). Each included organisation was contacted by email and given the opportunity to review the extracted data and provide additional information. Following this initial revision, we made further amendments to the extraction and therefore offered those organisations that had edited the original data the opportunity to review the data extraction again.

We extracted data according to 22 criteria addressing the following areas: planning or protocol development, evidence review, evidence integration, establishing reference values, making a final determination or conclusion, peer review and identifying and managing conflicts of interest. We used a modified version of AMSTAR (A Measurement Tool to Assess Systematic Reviews)[17,18] to assess the evidence review methods; the other criteria were based on recommendations made by the United

States National Academies of Science to improve toxicological assessments of environmental contaminants.[19]

We coded our data extraction into four categories: yes, no, N/A (not applicable) and unclear. We coded 'yes' if the content was identified. If an organisation did not provide any publicly available information on request and if it was clear that a criterion was not completed by an organisation, we coded it as a 'no'. 'N/A' was coded if a criterion was not applicable to an organisation (e.g. 'Use a process and method to select the evidence in establishing reference values' is not applicable to organisations only conducting HI). If we were unable to make a clear 'yes' or 'no' categorisation even after contacting the organisation, we classified it as 'unclear'.

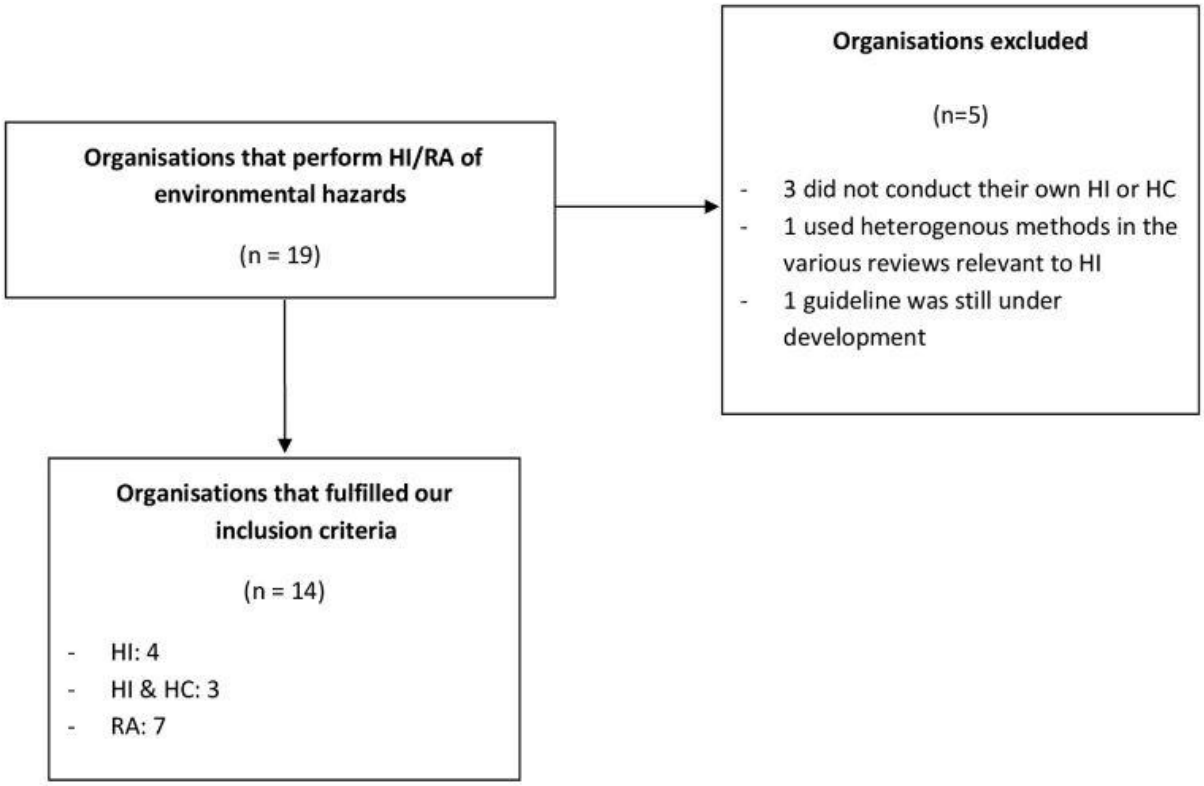
3. RESULTS

3.1. Characteristics of included organisations

We identified 19 organisations that perform HI and/or RA of the types of environmental hazards of interest to us. However, five of these organisations did not fulfil our inclusions criteria: three did not conduct their own HI or HC but rather used other organisations' HI and HC to set reference values;[20-23] one WHO unit used heterogeneous methods in the various reviews relevant to HI and HC to develop a single guideline[24] and another WHO unit had no published guidelines, with one guideline under development.[25] See Supplementary File A for information on the excluded organisations.

We thus included 14 organisations in our final analysis (Figure 1). The verbatim descriptions of the type of assessment conducted by each organisation are found in Supplementary File B. One of the included organisations was a WHO unit that assessed harms of hazardous exposures to inform guideline recommendations that make it comparable to the national and international organisations that completed HI/RA. See Supplementary File C for additional information on this guideline.

Figure 1. Flow diagram of the included organisations and the assessments they completed



HC, hazard characterisation; HI, hazard identification; RA, Risk Assessment

Eight (57%) of the 14 included organisations had publicly available guidance documents outlining the steps they used in the HI/RA process. The remainder did not have any specific guidance documents available: one (7%) had an outline of their methods in a preamble within a completed assessment;[26] and four (29%) organisations had descriptions of the processes and methods used in RA on their websites and in completed assessments.[27-31] One (7%) organisation did not have any publicly available resources outlining the processes and methods they used in RA and was therefore coded as

'no' for every criterion. Twelve (86%) organisations required review of three or more resources to complete the data extraction. Supplementary File D lists the resources used in data extraction.

Seven (50%) of the 14 organisations reviewed and edited the data extraction. Of the seven organisations that did not edit the extraction, one (7%) did not reply,[32] three (21%) recommended further resources,[27,28,31] two (14%) stated that their processes and methods were currently under revision,[33,34] and one (7%) organisation confirmed that they did not have any publicly available resources describing their methods used in RA.[35]

3.2. Processes and methods used by the organisations

Table 1 summarises the number of organisations that described specific aspects of the methods and processes used in HI/RA according to 22 criteria.

Table 1. Description of specific aspects of methods and processes used for hazard identification (HI) and risk assessment (RA)

Method or process	Number[a] (%)
Planning/protocol stage (n=14)	
Use a process for identifying the substances	12 (86)
Use a process for establishing the questions	5 (36)
Participants involved in the decision-making process for identifying the substances	8 (57)
Participants involved in the decision-making process for establishing the questions	3 (21)
Use a process for how the review/working group is established	7 (50)
Evidence review methods (n=14)	
Use systematic reviews	5 (36)
Use systematic review methods that meet 11 out of 11 AMSTAR items[b]	1 (7)
Conduct an assessment of individual study quality	10 (71)
Use well-defined, reproducible methods to assess study quality[c]	3 (21)
Use well-defined, reproducible methods to assess quality of the body of evidence[d]	3 (21)
Rate the overall confidence in the body of evidence	4 (29)
Integrating evidence streams (n=13) [e]	
Use well-defined methods to integrate evidence streams	3 (23)
Hazard identification (n=14)	
Use a process and method for making final HI conclusions	4 (29)
Rate the strength of the recommendation	5 (36)
Establishing reference values (n=10)[f]	

Have a separation between identification and synthesis of the scientific evidence used in HI and the formulation of reference values	3 (30)
Use a process and method to select the evidence in establishing reference values	3 (30)
Risk assessment conclusions (n=8)[g]	
Use a process and method for making final RA conclusions or guideline recommendations	3 (38)
Rate the strength of the recommendation	3 (38)
Review process (n=14)	
Include external peer review process of the assessment or guideline	6 (43)
Conflicts of interest and funding (n=14)	
Have a policy on conflicts of interest	8 (57)
Use a process for managing conflicts of interest	7 (50)
Disclose funders[h]	11 (79)

Abbreviations:

AMSTAR: A Measurement Tool to Assess Systematic Reviews

HI: Hazard Identification

RA: Risk Assessment

Legend:

a. Number of organisations that described the specific methods or processes. We used a modified version of AMSTAR (A Measurement Tool to Assess Systematic Reviews)[17,18] to assess the evidence review methods; the other criteria were based on recommendations made by the United States National Academies of Science to improve toxicological assessments of environmental contaminants.[19]

b. Number and description of the AMSTAR items met by each organisation in conducting evidence reviews are described in Supplementary File E.

c. We included organisations that referenced a tool or described reproducible criteria and methods to assess study quality. We did not include organisations that used the Organisation for Economic Co-operation and Development's (OECD) Test Guidelines and Good Laboratory Practice (GLP) standards to assess study quality.

d. We included organisations that described reproducible criteria and methods to assess the quality of the body of evidence. We did not include organisations that stated that they had used the 'Weight of Evidence' approach.

e. 'WHO guidelines on protecting workers from potential risks of manufactured nanomaterials'[36] is excluded from this summary as in the review relevant to HI by Lee et al.[37] it only used animal studies found in OECD dossiers to form classifications and evidence streams could not therefore be integrated.

f. Four organisations conducted HI only, so they are therefore excluded from this summary. 'WHO guidelines on protecting workers from potential risks of manufactured nanomaterials'[36] was included as the evidence reviews supporting this guideline distinguished between HI and establishing reference/guideline values (HC).

g. Six organisations conducted HI or HC only and are therefore excluded from this summary. 'WHO guidelines on protecting workers from potential risks of manufactured nanomaterials''[36] is included as they make final guideline recommendations.

h. Assessments published by the US Government were assumed to have been funded by the US Government. Assessments published by the European Commission were assumed to have been funded by the European Commission.

Table 2 summarises the specific methods and processes used in HI/RA described by each individual organisation. Details of all criteria assessed are available in Supplementary File F.

Table 2. Total number and key specific methods and processes used in hazard identification (HI) and risk assessment (RA) by the individual organisations

Organisation and program categorised by type of assessment they perform	Country	Total number of criterion completed (%)[a]	Use a process for establishing the questions	Use systematic reviews	Number of AMSTAR criteria met for systematic reviews (n=11) (%)	Use well-defined, reproducible methods to assess study quality	Use well-defined, reproducible methods to assess quality of the body of evidence	Use well-defined methods to integrate evidence streams	Include an external peer review process	Have a policy on conflicts of interest	Disclose funder(s)
Hazard Identification (n=18 criteria)[b]											
International Agency for Research on Cancer (IARC)	International	12 (67)	Unclear	Yes	4 (36)	No	No	Yes	Unclear	Yes	Yes
Office of the Report on Carcinogens (ROC), Division of the National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services	United States	16 (89)	Yes	No	8 (73)	Yes	Yes	Yes	Yes	Yes	Yes
National Centre for Environmental Assessment (NCEA), RTP Division, Office of Research and Development (ORD), U.S. Environmental Protection Agency, Integrated Science Assessment (ISA)	United States	7 (39)	Yes	No	4 (36)	No	No	Unclear	Yes	Unclear	Yes
Office of Health Assessment and Translation (OHAT), Division of the National Toxicology Program, National Institute of Environmental Health Sciences, U.S. Department of Health and Human Services	United States	18 (100)	Yes	Yes	11 (100)	Yes	Yes	Yes	Yes	Yes	Yes
Hazard Identification and Characterisation (n=20)[c]											
Scientific Committee on Occupational Exposure Limits (SCOEL)	International	4 (20)	No	No	1 (9)	No	No	No	No	Yes	Yes
National Centre for Environmental Assessment (NCEA), Office of Research and Development (ORD), U.S. Environmental Protection	United States	7 (35)	No	Yes	7 (64)	No	No	Unclear	Yes	No	Yes

Agency, Integrated Risk Information System (IRIS)											
Organisation and program categorised by type of assessment they perform	**Country**	**Total number of criterion completed (%)[a]**	**Use a process for establishing the questions**	**Use systematic reviews**	**Number of AMSTAR criteria met for systematic reviews (n=11) (%)**	**Use well-defined, reproducible methods to assess study quality**	**Use well-defined, reproducible methods to assess quality of the body of evidence**	**Use well-defined methods to integrate evidence streams**	**Include an external peer review process**	**Have a policy on conflicts of interest**	**Disclose funder(s)**
Department of Public Health, Environmental and Social Determinants of Health- 'WHO guidelines on protecting workers from potential risks of manufactured nanomaterials'	International	20 (95) (21 criteria used)[d]	Yes	Yes	6 (86) (7 criteria used)[e]	Yes	Yes	N/A[f]	Yes	Yes	Yes
Risk Assessment (n=22)[g]											
Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)	International	10 (45)	Yes	No	3 (27)	No	No	Unclear	No	Yes	Yes
Joint FAO/WHO Expert Committee on Food Additives (JECFA)	International	8 (36)	No	No	5 (45)	No	No	No	No	Yes	No
Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pesticide Programs (OPP), U.S. Environmental Protection Agency, Risk Assessment in the Pesticide Program	United States	2 (9)	No	No	3 (27)	No	No	No	Unclear	No	Yes
Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Pollution Prevention and Toxics (OPPT), U.S. Environmental Protection Agency, Assessing and Managing Chemicals under TSCA	United States	3 (14)	No	Yes	1 (9)	No	No	No	Unclear	No	Yes
National Institute for Occupational Safety and Health (NIOSH), Department of Health and Human Services, Centres for Disease Control and Prevention	United States	6 (27)	No	No	2 (18)	No	Unclear	Unclear	Yes	Yes	Yes

National Industrial Chemical Notification and Assessment Scheme (NICNAS), Department of Health, Australian Government	Australia	4 (18)	No	No	1 (9)	No	No	No	No	No	No
Organisation and program categorised by type of assessment they perform	**Country**	**Total number of criterion completed (%)[a]**	**Use a process for establishing the questions**	**Use systematic reviews**	**Number of AMSTAR criteria met for systematic reviews (n=11) (%)**	**Use well-defined, reproducible methods to assess study quality**	**Use well-defined, reproducible methods to assess quality of the body of evidence**	**Use well-defined, methods to integrate evidence streams**	**Include an external peer review process**	**Have a policy on conflicts of interest**	**Disclose funder(s)**
Australian Pesticides and Veterinary Medicines Authority (APVMA), Australian Government	Australia	0 (0)	No	No	0 (0)	No	No	No	No	No	No

Abbreviations:

AMSTAR: A Measurement Tool to Assess Systematic Reviews

HC: Hazard Characterisation

HI: Hazard Identification

N/A: Not Applicable

RA: Risk Assessment

Legend:

a. The 22 criteria are listed in Table 1 and Supplementary File F. We used a modified version of AMSTAR (A Measurement Tool to Assess Systematic Reviews)[17,18] to assess the evidence review methods; the other criteria were based on recommendations made by the United States National Academies of Science to improve toxicological assessments of environmental contaminants.[19]

b. Criteria for 'Establishing reference values' and 'Risk assessment conclusions' were not applicable for organisations conducting HI. Total number of criteria is therefore 18.

c. Criteria for 'Risk assessment conclusions' were not applicable for organisations that conduct HI and HC. Total number of criteria is therefore 20.

d. Criteria 'Use a process and method for making final RA conclusions or guideline recommendations' and 'Rate the strength of the recommendation' were applicable. Criterion 'Use well-defined methods to integrate evidence streams' was not applicable as the review by Lee N. et al.[37] used to assess the HI stage only used animal studies found in OECD dossiers and evidence streams could not therefore be integrated. Total number of criteria is therefore 21.

e. In the review by Lee N. et al.[37] , a systematic review of OECD dossiers was conducted to assess hazardous properties of manufactured nanomaterials and assign them according to the GHS (Globally Harmonized System) of classification and labelling. This was used for the evidence review methods included in the HI stage of this assessment. Several AMSTAR criteria for the systematic review process were thus not applicable and the overall rating is out of 7. The criteria that were assessed were: 1. An a priori design was used/will be provided; 2. Duplicate screening and data extraction was/will be conducted; 5. A list of included studies was/will be provided; 7. The characteristics of the included studies was/will be provided; 8. The scientific quality of the included studies was/will be assessed; 10. The methods to combine studies was described and appropriate; and 11. Industry sponsorship/author COI was/will be considered?

f. To assess the HI stage we used the review by Lee N. et al.[37] and it only used animal studies found in OECD dossiers to form classifications and evidence streams could not therefore be integrated. This criterion was therefore not applicable.

g. Organisations that conducted RA were assessed using all 22 criteria.

4. DISCUSSION

Divergent methods are used in HI and RA of environmental hazards by the organisations included in this analysis. Less than half of the organisations met all the criteria for synthesising evidence streams, establishing reference values, and formulating recommendations. Organisations that conduct RA meet the fewest number of criteria (no organisation met even half of the criteria), while organisations that conduct HI meet the most criteria for describing their processes and methods. The US Office of Health Assessment and Translation[38,39] and the World Health Organisation unit meet the greatest number of criteria in describing their processes and methods. Overall, the organisations that reviewed and edited our data extraction also meet the greatest number of criteria.

Our assessment of the processes and methods used in HI/RA by organisations was very difficult to complete: we had to examine multiple documents, undertake time-intensive searching to identify the relevant information, and initiate multiple email communications with most of the organisations. In addition, organisations did not use consistent terminology to describe their methods. Lack of easily identifiable processes and methods used in HI/RA makes it more difficult to determine the reliability and validity of the organisations' assessments, even when systematic and reproducible methods are used.

Reasons for the inconsistencies in methods across organisations may be due to lack of an internationally accepted "gold standard" and the ongoing evolution of methods for RA. Some variation in the methods used by the organisations may be justified depending on the resources available to the organisation,[40] type of assessment being made or the intended audience. However, to produce reliable and valid answers to environmental health questions, improvements are required in the processes used to formulate questions, search for evidence, assess quality at the individual study level and the overall body of evidence, integrate evidence streams, and make final recommendations.

While most of the organisations describe how substances are selected for assessment, few describe how the questions that are to be answered in the assessment process are established. The formation and use of answerable questions in a PECO (Population, Exposure, Comparator and Outcome) format has been recommended and implemented by various organisations conducting assessments in environmental health.[14,15] The use of PECO statements systematises review objectives and the methods that will be used to answer the defined questions.[16]

Only one organisation that conducts RA states that they use systematic reviews to search for, select and evaluate the evidence.[28] There has been increasing discussion on the limitations around the use of narrative reviews based on expert judgement,[8,14,41,42] and the need for systematic review methods in the assessment of environmental and occupational health to improve transparency and comparability amongst the assessments.[14] Only one organisation[38,39] uses systematic review methods that meet all of the AMSTAR (A Measurement Tool to Assess Systematic Reviews) items that were assessed. Although AMSTAR has limitations,[43] it has been demonstrated to be a reliable and valid tool to assess the methodological quality of systematic reviews.[18]

Approximately three quarters of organisations assess the quality of individual studies. However, less than one quarter of the organisations use or adapt their assessment of study quality from an existing tool or use well-defined, reproducible criteria. Several organisations state that they used the Organisation for Economic Co-operation and Development's Test Guidelines and Good Laboratory Practice (GLP) standards to assess study quality. These standards are preferred by chemical industry scientists and consultants. [44] Although GLP standards have improved the record keeping of many commercial laboratories, they are not an accurate measure of study quality and should not be relied upon to make public health decisions.[45]

To assess the body of evidence, less than one quarter of the organisations use well-defined and reproducible methods. Several organisations state that they use 'weight-of-evidence' methods in the assessment process. However, the steps involved in this process and how it is described vary considerably across organisations. [46-48] Formal procedures and consistent nomenclature for weight-of-evidence methods are lacking, and although authors frequently claim to have applied this process, adequate documentation is often absent.[48] The 2014 National Academy of Science (NAS) review of the Environmental Protection Agency's Integrated Risk Information System (IRIS) process found the weight-of evidence process to be judgement-based and of little scientific use.[19]

Less than half of the organisations describe the processes used for making final determinations or recommendations. While there is an element of subjectivity in the process, the use of objective processes versus expert judgment and opinion alone may be an important influence in how accurately the evidence is interpreted.[16] Further, when expert opinions are conflicting and undocumented, it is difficult to establish the most valid evaluation and synthesis of all the evidence.[16]

While approximately two thirds of organisations have a policy on disclosure of funding of the assessment or guideline, half do not have a policy on declaring or managing conflicts of interest. Lack of policies around conflicts interest in guideline development is cause for concern.[49]

4.1. Limitations of this study

We only had one assessor and extractor. Because we experienced difficulty identifying the information we needed for our evaluation, we offered each organisation the opportunity to review and revise our data extraction, including the AMSTAR assessments and offer guidance on the location of additional relevant resources. While every organisation responded, not every organisation reviewed the data in detail for accuracy and completeness. We did not cross check the methods

outlined in guidance documents with the methods used in completed assessments and it is possible that there may be some discordance.

The criteria that we used to examine the different steps in the HI/RA assessment process are not intended to be equally weighted or counted, thus comparisons of the percentages of organisations that described specific methods and processes should be made with caution. Although we based our criteria on existing, accepted, validated tools, [18,19] different criteria could have been used. In addition, because we used a snowball sampling strategy to identify organisations, we may not have included some important organisations that conduct HI/RA of environmental hazards.

4.2. Implications for policy-makers and future research

The recent different pronouncements on the harms of environmental hazards, such as those surrounding glyphosate[10,11] and bisphenol-A (BPA)[12,13] may be in part due to the limitations in chemical RA methods, including the lack of systematic reviews. Systematic reviews are rigorous evaluations of the literature, using a protocol with pre-defined questions and explicit methods, to search, select, evaluate and synthesise the scientific body of evidence, in order to minimise error and bias.[16,50] Several organisations and research groups have developed or adopted,[14,15,51,52] or recommended the use[19,53] of systematic reviews in the assessment of chemicals. Using systematic reviews can detect differences in how questions are formulated, searches are conducted, or studies are evaluated. Use of these methods may lead to improved transparency, objectivity and communication of HI/RA of harmful environmental substances.[16]

It is vital to the integrity of evidence-based evaluations of environment health hazards that the primary studies that underpin decision-making are assessed with transparent and accepted methods.[7] This highlights the need to develop tools to assess the risk of bias and methods for the types of human and animal evidence that is relevant to environmental RA.[8] Further development of

empirically-based tools to assess the quality of various types of evidence used within HI/RA is still required.[8]

Well-structured, flexible approaches that are not too prescriptive while accounting for the scientific issues that are present in the design, conduct and analysis of environmental epidemiological and animal toxicology studies may increase the level of transparency in making hazard assessment conclusions and prevent the introduction of a systematic bias.[7] A structured approach such as GRADE (Grading of Recommendations Assessment, Development and Evaluations) has been recommended for its transparent evaluation of the quality of the evidence and synthesis of evidence into normative guidance for clinical interventions.[54,55] While GRADE methods have not been developed to account for all important considerations related to RA in environmental health,[56] the GRADE system is now being modified for use in environmental health assessments.[38]

HI and RA of potentially hazardous substances require topic area experts such as toxicologists and epidemiologists. Conflicts of interest of these experts must be identified and managed. Several organisations have extensive policies on how to manage experts with conflicts of interest but whose participation is deemed essential to the development of a guideline.[57,58] The consistent use of rigorous and transparent policies on disclosure and management of conflicts of interest is required.

The processes and methods used by organisations conducting HI/RA of environmental hazards are inconsistent. There is therefore a need to develop explicit processes and adopt empirically-based tools and methods for the evaluation and synthesis of evidence, and the formulation of conclusions across all organisations that conduct HI and RA. These processes, tools and methods will lead to increased transparency, comparability and validity of the assessments.

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APPENDIX

Supplementary File A: Excluded organisations and reasons for exclusion

This table lists the organisations that were excluded from further analysis and reasons for their exclusion.

Organisation and program	**Reasons for exclusion**
International Commission on Non-Ionizing Radiation Protection (ICNIRP)[1,2]	• ICNIRP issues reviews to evaluate the current state of knowledge and identify the key questions relevant to the guideline process. • The WHO then launches a risk assessment, culminating in an EHC monograph. •The EHC is published under the joint sponsorship of ILO, ICNIRP and WHO, written by international experts selected by WHO. • This monograph is then used by ICNIRP as the scientific basis for issuing guidelines. • They do not conduct HI or HC that informs their guidelines or recommendations.
Office of Water, Office of Science and Technology, U.S. Environmental Protection Agency, Human Health Water Quality Criteria[3,4]	• AWQC are derived from hazard identification, hazard characterisation or risk assessment of other organisations, with the primary source of these values coming from IRIS assessments from the U.S. EPA. • They then use updated exposure factors, BAFs, and the human health toxicity values to derive the AWQC. • They do not conduct HI or HC in forming the AWQC.
Department of Public Health, Environmental and Social Determinants of Health, World Health Organization – 'Guidelines for drinking-water quality, fourth edition'[5]	• Existing international approaches including previous risk assessments developed by the IPCS, IARC, JMPR and JECFA are used in the development of guideline values.[5] • These values are then converted into GLVs following consideration of the relative source allocation. • They do not conduct HI or HC in forming the GLVs.
Department of Public Health, Environmental and Social Determinants of Health, World Health Organization – 'Indoor air quality guidelines: household fuel combustion'[6]	•There are stages of HI, HC and EA completed to answer 4 different scoping questions, across 11 evidence reviews to inform the Guideline recommendations. •Heterogenous methods are used in reviews 4, 8 and 9 that all assessed harms of hazardous exposures, to search for the evidence, evaluate individual study quality and the body of evidence, and make final conclusions.[7] •We therefore could not summarise the methods used in the guideline.
Regional Office for Europe, European Centre for Environment and Health,	•Guideline was still under development.

World Health Organization [8]	

Abbreviations:
AWQC: Ambient Water quality criteria values
BAFs: Bioaccumulation factors
EA: Exposure Assessment
EHC: Environmental Health Criteria
GLV: Guideline Values
HC: Hazard Characterisation
HI: Hazard Identification
IARC: International Agency for Research on Cancer IARC
ILO: International Labour Organisation
IPCS: International Programme on Chemical Safety
IRIS: Integrated Risk Information System assessments
JECFA: Joint FAO/WHO Expert Committee on Food Additives
JMPR: The Joint FAO/WHO Meeting on Pesticide Residues
U.S EPA: U.S. Environmental Protection Agency
WHO: World Health Organization

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Supplementary File B: Assessments completed by each organisation

The verbatim description of the assessments completed by the organisations included in the final analysis is described in this table. We have then categorised these assessments according to the definition of HI, HC and RA described in section 2.1 of the METHODS.

Due to the length of the supplementary file it has not been included in the current thesis. Available from https://www.sciencedirect.com/science/article/pii/S0160412018322979

Supplementary file C: Included World Health Organization Unit

This table describes how hazardous exposures were assessed in the WHO Guideline that make make it comparable to the national and international organisations that completed HI/RA.

WHO Unit and Guideline	Description of the hazard identification and hazard characterisation assessments completed in the Guideline
Department of Public Health, Environmental and Social Determinants of Health, World Health Organization - WHO guidelines on protecting workers from potential risks of manufactured nanomaterials[1]	• The HI in the guideline is partly through bridging or read-across to use information for similar materials based on toxicological considerations to assess if the MNMs assessed in the guidelines are hazardous. • A SR (Review 1) [2] was conducted of expert opinions to assess the possibility of grouping MNMs based on toxicological considerations (5.1 Classification of MNMs).[1] • A SR (Review 2) [3] to identify the toxicological data needed for hazard identification of the MNMs in the OECD sponsorship programme dossiers and to assign hazard classes to these MNMs according to the GHS was then conducted (6.1 Assess health hazards of MNMs).[1] • The HC in the guideline was based off a SR (Review 6) [4] of all available proposed OELs values for MNMs from various institutions and countries, with users recommended to make their own choice of the best applicable OEL (6.2 Assess exposure to MNMs).[1]

Abbreviations:

WHO: World Health Organization

HI: Hazard Identification

HC: Hazard Characterisation

MNMs: Manufactured nanomaterials

OECD: Organisation for Economic Co-operation and Development

GHS: Globally Harmonized System of classification and labelling of chemicals

OELs: Occupational Exposure Limits

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Supplementary File D: Included resources of organisations used in data extraction

Due to the length of the supplementary file it has not been included in the current thesis. Available from https://www.sciencedirect.com/science/article/pii/S0160412018322979

Supplementary File E: Number of AMSTAR criteria met by each organisation in conducting evidence reviews

Due to the length of the supplementary file it has not been included in the current thesis. Available from https://www.sciencedirect.com/science/article/pii/S0160412018322979

Supplementary File F. Verbatim description of key specific methods and processes used in hazard identification (HI) and risk assessment (RA) described by each individual organisation according to 22 criteria.

Due to the length of the supplementary file it has not been included in the current thesis. Available from https://www.sciencedirect.com/science/article/pii/S0160412018322979

Chapter Three

Understanding the Social Influences on Public Health Guideline Development

Publication details

This chapter contains the following manuscript:

1. **Chartres N**, Grundy Q, Parker L, Bero L. "It's not smooth sailing": Bridging the gap between methods and content expertise in public health guideline development. (under review)

Overview

As described in Chapter Two of this dissertation, the methods and processes used for the development of public health guidelines, such as those described in our assessment of the organisations responsible for hazard identification and / or risk assessment of hazardous exposures are very heterogeneous and, at times, lacking all together. However, there has also been limited empirical examination into the experiences of public health guidelines developers. To gain a full understanding of the process, I interviewed individuals involved in developing National Health and Medical Research Council of Australia (NHMRC) public health guidelines. I interviewed members of the independent evidence review groups responsible for conducting the systematic reviews of the evidence and of the working committees, who oversee the evidence reviews and facilitate the guideline process.

The guideline development process for guidelines developed or approved by NHMRC is depicted in Figure 1.

Figure 1. Guideline development process for guidelines developed or approved by the National Health and Medical Research Council of Australia (NHMRC)[1]

Legend:

Steps of the guideline process completed by the guideline working committees

Steps of the Systematic review process and grading of the evidence completed by the independent evidence review groups. These reviews and evaluations are reviewed and commented on by the guideline working committees

Recommendations in the guidelines included in our study were made by the Council and CEO of NHMRC based off key issues and considerations identified by the guideline working committees

To improve the standards of public health guideline development within Australia, we sought to understand the experiences of the two major groups of participants involved, working committee members and evidence review groups, and learn of the key issues being faced by public health guideline committees within Australia. These experiences are transferable to other countries and organisations throughout the world responsible for developing public health guidelines and will assist the NHMRC in improving current guideline development processes. Specifically, the manuscript presented here in Chapter Three of this dissertation aimed to explore what hidden influences in the guideline development process were present, if any, that may impact on the final recommendations that are made. By learning about these influences, we wanted to identify potential solutions to improve current practice.

This study found that the public health guideline process in Australia is a divided one that limits the ability of the two groups involved in their development to work cohesively and collaboratively throughout the guideline process. We identified three related theoretical concepts that drive this division: the disciplinary backgrounds that these two groups bring to the process; the challenges that are imposed on them by the methodological limitations of the frameworks that they are required to use to evaluate the evidence; and barriers to communication between content experts and evidence reviewers around respective roles and methodological limitations. We propose that by working more closely together from the outset, these two groups would be able to transfer critical knowledge and ideas more easily between one another and therefore improve the guideline process.

In the final chapter of this dissertation, Chapter Four, I propose solutions to minimise the biases identified in these preceding chapters to ensure that the guideline development process is improved, and that the public's health is therefore protected.

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MANUSCRIPT SIX

"It's not smooth sailing": Bridging the gap between methods and content expertise in public health guideline development

(Under Review)

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

Grundy Q, University of Toronto, Faculty of Nursing, Suite 130, 155 College St, Toronto ON, M5T 1P8 Canada, Assistant Professor

Parker L, The University of Sydney, D17, The Hub, 6th floor, Charles Perkins Centre, The University of Sydney, NSW, 2006, Australia, Postdoctoral Research Associate

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

Keywords: Guidelines, Guideline Development, Public Health, Methods

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Authors Contributions: NC and LB initiated the study. NC designed the study, conducted the interviews and prepared the original drafts of the manuscript. QG and LB assisted with the design. QG, LB and LP assisted with the data analysis. QG and LP trained and supported NC in the data

collection and analysis methods. All authors made significant contributions to the final manuscript. NC and LB are guarantors.

Conflicts of interest: The authors have no conflicts of interest.

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Data sharing statement: No additional data are available

ABSTRACT

Background: The development of reliable, high quality health-related guidelines depends on explicit and transparent processes, methods aimed at minimising risks of bias and the inclusion of all relevant expertise and perspectives. While the methodological aspects of guidelines have been a focus to improve their quality, less is known about the social processes involved. With this in in mind, we aimed to empirically examine the perspectives and experiences of the key participants involved in developing public health guidelines for the Australian National Health and Medical Research Council (NHMRC).

Design: This study was conducted using constructivist grounded theory as described by Charmaz, which informed our sampling, data collection, coding and analysis of interviews with key participants involved in developing public health guidelines.

Setting: Australian public health guidelines commissioned by the NHMRC**.**

Participants: 20 experts that were involved in Australian NHMRC public health guideline development, including working committee members with content topic expertise (n=16) and members of evidence review groups responsible for evaluating the evidence (n=4).

Results: Public health guideline development in Australia is a divided process. The division is driven by three related factors: the divergent disciplinary background and expertise that each group brings to the process; the methodological limitations of the framework, inherited from clinical medicine, that is used to assess the evidence; and barriers to communication between content experts and evidence reviewers around respective roles and methodological limitations.

Conclusions: Our findings suggest several improvements for a more functional and unified guideline development process: greater education of the working committee on the methodological process employed to evaluate evidence, improved communication on the role of the evidence review group

and better facilitation of the process so that the evidence review groups feel their contribution is respected and valued.

Key Messages:

Implications for policy makers

- Improvements in the social processes of guideline development could reduce the tensions and division that have been identified between the two key groups of participants involved in this study – evidence evaluators and content experts.
- More pragmatic advice and training for the working committee members unfamiliar with the methodological frameworks used to assess the body of evidence is necessary.
- The evidence review groups need to feel appropriately supported in their roles when presenting the evidence reviews, particularly by the working group chairs.
- There is a need to work collaboratively from the outset and throughout the duration of the guideline process, to make it more collegial, effective and efficient.
- To enhance the transfer of ideas, knowledge and expertise, the physical separation that is currently present between the two groups should be reduced by integrating the groups, with subgroups to evaluate the evidence for particular questions.

Implications for public

Public health guidelines are designed to protect the public's health. Therefore, the methods and processes that are used to evaluate the evidence and formulate the recommendations need to be rigorous, transparent and free of bias. Further, the two groups that are responsible for developing these guidelines, the evidence review groups and working committees with content expertise, must also work effectively together. However, the current practise of these groups working separately throughout the guideline development process leads to division and conflict. The recommendations we have made in this study will lead to a more functional and unified guideline development process

that best uses all the relevant expertise, and therefore may contribute to better health outcomes for the public.

BACKGROUND

Due to the large number of organisations and governments that produce guidelines, end-users are often presented with contradictory recommendations and guidelines of varying quality.[1,2] In order to improve the quality of guidelines, several organisations around the world such as the World Health Organization (WHO),[3] the National Institute for Health and Care Excellence (NICE)[4], and the United States Community Preventive Services Task Force (CPSTF) [5] have developed standards and criteria for their development. For example, the WHO Handbook for Guideline Development, 2nd Edition requires that the process for developing a recommendation is explicit, transparent, and uses methods aimed to minimise risk of bias; the guideline development group includes all relevant expertise and perspectives, and that recommendations consider benefits and harms as well as other relevant factors.[3] Currently in Australia, there are standards for guidelines approved by the National Health and Medical Research Council (NHMRC) and guidance to achieve these standards is being developed.[6,7]

GRADE (The Grading of Recommendations Assessment, Development and Evaluation) is widely endorsed as a methodology for clinical guideline development worldwide, including by the WHO and NHMRC.[3] GRADE allows for a transparent rating of the quality of evidence and rates the confidence in effect estimates for benefits and harms as high, moderate, low, or very low.[8] GRADE has been optimised for evaluating clinical interventions and randomised controlled trials.

Public health guidelines offer recommendations to prevent ill health or to improve the health of a population, which are tailored to a specific audience (i.e. public health policy-makers, health-care providers, patients, caregivers, the public and other relevant stakeholders).[3,9] For example, NHMRC guidelines assess the health harms of living near a windfarm[10] or provide dietary advice for

Australians.[11] Unlike clinical practice guidelines, the available evidence for the development of public health guidelines is seldom from randomised controlled trials but instead is often derived from observational studies such as cohort studies, case controls, or time series analyses. Further, GRADE has not been developed to account for all important considerations related to public health guideline development, for example it does not provide explicit guidance for when evidence is linked across a causal pathway.[12] It also downgrades non- randomised controlled trial evidence, even if this is the only and most appropriate type of evidence available. The use of GRADE for developing public health guidelines or conducting systematic reviews in the field of public health has been previously studied.[13] While it has been recognised as a systematic and transparent process of evaluating the evidence, challenges have been identified in its use due to the complex nature of public health exposures.

Evidence may not be the greatest influence in the formation of guidelines.[14] In clinical practice guideline development, previous experiences and beliefs that were not consistent with the research evidence were prioritised when developing recommendations.[15] Further, the status and, therefore, power of the guideline development groups have been shown to override both the evidence and formal decision criteria when forming recommendations.[16]

Several studies have examined the social processes of the participants involved in public health guidelines and how they translate evidence into recommendations. It has been identified that guideline development groups members conceptualised the guideline development task differently, with some prioritising the evidence in informing their decision making, while others prioritised their disciplinary expertise.[17]Although the diversity of opinions in these groups brought tensions, it was seen to be vital in making informed judgements, relevant to making recommendations.[17,18] Tensions

have also been experienced between guideline development groups and those conducting the evidence synthesis. [19]

While the methodological aspects of the guideline process have been a focus for improving the quality of guidelines,[3-5] less is known about the guideline development groups social processes. We aimed to understand the perspectives and experiences of the two key groups of people involved in developing public health guidelines for the NHMRC: the evidence review group and the working committee (See Table 1 for a description of these roles). We included these two groups to allow a broad understanding of the guideline process, to learn about the relationships these groups of participants have with one another, and how, if at all, these relationships shape the guideline process. By understanding these viewpoints, we aimed to gain a greater understanding of the social influences on the guideline development process that are not apparent in the various handbooks written on the methodological procedures and technical aspects of guideline development.

Table 1. Roles and responsibilities of the working committee[#] (verbatim description from NHMRC Guidelines for Guidelines website) [20] and evidence review group

Group Member	Key Responsibilities
All Members	• Agree on the scope, questions and P[I/E]CO • Contribute constructively to meetings, including approving the minutes • Declare all relevant interests so that conflicts of interest can be identified and managed • Develop actionable recommendations based on reviews of evidence • Identify potential implementation issues and propose steps to overcome them • Assess the acceptability and feasibility of the recommendations • Weigh the potential risks and benefits of treatment • Make decisions on what information should be included • Consider and deliberate on public consultation submissions
Chair	• Contribute to the drafting of terms of reference and formation of the guideline development group

	• Facilitate group processes and promote balanced participation of group members • Support effective consumer involvement • Manage conflicts of interest during meetings • Ensure that the group stays focused and task oriented • Delegate work and co-ordinate output of the group
Content Experts	• Apply their knowledge to improving the identification of relevant evidence • Advise on how to identify best practice in areas for which limited evidence is available • Identify, critically appraise and synthesise evidence into a format useful for developing recommendations* • Assist the group in understanding the evidence and evidence-to-decision process*
Consumers	• Consider to what extent published evidence reflects outcome measures that consumers consider important. • Ensure that questions and recommendations address consumer issues and concerns • Ensure that the guideline is worded appropriately
Methodological experts[##]	• Identify, critically appraise and synthesise evidence into a format useful for developing recommendations • Assist the group in understanding the evidence and evidence-to-decision process • Maintain comprehensive records
Evidence Review Group[###]	• Conduct an independent evidence evaluation of all the relevant scientific research, using internationally recognised systematic review methods to perform the evidence evaluation to the highest possible standard • Assist the guideline working committee to understand the evidence evaluations

** This is often considered a core task of content experts, particularly in the absence of a methodological expert*

#In the current NHMRC Guideline for Guidelines website from which we sourced this table, the working committees we refer to are called 'guideline development groups'. However, for consistency with how they are described in our study we have called them Working Committees. There were 16 Working Committee members included in this present study

There are methodologists on the working committee, but they do not complete the reviews as described here.

Not verbatim text. There were 4 Evidence Review Group members included in this present study.

METHODS

Methodology

This study was conducted using constructivist grounded theory as described by Charmaz, which informed our sampling, data collection, coding and analysis.[21] This type of grounded theory asserts

that the knowledge produced is contextually created by the participants of the research and by the researcher. We sought to understand the diverse worlds, multiple realities, and complexities of the participants we interviewed.[22] We sought to learn about the various unseen situations, relationships and tacit networks in the guideline process, seeking to unearth any relationships of power and communication, that are not captured in the published guideline documents.[22] We remained aware of our professional and disciplinary expertise and kept coding and interpretation close to the data.

Participants and sampling

We selected participants that were part of the development of a public health guideline published or currently under development for the NHMRC in Australia, over the last 10 years.

We use the term 'guideline' in this study to represent the guidelines, information papers and statements that the included groups produced for the NHMRC. We use the term 'working committee' in this study to represent those participants that were part of working committees, reference groups and advisory groups that reported to the Council of the NHMRC (Table 1).We use the term 'evidence review group' to represent those participants that were contracted by NHMRC to review and evaluate the evidence for targeted questions that informed the development of a 'guideline' (Table 1).

Initially we sampled purposively to seek multiple perspectives on the guideline development process. We reasoned that the perspectives and opinions of the process would vary between guidelines and the roles that were undertaken. We therefore invited members of guideline working committees and evidence review groups to be part of the study. As we used constant comparative analysis techniques throughout the process, after our initial data collection and analysis, we used

theoretical sampling to seek data to continue to develop and refine our emerging theoretical concepts.[21] We continued to modify the questions to ask in the interviews and who to interview.

We identified participants by emailing the contact addresses for randomly selected public health guideline topics on the NHMRC websites and asked the NHMRC contact person to invite participants. We provided a participant information statement to share with eligible participants. If a guideline participant expressed interest in being involved in the study, we were given their contact information by the NHMRC. We also contacted potential participants suggested by colleagues or other participants that we interviewed. We were able to identify all information necessary to contact these participants in the public domain.

Data collection

Between April 2018 to July 2018, in-depth, semi-structured interviews were conducted face to face in the participant's or our research team workplace, or over the telephone when participants were unavailable to meet in person. Both face to face and interviews conducted over the phone were of similar nature and length[23] (39-77 minutes; average 57 minutes). The interview guide was designed to evoke the participants' opinions and experiences in being involved in the guideline development process (see Supplementary file 1). The interviews were digitally recorded and professionally transcribed. Every participant in the study gave written or verbal consent and all were informed that they were free to withdraw from the study at any stage during the process.

This project was approved by The University of Sydney Human Research Ethics Committee Project number.: 2017/220

Analysis

NC wrote field notes immediately after each interview to capture thoughts on the interview, participants, and initial ideas. Transcripts were analysed as soon as they were received. We used initial line by line coding to inductively generate multiple ideas from our early interviews and data.[21] We identified a group of codes that captured the relationships between the various groups of participants and their views on the methodological challenges of the guideline development process.

Throughout the study the investigator wrote case based and conceptual memos.[21] These memos were used to explore the initial codes, our thinking on how these processes took place, how they were different between the various groups of guideline participants and the consequences of these processes. Comparing memos, we sought to find similarities and differences in these experiences and to identify questions for future interviews. To ensure the rigour of the study, discussions around the emerging concepts from the data were discussed between all authors in regular meetings.

RESULTS

We approached 36 potential participants via email and interviewed 20 (10 male and 10 female). Thirteen people did not respond to emails and three could not commit to a time. We had a lower response rate from individuals in evidence review groups. We interviewed sixteen working committee members, and four evidence review group members. By interview 16, similar narratives were shared. We conducted 4 more and determined saturation at interview 20.[21]

The experiences of the guideline development process were markedly different for the two key groups of participants involved in the process, the evidence review groups and the working

committees. These experiences suggest that public health guideline development in Australia is a divided process. The division is driven by three related factors: the divergent disciplinary background and expertise that each group brings to the process; the methodological limitations of the framework, inherited from clinical medicine, that is used to assess the evidence; and barriers to communication between content experts and evidence reviewers around respective roles and methodological limitations.

Divergent Disciplines

Participants had divergent disciplinary backgrounds and held varying, sometimes conflicting beliefs about what constituted 'good' evidence. Many experts on the working committee viewed their primary role as protecting the public's health through reducing possible harms to hazardous exposures or recommending interventions that would improve health outcomes. These individuals often viewed 'good' or 'important' evidence from the perspective of their own knowledge and expertise and not from the standards of methodological rigour used by the evidence review groups.

For example, one working committee member often felt that studies with statistically significant harms or benefits should be included in the body of evidence to form recommendations, even if they had been excluded by the evidence review groups on methodological grounds.

"There was a critical study which, you know, some of the older studies were omitted because they were methodologically not considered acceptable; but, they were strong results, so it was thought they couldn't be dismissed." (participant #18, working committee member)"

The evidence review groups, however, were contracted to evaluate the evidence using explicit methodological frameworks, such as systematic reviews and GRADE, that had very clear criteria for how the evidence was to be evaluated. The evidence review groups were aware of these disciplinary backgrounds and beliefs that the working committees brought to the guideline development and recognised the importance of having these experts involved in the process. However, they were also aware of the challenges that this presented because the evidence known and used by experts often didn't meet the necessary criteria for inclusion.

"……So you want experts, sure and of course a lot of these experts, they're very professional and they produce really good research and of course they're attached to that research… My experience has been a common thing when you first present the evidence review or the systematic reviews you've done, they get upset because it's not what they know and it's different - it's looked through a different lens." (participant #19, evidence review group)

These divergent roles and epistemological beliefs led to conflict and division between the groups. Many of the working committee members believed that in order to best protect the public's health, the evidence presented by the review groups should at times be challenged.

"so there were some controversies which came up in the course of our deliberation, and so there were interesting questions of whether methodological purity should be allowed to rule out evidence which might be relevant." (participant #18, working committee)

The evidence reviews groups however, saw this process as being hostile, aggressive and at times they felt victimised for doing their job. They felt that the evidence-review role they had been contracted to complete was not respected by some working committee members.

"we're trying to do the best we can, we're not content experts, we're methodology experts, you know, we're not deliberately trying to sabotage the process, we've got to work with people, but it always seems to come back to what feels like a very personal attack… it often is quite aggressive" (participant #10, evidence review group)

For at least some participants, the guideline development process was a divided one, with one dominant group offering content expertise and the other group attempting to provide methodological expertise.

"Methodological Limitations"

It was widely considered by all participants that the evidence reviews, and guideline development processes should be rigorous and transparent and that this would enhance the credibility of the guidelines.

"I think that's NHMRCs main goal of this whole process is that it would be as transparent and reproducible as possible that every decision is documented, and process driven as much as possible but there's a framework for each step, and I think that's working reasonably well." (participant #4, working committee)

Although working committee members were generally supportive of the processes they used, they acknowledged methodological limitations. For example, several working committee members recognised that the methods used in evaluating the evidence for their public health guideline topic were designed for clinical medicine and evaluation of randomised controlled trials.

"the problem is that NHMRC holds you to their standards of evidence, which are designed for other forms of evidence. They're designed mainly in the medical domain and drug domain. So, to apply them to something like (topic) is ridiculous" (participant #12, working committee)

They described how relevant and important evidence was consistently being downgraded, leading to a body of evidence used that appeared low quality.

"So, because it was this public health type evidence, what it meant was that none of the gradings were very high. And that we thought that – and I think many people have had the same views – that it was really not appropriate. And that the randomised clinical trial approach to evidence obviously a gold standard and so on, but that it was important not to throw out all the other things where – where randomised clinical trials were never going to be possible." (participant # 7, working committee chair)

When following GRADE guidance, low quality evidence leads to recommendations that are rated as "weak." Several working committee participants and chairs were concerned that weak recommendations would not be understood by policy makers in determining appropriate action to protect the public's health or would be misrepresented by industries that may wish to discredit their findings.

"But we had to, and we argued a lot about how to word this exactly, because if you say there's no evidence it could mean that there just isn't enough research to know or there is evidence that it doesn't cause that. So we had to be very careful with the wording…So I remember we argued, and argued and argued about the wording of that to get it to a situation that we were all happy with." (participant # 16, working committee)

However, the evidence reviews groups often felt that they, and not the methodological frameworks, were blamed for the way the evidence was evaluated.

"*I mean, that's essentially what we did but it's a very uncomfortable position to be in. I feel like they like the idea of it. But in practise when you give the results their sort of like, they're shocked, and I mean, the methods can only do so much and they're not flawless, there's limitations they just don't often expect what they get at the end*" (participant #1, evidence review group)

Despite such criticism, the evidence reviews group members who had intimate knowledge of the methodological process and were aware of how the evidence would be presented, understood why the working committee were frustrated, and were even empathetic to these issues as they knew what the limitations of the framework were.

"*I don't mean to be critical of the working group or the NHMRC and I think this was very challenging right from the beginning because it's public health intervention and a good example of using the*

GRADE process. It's very difficult because they're all observational studies…and there were quite a lot of issues." (participant #19, evidence review group)

Barriers to Communication

The evidence review group contracted by the NHMRC worked independently from the working committee for most of the process. Review group members were unable to share with the working committee insights and opinions on the best approach to identifying or evaluating the evidence. Further, the two groups were unable to help one another to understand each other's point of view. The transfer of ideas, knowledge and expertise was limited by the separation of the two groups.

"No, no, that's actually a challenge too, because they decided to outsource them to a body that has expertise in doing systematic reviews, but not topic specific expertise." (participant #5, working committee chair).

Not including content experts in the evidence review process provided the opportunity for working committees to be critical of the evaluations of the evidence review groups. For example, the content experts felt the that evidence review experts lacked the necessary knowledge on a guideline topic to identify all the relevant literature necessary to inform the guideline.

While conversely, the complexity of the methodology meant that unless working committee members had a methodological background, they found it difficult to understand and follow the evidence evaluations, when they were presented by the evidence review groups.

"So, they would, we'd have these two-day meetings and the people who run the tender to do the systematic review would kind of explain the methodology and, I'm not a methodologist so a lot of it went past me, about what you should include and what kind of grade recommendations could be supported, by what kind of evidence and so forth." (participant #16, working committee)

This highlights how by not working with the evidence review groups regularly from the outset and understanding the methods thoroughly, some working committee members felt limited in their ability to contribute to the guideline process due to their lack of methodological knowledge and training.

This separation between the groups was also seen by the evidence review groups as a major limitation in how the guideline process was conducted. The irregularity of the meetings at which the evidence reviews groups presented their findings to the working committees meant it became an ineffective way of communicating with the working committee on how the evidence was being evaluated with the methodology employed.

"Here it would include the GRADE process, and everyone goes yeah, okay, we understand that, that's good, but when it comes to the presentation it's usually so long after they've forgotten - even for us it's challenging." (participant#19, evidence review group)

As a result of this, when evidence review groups did advise the working committee on what evidence should or should not be included, they were criticised for their suggestions.

"I don't know. What we were told is don't tell us what to do, which shook us quite a bit because we were like well, we're just giving advice. Like, we don't mind if you don't take it but this is a wee bit challenging. So, then you don't know what your role is" (participant #19, evidence review group)

The evidence reviews groups felt that this criticism from the working committees grew from the separation of duties, and failure to have effective communication strategies in place. The evidence review groups members felt that many of the tensions that were experienced between groups of participants could have been limited if working committees were provided with clear information about the different roles of the two groups.

"But certainly for these two NHMRC ones it felt combative and I don't - and it's been an unpleasant process for us and we've felt that either the Chair should stand up and just – it's just little things, like just saying, you know, if someone's attacking the work, just stop in and say, look, these guys have done and spent a lot of time and a lot of work on this so let's just calm down and let them talk through the methodology of how they've done it". (participant #10, evidence review group)

Throughout the process evidence review groups felt a lack of support when delivering their work that was at times confronting and difficult for some working committee members to accept. Evidence review groups recognised an unequal and unfair power dynamic between the two groups. This led to the evidence review group members feeling that they were not valued or respected contributors to the guideline process.

"But it's my experience in working with these advisory committees, particularly with the NHMRC that it's the committee that makes the decision and the evaluation group is very much, you know, in a responsive position and pretty much on the back foot." (participant #10, evidence review group)

While the roles and responsibilities of these two groups in the guideline process may not be intended to be equal, it is highlighted here that the evidence review groups felt that they played a passive role. Being in a 'responsive position' demonstrates how this division is perceived by the evidence review groups as a process that is dominated by a working committee that do not fully respect or value their contribution to the guideline process.

DISCUSSION

The methods experts and content area experts interviewed for our study agree that rigorous methods should be used to develop public health guidelines that are considered valid and trustworthy. Our findings suggest that more attention needs to be given to the social processes influencing guideline development in order for the experts to achieve this shared goal. The division that is present in the public health guideline development in Australia is driven by the divergent disciplines the two key groups of participants bring to the process, the methodological limitations of the framework that is used to assess the body of evidence, and the inadequate integration and clarity of the respective roles of the evidence review and working committees. These divisions were emphasised by the lack of interaction between the groups. These themes are echoed in the literature exploring the experiences of different guideline working committees using similar methodological approaches.[18,19] Our study however, extends this prior research by not only understanding the experiences of the working committees, but also giving a voice to members of the

evidence reviews groups to understand the experience from their perspective, and the social processes involved in public health guideline development.

Strengths and limitations

This is the first comprehensive empirical investigation, to best of our knowledge, into the process of public health guideline development in Australia. This study included several guideline topics and participants from diverse backgrounds thus allowing us to analyse the experience of different groups of participants involved in the process.

This work reflects the opinions and experiences of the participants involved in the development of a sample of guidelines, and therefore it is possible that the experiences represented here may be different to those who did not participate. However, we sought to minimise this bias by including a diverse range of guideline topics. Three quarters of the respondents were working committee members, while only one quarter from the evidence review groups. While we attempted to contact more members of the evidence review groups, their response rate was much lower. The reason for this low response rate may be due to the evidence review groups being contracted by the NHMRC to conduct the evidence reviews and they therefore may feel conflicted in contributing as they are paid by the developer. Alternatively, they may have felt uncomfortable with sharing their thoughts and insights on the guidelines process as these experiences revealed in this study were often challenging. Future research should aim to understand these experiences further.

We feel however the concepts we represent here were expressed by both groups as we continued our sampling and analysis until we reached thematic saturation.[24]

Our results in relation to other studies

The prioritisation of disciplinary expertise that working committee members may have over the methodological expertise typical of the evidence review groups, is consistent with previous studies that have examined how evidence is conceptualised and used in forming recommendations in public health guidelines.[17] A previous qualitative study that explored the social processes of how evidence is understood and used by guideline advisory groups found that different group members prioritised the 'scientific' evidence, such as randomised controlled trials in informing their decision making, while others their professional experiences.[17] Clinical and practical experiences have also been shown to take precedence over the evidence in forming recommendations when using the GRADE process in the developing WHO guidelines that included public health topics.[18] Our study expands on these studies by showing that the content and evidence review experts have differences in valuing randomised, clinical trials vs. clinical expertise and in how they value observational design studies needed for public health guideline development.

The specific methodological challenges involved with evaluating the evidence used in public health guideline development described by the participants in this study have previously been identified in a study that explored the experiences of groups that have applied GRADE for developing guidelines or systematic reviews in the field of public health.[13] The difficulties identified included which studies to include or exclude, the inability to upgrade the quality of evidence from observational studies higher and concerns that policy makers may potentially misinterpret low quality evidence when determining what course of action to take. Further, the limited understanding of the GRADE process used to evaluate the evidence by the working committee discussed in our present study, was also demonstrated with previous investigations into the guideline development process by WHO guideline groups.[18,19]

The tensions felt by the evidence review groups with the working committee members in this present study has also been shown in a previous study that explored the experiences of methodologists working on WHO guidelines with discordant recommendations.[19] Although methodologists were also part of the working committee in our current study, the evidence review groups were responsible for conducting and presenting the results of the initial evaluation and grading of the evidence, which makes their experiences similar to this previous investigation. Therefore, the experiences of feeling tension with the working committee members, the need for their role to be clearly articulated and the need to receive greater support from the NHMRC throughout the process, are relevant and consistent with these previous findings.[19]

Implications for practice, policy and research

Bridging the Gap in the divided process.

While there are methodological challenges and considerations that go beyond the scope of this paper,[12] a number of steps could be put into place to help optimise the public health guideline development process in Australia and globally. Improvements in the social processes of guideline development could reduce the tensions and division that have been identified between the two key groups of participants involved in this study. Firstly, more pragmatic advice and training by the NHMRC for the working committee members unfamiliar with the frameworks used to assess the body of evidence is necessary not only at the commencement of the process but should be ongoing thereafter. Both the working committee and evidence review groups viewed understanding the methods as a significant challenge to the current process. Inadequate understanding of the methods restricts the level of input certain working committee members can have in the process and creates tensions between the groups.[13,18,19]

Secondly, the role of the evidence review groups needs to be clearly articulated from the start and reinforced throughout guideline development process.[19] The evidence review groups also need to feel appropriately supported in their roles when presenting the evidence reviews, particularly by the working group chairs. Therefore, the power imbalances created between the two groups must be minimised through strong facilitation, which would allow for the evidence review groups to feel their contribution is respected and valued and their opinions heard throughout the process. These power imbalances could also potentially be minimised by paying attention to differences in age, experience gender, or region between the evidence review groups and working committees.[25]

Finally, there is a need to work collaboratively from the outset and throughout the duration of the guideline process, to make it more collegial, effective and efficient. To enhance the transfer of ideas, knowledge and expertise, the physical separation that is currently present between the two groups should be reduced. While there may be benefits to keeping expert opinion influence away from the evidence review process, the infrequent meetings and lack of communication between the groups appears to be a significant factor in tensions that are made apparent when the evidence reviews groups present their findings to the working committees.[25,26] By integrating the groups, with subgroups to evaluate the evidence for particular questions, the tensions identified from this lack of contact and communication will be significantly reduced.

Through greater education of the working committee on the methodological process employed to evaluate evidence, improved communication on the role the evidence review groups play, along with better facilitation of the process so that the evidence review groups feel their contribution is respected and valued, an enhanced transfer of ideas, knowledge and expertise in the guideline development process will be possible.

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Supplementary file 1. Original interview questions

- Tell me a little about your role in the guideline development?
    - *Prompt:* Specific responsibilities? Level of responsibility? Level of input?

- Tell me about the guideline development process?
    - *Prompt:* How was evidence defined? How was the evidence summarised? How was the quality of the evidence assessed, if at all? How was evidence synthesised? What other factors contributed to rating the quality of the overall body of evidence? What factors (other than the evidence reviewed) contributed to the rating of recommendations?

- If any, what do you feel were the key challenges in the process?
    - *Prompt:* What was done in the absence of evidence? Were there challenges in assessing the risks of bias or quality of the evidence? Was a formal method applied for rating recommendations? E.g., GRADE. If so, what worked or did not work about this method?

- What else should I know about the process?
    - *Prompt:* Stakeholder input? Relationships between various experts? Lack of standardize criteria?

Chapter Four

Discussion; Solutions to Reduce Commercial and Methodological Bias in Nutrition Research and Public Health Guidelines

The conflicts of interest that arise when the food industry sponsor scientific research remain a threat to the credibility of nutrition research and dietary guidelines.[1] While this thesis has limitations, my research has shown that there is an association between studies funded by the food industry and the results that are used in the development of dietary guidelines. The presence of this funding bias therefore not only threatens the quality of the research and the guidelines that are developed from this evidence base, but also diminishes the public's trust in them.

Not only do private companies have a duty to maximize returns to their shareholders, those running these corporations are heavily incentivised to achieve such outcomes.[2] In order to account for and minimise this potential bias due to food industry sponsorship of research, I will propose a suite of recommendations for future practice and research. Further, to ensure that the dietary recommendations that are made in guidelines are also free of bias, I will make suggestions on how the current public health guideline development process can be improved.

Reducing Commercial influence in Nutrition Research

Disclosures and Transparency of Funding Sources and Author Conflicts of Interest

The first and most essential step in quantifying the influence of industry sponsorship on nutrition research is being able to identify who the funders of the research are and whether the authors of the study have a conflict of interest with the food industry. My work has clearly shown that disclosures in the bodies of evidence I examined are inadequate or missing. The implementation of policies on disclosure are the responsibility of the journals that publish nutrition research and it is they who should ensure that disclosure of funding source and author conflicts of interest is done in full for every manuscript. A recent analysis to estimate prevalence of conflict of interest disclosures in biomedical research in journals conforming to the International Committee of Medical Journal Editors (ICMJE) policies found that 22.9% of articles conformed to ICMJE disclosure standards and included a conflict of interest disclosure. The authors found that there was variability in the disclosure rates based on impact factor and altmetric score, with those with higher impact by these measures having higher levels of disclosure.[3] While disclosure rates have been improving in clinical journals in the last decade, a systematic analysis of conflicts of interest policies of nutrition journals is needed.

The Cochrane Collaboration and its policies on funding and author conflicts of interest are a standard that all nutrition journals could follow. In a 2018 analysis of Cochrane's funding and author conflict of interest policies compared to other major medical journals, it was found that Cochrane's policy regarding the funding of systematic review or primary research was stricter than the other 11 major biomedical journals in the sample. Cochrane reviews cannot be commissioned or funded by any commercial sponsor that may have a vested interest in the findings of the review. Other journals

including the BMJ (British Medical Journal) and PLoS Medicine do not publish research funded by the tobacco industry. Industry sponsored studies whereby the data analysis has been undertaken by statisticians employed by the funding company cannot be published in JAMA (The Journal of the American Medical Association) and JAMA Internal Medicine. However, Cochrane's policies are the strongest. [4]

Almost no journals have restrictions, other than a requirement for disclosure, on author conflicts of interest. Cochrane again has the strongest policy. All authors of Cochrane reviews must disclose all conflicts of interest according to ICMJE recommendations before the publication of a protocol, review or update. [4] In addition, Cochrane's policy that there must be a majority of authors that do not have a conflict of interest for any review and that the first author must have no conflicts, should be also be modelled.

However, lack of disclosures is seen consistently across multiple fields of research, with authors that fail to comply with disclosure policies, not just in nutrition.[5-8] Several groups including the ICMJE, The US Institute of Medicine (IOM) and the Collegium Ramazzini have all highlighted the need for greater transparency and accountability in relation to policies on author conflict of interest disclosures.[9-11] Therefore, other mechanisms may be required to identify undisclosed conflicts of interest, including searching transparency databases of industry payments to health professionals or previously published manuscripts of the authors. The implementation of procedures to identify undisclosed conflicts of interest could deter authors from failing to disclose by enforcing penalties for non-compliance to journal policies.

As has been demonstrated in Chapter One of this dissertation, the low disclosure rates in observational studies measuring the effects of wholegrain foods on cardiovascular disease outcomes that are used in the development of dietary guidelines, suggest that it may be necessary to search different data bases and additional resources, such as related research articles, in order to identify conflicts of interest in research used for guideline development.[12,13] The global enactment of pharmaceutical industry transparency databases has enabled the identification of undisclosed financial ties of health professionals and researchers to pharmaceutical companies. In the United Sates (US) the Open Payments database mandated by the US Sunshine Act requires all pharmaceutical companies to report payments to US based physicians.[14] Other countries are now implementing similar databases to Open Payments to manage critical data on the disclosure of investigators with a conflict of interest involved in clinical research.

As discussed in the introduction of this dissertation, even though some transparency databases for the food industry exist, they are voluntary and deficient.[15] The authors of the study that examined food industry-funded projects from food company websites and the publications that resulted from them found that of ten companies that were identified, only two could be analysed due to insufficient detail provided on the food company websites. Therefore, there is a need for transparency databases of payments to researchers from the food industry, and these should be mandated by law, similar to the Open Payments database.

Previous publications have also been used to identify undisclosed conflicts of interest in pharmaceutical research.[16] In a study to investigate the level of undisclosed financial ties between clinical practice guideline writers in Australia and pharmaceutical companies, the authors conducted a search of the writer's publications in the five years before the guideline publication date for any guideline writer with no disclosure or who declared no conflicts of interest. It was found that

approximately one in four guideline writers with no disclosed conflicts, could have had relevant undisclosed ties with the pharmaceutical industry. This highlights the need for enhanced strategies to ensure greater transparency on industry funding of researchers.

The solution for this fragmented disclosure landscape could be the creation of a central registry. By establishing a central database of author conflicts of interests in nutrition research, readers of articles, or researchers attempting to quantify this bias or at least take it into account when reading a manuscript, can identify if the publishing authors have undisclosed ties to the food industry.

Journals Policies & Penalties

If authors are found not to disclose conflicts of interest that they have with the food industry, penalties for noncompliance may be necessary.[12] Prohibiting authors from publishing future manuscripts across all journals that register to implement a disclosure policy would be a significant deterrent for authors that do not to comply, and one that should be implemented immediately.

Rethinking Current Risk of Bias Tools to Include Funding Bias

Risk of bias tools are used to evaluate studies that are included in systematic reviews or other evidence reviews used for guideline development. To account for the potential bias that may be present in studies with industry sponsorship and or authors with a conflict of interest with the food industry, current risk of bias tools need to be amended to include these items as individual domains. The Cochrane Cochrane Collaboration's tool for assessing risk of bias in randomised trials for example, assesses bias across seven domains ('Random sequence generation', 'Allocation concealment', 'Blinding of participants and personnel', 'Blinding of outcomes assessment', 'Incomplete outcome data', 'Selective reporting' and 'Other sources of bias'), with each domain

assessed as having a low, unclear or high risk of bias. However, funding or conflict of interest bias is not usually included as a domain.

While the inclusion of funding and conflict of interest bias into the Cochrane risk of bias tool for randomised studies has been previously debated,[17,18] a separate tool to assess these biases is now being developed by Cochrane. However, it is now widely agreed by other organisations that funding and conflict of interest bias should be accounted for as a domain within the tool.[12] Some organisations, such as the National Toxicology Program's, Office of Health Assessment and Translation (OHAT) have already begun including funding bias in their risk of bias evaluations of primary studies.[19] The Navigation Guide assesses both author conflicts of interest and funding sources as a risk of bias in human and animal studies.[20]

As I have described in the Introduction and demonstrated in Chapter One of this dissertation, biases that are related to the funding of a study by a commercial sponsor may be due to influences on how the study is designed, conducted, analysed published or reported. Importantly, it may result from one or all of these mechanisms.[21] In order to determine if a study has been designed deliberately to introduce a bias, or the outcomes selectively reported or analysed, internal industry documents would be required.[12] Therefore, it is unfeasible to suggest that these potential mechanisms can each be identified, measured and then incorporated quantitatively in the results of meta-analysis as argued by those against the inclusion of funding source into the Cochrane risk of bias tool.[18]

Further, in a Cochrane review that assessed whether drug and device studies sponsored by industry had more favourable outcomes or differed in their risk of bias, compared with studies having other sources of sponsorship, no difference was found in methodological risks of bias. For example,

industry sponsored studies did not differ from non-industry sponsored studies in random sequence generation, allocation concealment, or follow-up and selective outcome reporting.[22] For the domain of blinding, it was found that industry sponsored studies were more likely to have a low risk of bias. Blinding protects against performance bias so studies with adequate blinding should, in fact, yield less favourable, not more favourable results than was demonstrated in this study.[22,23] Similarly, in all three of our meta-analyses presented in Chapter One of this dissertation, we showed that industry sponsored studies were more likely to report more favourable outcomes, including effect estimates. This could not be explained by the study characteristics assessed with the Cochrane risk of bias tool, or the ROBINS-E tool we used. Thus, the bias towards favourable results in the industry sponsored studies is likely due to characteristics other than the study methods, such as publication bias or the framing of the question.

Nutrition studies included in systematic reviews used to develop dietary guidelines should be assessed using empirical methods to identify factors that are associated with study results, and funding source should be considered a separate risk of bias domain. Therefore, current risk of bias tools need be amended to include this as a separate domain.

Introduction of Nutrition Study Registries

While disclosure of author conflicts of interest remains inadequate and funding bias is not considered as a part of tools to assess risk of bias in primary nutrition studies used in the development of dietary guidelines, the need to minimise the potential for other mechanisms of bias, such as publication and reporting bias, is needed. One such measure is through the use of study registries. Publication bias, both in the selective reporting of results and, or failure to publish studies not in favor of the study sponsor, could be minimised with the introduction of study registries for

nutrition research, as has been established in pharmaceutical research.[24] As described in the Introduction of this dissertation, the selective reporting of results or studies in their entirety may bias the body of evidence as only favorable study results are published, which therefore skew the available data that is available to be used in the development of dietary guidelines.[25] When assessing the entire body of evidence to make recommendations on how to reduce the incidence of non-communicable diseases, such as cardiovascular disease, diabetes and cancer, the true effect of nutrition studies could be measured if these studies are pre-registered. Further, by understating this true effect, funding used on nutrition research could be used in answering important public health questions where gaps in knowledge may truly exist and not spent on research that serves industry's interest.

Therefore, the current requirement of prospective clinical trial registration by the ICMJE should be extended in nutrition research.[26] Although existing registries, such as the US National Institutes of Health registry, allow for registration of observational studies on any topic, this rarely occurs. As our study demonstrated (Appendix v. 'Associations between industry involvement and study characteristics at the time of trial registration in medical research'), valuable information on the different characteristics of nutrition studies funded by industry could be also be assessed if these registries were used for nutrition research.

Reducing Bias in Public Health Guidelines

In order to improve the standards of high quality and trustworthy guidelines, several organisations around the world such as the World Health Organization (WHO),[27] the National Institute for Health and Care Excellence (NICE),[28] and the United States Community Preventive Services Task Force [29]

have developed standards and criteria for the development of guidelines. Although these standards apply primarily to the development of clinical practice guidelines,[30] they could also be applied to public health guidelines.[31]

As demonstrated in Chapter Two of this dissertation, current practices among the organisations that are responsible for conducting hazard identification and / or risk of assessment of hazardous exposures demonstrate heterogenous methods that may reduce the level of confidence the public has in the conclusions of the assessments. Across the organisations, only three assessed the quality of the included studies and the body of evidence using explicit criteria, only one used systematic review methods and only half had a conflict of interest policy and process for managing them. A recent evaluation of national food-based dietary guidelines found similar variations and deficiencies in methods used to review evidence, rate evidence quality, and grade recommendations.[32] Therefore, the following recommendations are necessary to reduce bias in the public health guideline development process.

Rethinking How Bias in Observational Design Studies is Assessed

Although there are multiple influences on public health guidelines, including social, economic and political factors, if the primary evidence used in their development is biased, then the foundation for the evidence reviews, systematic or not, crumbles. Therefore, the first step in reducing bias in public health guidelines is to eliminate, or account for it in the evidence base used to develop them. Assessing risk of bias, including funding source and author conflicts of interest, in the primary studies included in reviews is a critical step in the process. In Chapter Two of this dissertation I highlighted that there was a need for empirically based tools and methods to be adopted for the evaluation of evidence amongst the organisations that conduct hazard identification and / or risk assessment of

environmental exposures as currently there is no agreed upon method. As similar study designs are also used in nutrition research to observe the association of dietary exposures and health outcomes, the need for the development of these tools is transferable across all public health topics and guidelines.

As already discussed in this Chapter, there is the need to include funding bias as a separate domain in any risk of bias tool used to assess studies in developing public health guidelines, such as primary nutrition studies or those related to exposure of environmental hazards. Assessing the risk of bias in observational studies, outside of funding bias is equally important. However, as we have established in our assessment of a tool currently being developed and used to assess the risk of bias in observational studies (ROBINS-E), it is essential to rethink the tool, and the further development of additional tools is required.[33]

Amongst the concerns we identified with ROBINS-E, other than the fact that it did not contain a domain to asses funding bias, was the use of an overall risk of bias rating for the study, which does not allow for the discrimination of studies with multiple risk of bias or just one risk of bias. The use of such overall ratings is not recommended. The Cochrane Collaboration, who is a pivotal locus as the world's leading authority on systematic review methods states:

"The current standard in evaluation of clinical research calls for reporting each component of the assessment tool separately and not calculating an overall numeric score. "[34]

Additionally, in its review of the US Environmental Protection Agencies (EPA) IRIS program the National Academy of Sciences (NAS) strongly recommended using a methodology that did not incorporate quantitative scoring of a study.[35]

Current risk of bias tools used to assess observational design studies may therefore play into industry's hands as important evidence assessed as having a high risk of bias in only one domain, results in an overall high risk of bias rating. Such evidence may therefore be excluded for inclusion to assess the harms of environmental or dietary exposures. Studies that are rated as high risk of bias using these existing tools may be sufficiently designed to ensure bias is eliminated, however because the study fails to report these details in the study being reviewed, it will be rated with a low score.[36] In addition, some important features of observational study designs are not assessed with existing tools, such as determining whether over adjusting for a large number of confounders (factors that are associated with the exposure and prognostic for the outcome but are not on the causal pathway), could bias the outcomes. Additionally, lack of consideration of differential biases in exposure measurement across study participant groups when measuring exposures such as air pollution, could attenuate the observed effects.

Some progress is being made in this area. In a recent review that was conducted of tools used for assessing observational studies of exposure, over 60 tools were assessed. Although the authors were unable to recommend one tool to use, they offered guidance on how to select one.[37] Therefore, while a tool based on empirical evidence of bias is yet to be developed, stakeholders involved in the public health topic that is under review should be involved in determining what the most suitable tools are to assess bias for that topic.[38]

Standardising the Use of Systematic Review Methods

As identified in Chapter Two of this dissertation, only one organisation that conducts risk assessment of environmental exposures that was included in our study stated that they use systematic reviews

to evaluate the evidence.[39] This is in sharp contrast to the increasing use of systematic reviews in clinical practice guidelines.[27,40] Systematic reviews increase the transparency and objectivity of public health guideline development as they allow end users to identify how the questions are formulated, the searches of evidence conducted and how the evidence used in the final recommendation is evaluated. These steps therefore reduce and limit bias in each part of the guideline development process.[40,41]

Systematic review methods in the assessment of hazardous exposures and in the development of dietary guidelines, need to be a standardised across all public health guidelines.[20,32,42-45] One such attempt to coordinate the use of systematic reviews in nutrition and in the development of dietary guidelines is being led by Cochrane Nutrition.[46] This effort is aimed at strengthening both the methods of systematic reviews and in the primary nutrition studies by enhancing current methodology and promoting activities to enhance the quality and reporting of primary nutrition research. In the area of environmental health, groups including the OHAT and The Program on Reproductive Health and the Environment in its development of the Navigation Guide, have made similar advances in the use and uptake of systematic review methods.[19,20] Both groups have led international calls to reform the current methods and processes that are used in assessing the harms caused by environmental exposures. Further, following the recommendations that were made by the NAS on the US EPA IRIS program, the US Congress officially mandated that the EPA must now use systematic reviews in all environmental risk assessments. [31,47]

In addition, standard definitions and criteria for what constitutes a systematic review need to be agreed upon by the organisations using them. The term "systematic review" is defined in different ways and, sometimes, crucial steps in the process, such as risk of bias assessment of individual

studies, are missing. Furthermore, a lack of standardisation of the definition has led industry groups to claim they are conducting systematic reviews when they are not.[48]

Grading Evidence and Forming Recommendations.

The recent NAS report on improving the methods to be used in US Dietary Guidelines did not make any recommendations on how to translate the evaluations of evidence into recommendations.[49] Yet, the translation of evidence into recommendations is a vital step to the integrity of the guideline process. As described in Chapter Two of this dissertation, while a degree of subjectivity is inevitable in this final decision making process, the use of objective processes versus the expert judgment and opinion of those guideline advisory committee members alone, may be instrumental in how the evidence is interpreted and recommendations formed.[41] Therefore, if the role of expert opinions vs. evidence are undocumented, it is difficult for policy makers and end users to identify the most valid evaluation of the evidence, or what other considerations influenced the final recommendations that were made.[41]

There are many options available for guideline developers to move from the evaluations of the evidence to the recommendations, including quantitative methods, such as Bayesian, and structured consensus approaches such as GRADE (Grading of Recommendations Assessment, Development and Evaluation).[50] While the GRADE methods have not been fully developed to account for all important considerations related to public health,[51] there use has been recommended by the US EPA IRIS program and have also begun being adopted by some dietary guideline developers.[32]

However, one central concern over the use of GRADE in forming recommendations in public health guidelines is that the GRADE approach normally rates the primary study designs used in public

health guidelines, such as observational design studies, as lower quality evidence. This means that the recommendations made in public health guidelines may be rated as weak because they are based on low quality evidence. Weak recommendations are less likely to be implemented than strong recommendations, thus potentially hindering the implementation of recommendations that promote public health. Some groups responsible for conducting assessment of hazardous environmental exposures such as the OHAT have begun adapting GRADE to account for this concern and rating these types of evidence as high quality.[19] However, as discussed in Chapter Three of this dissertation, these methodological limitations are difficult to overcome without clear guidance and can lead to division in the guideline development process.

Regardless of the approach taken, more transparent and standardised processes for summarising the evidence are required. Further, organisations across the world that are wanting to move these methods forward to protect the public's health and achieve better health outcomes, should collaborate and harmonise these methods. By collaborating, expertise, knowledge and skills may be transferred, and importantly the use of transparent and consistent methods will help the public feel confident in the recommendations made in public health guidelines.

Improving Conflict of Interest Policies in Guideline Development

As I established in Chapter Two of this dissertation, the disclosure and management of conflicts of interest of those responsible for the development of hazard identification and / or risk assessments of environmental exposures is inadequate.[39] Several organisations in other areas of clinical health, including the IOM, have extensive policies of disclosing and managing experts with conflicts of interest whose participation is considered necessary in the development of a guideline.[52,53] In the area of public health, including nutrition, there is a need for significant improvements in conflicts of

interest policies and their implementation to ensure the quality and credibility of these guidelines. In the report published by the NAS critiquing the process used in developing the US Dietary Guidelines, concerns were raised on how the guideline committees were formed.[49] The reports stated that to build trust and enhance the integrity of the selection process that:

"Actual and or perceived conflicts of interest—both financial and nonfinancial—should be eliminated to the extent possible or their effects be minimized." (Chapter 3, pp 66)[49]

They recommended that the U.S. Department of Agriculture (USDA) and the U.S. Department of Health and Human Services (HHS), develop an explicit policy to addresses these conflicts that would be shared with the public. In this same report, the NAS highlighted five examples of organisations 'with unique conflict of interest procedures' that the NAS identified as having transparent processes. One of these organisations was the Australian Government National Health and Medical Research Council (NHMRC) that is commissioned under Australian law to develop evidence-based guidelines 'in population health, ethics, and clinical practice', and carry this process out by appointing expert task-based committees. The NHMRC's vetting process of potential conflicts of interest is extensive and includes: the identification and disclosure of any potential conflicts that include financial, intellectual, and organisational; determining whether a conflict of interest exists with the committee member; and finally implementing the necessary procedures to manage any conflicts of interest. Further, the committee chair must be free of any conflicts of interest.[54] Such procedures should be considered as a model to follow across all public health guidelines that are developed.

Improving Knowledge and Skill Transfer Between Guidelines Developers

As suggested in Chapter Three of this dissertation, evidence may not be the greatest influence in the formation of guidelines and their recommendations.[55] In fact, I found that the groups responsible for

the evidence reviews and the working committees that formulate the recommendations may be at odds with each other. Cohesion between these two groups is essential for ensuring the development of credible, rigorous guidelines.

To allow for the transfer of ideas, knowledge and expertise that the various participants in the guideline development process possess, these groups need to work closely together. As has been suggested by my dissertation advisor, Professor Lisa Bero, systematic reviews in the area of nutrition are highly complex and excluding systematic reviewers from the development of dietary guidelines could significantly impact the working group's understanding of some of these methodological complexities. [31] For example, the guideline development group needs to understand study heterogeneity and other important characteristics that may influence the data and therefore the usefulness of systematic reviews for developing dietary guidelines.[31] By having systematic review groups work alongside working committees and not in isolation, these committees could also better understand risk of bias assessments and meta-analysis.[31] Further, by not working together through a highly complex body of evidence, with highly complex methodological procedures that require extensive training and skills, there is the potential for the guideline process to be driven by a few members with experience in the methodology or content expertise.

Conclusion

While the influence of corporate funding on nutrition research may always be present, the steps that have been recommended in the concluding Chapter of this dissertation will allow those committees responsible for the development of dietary guidelines, policy makers and consumers, to identify and account for the bias associated with corporate funding of the primary nutrition studies. Through greater transparency of funding practices and author conflicts of interest, the development of

nutrition registries to ensure all research is published in its entirety and improvements in the risk of bias tools used to evaluate the body of evidence, industry influence on the outcomes of nutrition studies relevant to dietary guidelines can be quantified and considered.

Finally, to then ensure that the recommendations that are made from the evidence base are free of bias, the steps described in this Chapter to enhance public health guideline development are just as critical. Although these guidelines appear more complex to develop than those for clinical practice, the use of standardised, transparent methodological processes and procedures, including explicit conflict of interest policies for guideline committee members, is an essential step in allowing the public and policy makers to have greater confidence in the recommendations that are made from them. Developing processes to increase collaboration between the systematic review teams and guideline development groups is also necessary. The use of these methodological processes and procedures will lead to increased transparency, comparability and validity of the guidelines, but most importantly, they will ensure that the recommendations made from them will protect the public's health.

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Appendix

Additional Related Publications

The additional manuscripts contained in the Appendix are related to the worked presented in this thesis. The manuscripts have been included in the Appendix as the PhD candidate is not the lead author but has contributed to these studies as a co-author.

Appendix i: Fabbri A, **Chartres N**, Scrinis G, Bero LA. Study sponsorship and the nutrition research agenda: analysis of randomized controlled trials included in systematic reviews of nutrition interventions to address obesity. *Public health nutrition.* 2017;20(7):1306-1313.

Appendix ii: Fabbri A, **Chartres N**, Bero LA. Study sponsorship and the nutrition research agenda: analysis of cohort studies examining the association between nutrition and obesity. *Public health nutrition.* 2017;20(17):3193-3199.

Appendix iii: de Rezende LFM, Rey-Lopez JP, de Sa TH, **Chartres N**, Fabbri A, Powell L, Stamatakis E, Bero L. Reporting bias in the literature on the associations of health-related behaviors and statins with cardiovascular disease and all-cause mortality. *PLoS biology.* 2018;16(6):e2005761.

Appendix iv: Bero L, **Chartres N**, Diong J, et al. The risk of bias in observational studies of exposures (ROBINS-E) tool: concerns arising from application to observational studies of exposures. *Syst Rev.* 2018;7(1):242.

Appendix v: Seidler LA, Hunter K, **Chartres**, N, Askie L. Associations between industry involvement and study characteristics at the time of trial registration in medical research. (under review)

APPENDIX i

Study Sponsorship and the Nutrition Research Agenda:

Analysis of randomized controlled trials included in systematic reviews of nutrition interventions to address obesity

(Public Health Nutrition 2016, doi:10.1017/S1368980016003128)

Alice Fabbri[1,2], Nicholas Chartres[2], Gyorgy Scrinis[3], Lisa A Bero[2]

[1]Centre for Research in Medical Pharmacology, University of Insubria, Varese, Italy

[2]Charles Perkins Centre and Faculty of Pharmacy, The University of Sydney, Australia

[3]Faculty of Veterinary and Agricultural Sciences, The University of Melbourne, Australia

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Conflict of interest: LAB is Co-Chair of the Cochrane Steering Group, for which The University of Sydney receives payment.

Authorship: AF, GS, LAB conceived the study and designed the data collection tool. AF, NG collected the data. AF, NG, LAB analysed the data. AF wrote the first draft of the paper. NG, GS, LAB contributed to the writing of the paper and approved the final version.

Abstract

Objective: To categorize the research topics covered by a sample of randomized controlled trials (RCT) included in systematic reviews of nutrition interventions to address obesity; to describe their funding sources; and to explore the association between funding sources and nutrition research topics.

Design: Cross-sectional study.

Subjects: RCT included in Cochrane Reviews of nutrition interventions to address obesity and/or overweight.

Results: Two hundred and thirteen RCT from seventeen Cochrane Reviews were included. Funding source and authors' conflicts of interest were disclosed in 82·6 and 29·6 % of the studies, respectively. RCT were more likely to test an intervention to manipulate nutrients in the context of reduced energy intake (44·2 % of studies) than food-level (11·3 %) and dietary pattern-level (0·9 %) interventions. Most of the food industry-sponsored studies focused on interventions involving manipulations of specific nutrients (66·7 %). Only 33·1 % of the industry-funded studies addressed dietary behaviours compared with 66·9 % of the non-industry-funded ones (P=0·002). The level of food processing was poorly considered across all funding sources.

Conclusions: The predominance of RCT examining nutrient-specific questions could limit the public health relevance of rigorous evidence available for systematic reviews and dietary guidelines.

INTRODUCTION

Public health nutrition policies are essential for controlling the epidemics of obesity, cardiovascular diseases and type 2 diabetes.[1,2] Many political, social and economic factors contribute to dietary guideline and nutrition policy development, but a fundamental principle is that they should be informed by relevant, rigorous evidence.[3] Systematic reviews have been extensively used as the evidence base for the development of both clinical and public health guidelines.[4] In recent years the use of systematic reviews has also become increasingly common to address nutrition-related questions. The most recent national dietary guidelines in the United States and Australia were based on systematic reviews and Food Standards Australia New Zealand currently requires systematic reviews to support high level health claims on food labels.[5-7] The Cochrane Collaboration has launched the Cochrane Nutrition Field to increase the number, quality and relevance of Cochrane Nutrition Reviews.[8]

A major limitation of the growing use of systematic reviews for the development of guidelines, policies and regulations is that their scope is limited by the topics of the original research studies available to be included in the reviews. In addition, systematic reviews are often limited to randomized controlled trials. This could lead to systematic reviews that are not relevant or representative of the target population for the guidelines.[9]

The characteristics of the research agenda (namely the questions being studied) are particularly important in nutrition because the questions asked, such as nutrient-specific questions, could produce evidence that is disproportionately focused on certain policy solutions, such as food fortification.[10] This research could then distract from considering other possible public health solutions, such as taxes or regulating food advertising or processed food commodities. Studies to

address complex policy questions relevant to public health nutrition also present methodological challenges that may contribute to them being less studied.[11]

Several actors (industry, government, and non-profit stakeholders) have the potential to affect the policy making process by influencing the nutrition research agenda.[12,13] Data from other sectors (e.g. tobacco, pharmaceuticals) has previously demonstrated biases in the design, conduct and publication of research that are related to funding sources and investigators' conflicts of interest.[14-16] Corporate interests can manipulate the research agenda by funding research that supports their position and suppressing research that does not.[17] For example, the tobacco industry undermined the research agenda on the health effects of second hand smoke by funding studies suggesting that other components of indoor air were more harmful than tobacco.[18] Echoing tactics used by the tobacco industry, the sugar industry has influenced the dental research agenda *"as part of a strategy to deflect attention away from sugar restriction as a means to control caries"*.[19]

Despite some case studies documenting discrepancies in the design and conclusions of research sponsored by the food industry compared to other funders,[20-23] a systematic analysis examining whether funding sources influence the nutrition research agenda has not been done. Analysing the relationship between funders and the nutrition research agenda could assist both researchers and policymakers in understanding whether an entire area of research has been funded only by stakeholders with conflicts of interest and in identifying new or neglected areas which may require further investigation.

The objectives of this study are:

1. Categorize the research topics covered by a sample of randomized controlled trials included in systematic reviews of nutrition interventions to address obesity;
2. Describe their funding sources;

3. Explore the association between funding sources and nutrition research topics.

METHODS

Study Selection

We analysed randomized controlled trials that were included in Cochrane Reviews of nutrition interventions aimed at reducing obesity. Cochrane Reviews cover a broad range of clinical and public health interventions and have been used to support the World Health Organization Nutrition Guidelines Program.[8] We searched the *Cochrane Database of Systematic Reviews* on July 24th 2015 using the following broad search strategy: *obesity AND (nutrition* OR diet*)* to identify reviews that included nutrition interventions to prevent or reduce obesity. We focused on obesity because this is a complex condition that could be addressed by a variety of interventions ranging from patient specific to system-wide interventions.[24] Two investigators screened the retrieved records for obvious exclusions. We excluded reviews that did not include studies of nutrition interventions or did not have measures of obesity or overweight as primary or secondary outcomes.(See Supplementary File 1 for the list of included and excluded Cochrane Reviews) Since the emphasis of Cochrane Reviews has been on the identification and assessment of randomized controlled trials (RCTs), we then included all the RCTs that were included in the selected reviews if they investigated nutrition interventions or a combination of nutrition and non-nutrition interventions (e.g. drug, physical activity). For this review, we defined nutrition interventions as all dietary interventions that modify energy, dietary patterns, whole food and/or nutrient intake. We included studies where the primary or secondary outcomes were BMI score or other measures of overweight and obesity (e.g. body composition, waist to hip ratio).

Data extraction

The full text was retrieved for each included RCT. If the same study appeared in more than one Cochrane Review, we included it only once. The following data were collected from each RCT publication:

- study characteristics: target group, location, year of publication.
- disclosed funding source(s). These were classified as: food industry, pharmaceutical industry, other for profit entities, governmental agencies, not for profit, mixed funding sources, unknown (when the funding source was disclosed in the article, but information about the sponsor could not be retrieved from the Internet), or no funding disclosed;
- disclosure of investigators' conflicts of interest;
- research topics classified according to the categories in Table 1.

The taxonomy we used to code research topics was inspired by a framework for food classification[25] that was informed by iterative coding of a sample of nutrition intervention studies and by input from a multidisciplinary group of public health researchers, physicians, dieticians, nutritionists and social scientists. We coded research topics by 1) the level of dietary composition, 2) level of food processing and 3) dietary behaviours. Each category was coded as yes or no. The coding categories are described in more detail below:

1. Level of dietary composition

This categorization is based on the differentiation between the three levels of dietary composition discussed in the nutrition literature: the nutrient level, the food level and the dietary pattern level.[25,26] Since our sample included nutrition interventions to address obesity, we expected most of the studies to have an energy component, often without the study specifying the restriction of one nutrient over another to achieve caloric restriction, therefore the additional category of energy was

added to the initial taxonomy. Specifically, we assessed whether the intervention described in the article focused on:

- energy level: focus on caloric restriction.
- nutrient level: focus on changing intake of specific nutrients such as fat, protein, carbohydrates, etc;
- food level: focus on changing consumption of a single food or food product, food groups or food combinations such as vegetables, fruit, grain foods, meats, fish, eggs, or processed foods such as sugar-sweetened beverages, high-energy snacks, fast foods etc;
- dietary pattern level: focus on the overall dietary pattern or cuisine, for example the Mediterranean diet;
- not applicable: when there was not enough information in the article or the intervention did not fit in any of the above categories.

Our *a priori* hypothesis was that while a focus on the nutrient level is a common feature of nutrition research[27], the food industry has supported nutrient level studies as a means of generating evidence to support its nutritional claims on food products.[25]

2. Level of food processing

We determined whether the nutrition intervention studied in each RCT mentioned food processing - the type, level and intensity of technological intervention used in the production of food.[25] A study was rated as 'yes' if it mentioned highly processed foods, defined as foods that are constructed primarily out of processed- reconstituted and refined- extracted materials, either specifically (e.g., sugar sweetened beverages), descriptively (e.g., foods high in calories with low nutrient density), or as part of a complex intervention (e.g., mentioning limiting consumption of high-calorie snacks and fast foods on one part of a nine-part weight reduction intervention). The initial version of our taxonomy included the multiple levels of processing: whole foods, refined-processed foods, and processed-reconstituted foods. However, when we pilot tested the taxonomy, we found that some

studies defined the level of processing very poorly and many of the complex interventions included all three levels of food processing. Therefore, we modified the initial taxonomy to code for the mention of highly processed foods or not.

Our *a priori* hypothesis was that there is currently a lack of studies focusing on the evaluation of nutrients, food and dietary patterns in terms of the levels of processing and that the food industry is not funding this kind of research.[25,28]

3. Dietary behaviours

A study was coded as 'yes' for dietary behaviours if the nutrition intervention addressed dietary behaviours (e.g. portions size, menu planning and cooking style, timing of meals, eating while watching television, meal skipping, self-control/self-monitoring of food intake). Our *a priori* hypothesis was that the food industry is less likely to fund studies aimed at improving dietary behaviours.

Double coding

For the analysis of the nutrition research topics, 30% of the publications were randomly selected to be coded independently by two reviewers and any disagreement was resolved by consensus.

On average the percentage of agreement between the two coders was 91.4%.

Analysis

Categorical variables were described using frequency tables. Cross tabulations were performed for evaluating possible associations between the funding sources and the research topics using the chi-square test. All analyses were performed using SPSS Version 22.

RESULTS

Study selection

The electronic database search yielded 44 Cochrane Reviews. (Figure 1) Of these, 27 were excluded because they did not match our inclusion criteria. (Supplementary File 1)

Of the 272 RCTs, 59 were excluded because they did not match the inclusion criteria. (Figure 1) Five studies appeared in more than one Cochrane Review, and they were each included once. The 213 included RCTs evaluated a broad range of nutrition interventions targeting children/adolescents (n=25; 11.7%), adults (n=114; 53.5%) or both (n=74; 34.7%). The range of publication dates was 1978-2013 and 31.5% of the included studies were published before 2000. The majority of the RCTs were conducted in America; United States based studies represented 55.4% (n=118) of the total sample.(Table 1)

Funding disclosure

Of the 213 included RCTs, 82.6% (n=176) disclosed their funding source. Of these, 175 RCTs disclosed the presence of one or multiple sponsors while in one study the investigators stated they received no funding for their work. Of the 175 RCTs that disclosed having a sponsor, 37.1% (n=65) were funded by governmental or intergovernmental agencies, while food industry sponsorship (alone or with other sponsors) was disclosed in 13.7% (n=24) of the studies.(Table 2). The disclosure rate increased over time: from 74.2% for the studies published before the year 2000, to 85.3% for the ones published between 2000 and 2009, to 93.3% for the ones published after 2009. We chose these cut-offs because of the increasing attention that has been given to the need for transparency in recent years and the consequent adoption of disclosure policies by most scientific journals.[29,30]

Investigators' conflicts of interest disclosure

Of the 213 included RCTs, 70.4% (n=150) did not contain a conflicts of interest disclosure. In 22 studies (10.3%) the authors disclosed financial conflicts of interest, in 1 study (0.5%) the authors disclosed non-financial conflicts of interest, and in 40 (18.8%) the authors stated they had no financial conflicts of interest. The disclosure rate increased over time. Conflicts of interest disclosure was completely absent in the papers published before the year 2000, the disclosure rate was 39.0% in the papers published between 2000 and 2009, and 66.7% in the papers published after 2009.

Research topics

Table 3 shows the nutrition research topics studied in the included RCTs. Most of the RCTs studied interventions that involved a combination of energy, nutrient and food level approaches. As anticipated for interventions to reduce obesity, most trials aimed to restrict energy intake and vary the dietary composition, while 16 (7.5%) only varied energy intake. Ninety-four trials (44.2%) tested interventions focused on specific nutrients, 58 (27.2%) analysed a combination of nutrients and foods, while only 24 (11.3%) analysed whole foods. Only two trials included an analysis of dietary patterns (e.g. Mediterranean diet). Highly processed foods were considered in less than one third of the tested interventions and slightly more than half the interventions considered dietary behaviours such as portions size or timing of meals.

Research topics by funding sources

Table 4 shows the results of the analysis of nutrition research topics by funding sources. To test our hypotheses that research with a focus on nutrients has been supported by the food industry, while research including an analysis of food processing has not been supported by the food industry, we compared the research topics of food industry to non-food industry sponsored studies. The food industry sponsored category includes studies sponsored solely by the food industry or with mixed food industry and other funding (n = 24). The non-food industry category includes studies funded by

governmental agencies, non-profit sector and mixed funding sources without the presence of food industry (n = 127). We did not include in this analysis the trials funded by pharmaceutical companies and the ones with undisclosed funding sources, therefore the total number of included RCTs is 151.

As shown in Table 4, most of the food industry sponsored studies focused on interventions involving manipulations of specific nutrients (66.7%). The non-food industry funded trials addressed different levels of dietary composition, including whole foods and a combination of foods and nutrients. The dietary pattern level was poorly considered across all funding sources. There was no statistically significant association between the research sponsorship and the different levels of dietary composition addressed in the included RCTs (chi-square test: p=0.083). With regard to the food processing, only 25% (n=6) of industry funded studies and 31.5% (n=40) of the non-industry funded interventions mentioned the issue of highly processed foods. No statistically significant differences were observed between the two categories of funding sources (chi-square test: p=0.526). Finally, non-industry funded trials were more likely to address dietary behaviours compared to food industry sponsored studies (chi-square test: p=0.002).

DISCUSSION

The nutrition research agenda

Our findings show a gap in the research topics covered by randomized controlled trials of nutrition interventions studies. The majority of the included RCTs involved some manipulation of nutrients in a context of a reduced caloric intake, while there was less study of food level and dietary pattern level interventions. A reductive focus on nutrients has been a feature of nutrition research in the past decades.[26,27,31] A fundamental characteristic of nutritional reductionism is that *"the role of nutrients has often been interpreted outside the context of the foods, dietary patterns, and broader social contexts in which they are embedded".*[25] While recognizing the importance of understanding

the biological effect of nutrients, a nutrient approach is likely to offer only a decontextualized, context-free interpretation of the complex relationship between diet and health outcomes. In this regard, some researchers have already called for an alternative research approach, namely a "top-down" approach that works *"from complex to simple,"*[27] starting from the dietary pattern level and working backward to the nutrient level.[31] In addition, nutritional ecology studies suggest that powerful insights into the causes of obesity can be gained by studying the *interactive* rather than independent effects of nutrients.[32] Since people eat foods and not isolated nutrients, dietary guidelines and policies built upon research on foods and dietary patterns might more effectively inform people's behaviours and food choices.[26,33]

Our findings also suggest that the research agenda may be influenced by industry interests. We found that most of the food industry sponsored studies focused on interventions involving manipulations of specific nutrients. Some researchers have argued that in response to concerns about how diet contributes to the obesity epidemic, the food manufacturing industry has responded by emphasising the benefits of particular nutrients in their foods.[25] Thus, the food industry may have an incentive to fund research showing that certain types of nutrients are beneficial to health. A focus on nutrients – rather than on dietary patterns or interactions among nutrients within foods and within the body - may produce evidence that will allow the food industry to market highly processed foods using nutrient content claims (e.g. functional foods). For example, a systematic review of highly processed breakfast cereals commissioned by the Australian Breakfast Cereal Manufacturers Forum suggests that cereal consumption is associated with lower rates of diabetes and cardiovascular disease[34] and cereals are often advertised as having beneficial health outcomes.[25]

Despite the evidence that processed foods are a significant driver in the global rise of overweight, obesity and associated diseases[13,35], our findings showed that little research describes the level of

processing of the food being studied. This lack of data cannot provide the evidence needed to inform guidelines and policies that could limit consumption of processed foods. Food classifications have often grouped foods according to their nutrient profile or unprocessed food groups (e.g. fruits, vegetables), whereas the nature and extent of food processing should also be included as part of the description of the intervention.[36] This lack of categorization by level of food processing has led to examples of processed foods such as ketchup being classified as a school-lunch vegetable in the United States.[37]

Our findings identified that food industry sponsored studies were significantly less likely to address dietary behaviours as part of an intervention compared to non-food industry sponsored studies. While nutrition specific interventions are necessary to measure the effect of specific nutrients, there is evidence to suggest that they fail to address the underlying complexities of what is required to achieve and maintain weight loss in obese populations.[38,39] In a food system where dietary intake is no longer influenced primarily by food availability, a research agenda that continues to mostly examine nutrients and food in isolation and not in the context of dietary and other behaviours will likely fail to ease the growing burden of obesity.

Sponsor's interests are not the only drivers of a nutrient focus. Studies to address complex nutrition policy problems present enduring challenges that may contribute to them receiving less attention and funding.[11] Moreover, the current process for evidence synthesis and translation itself tends to favour a nutrient-oriented approach. A recent study has shown that in the field of undernutrition there are significantly more systematic reviews, guidelines and policy statements related to nutrition-specific interventions (e.g. fortification and supplementation) compared to nutrition-sensitive interventions that could instead address the underlying causes of the problem.[10]

Finally, our results show a gap in the research topics covered by RCTs of nutrition interventions to decrease obesity, but diet-disease relationships are often evaluated using non-randomised studies and many dietary guidelines are currently supported by evidence from observational studies.[6] Cochrane is currently exploring evidence synthesis methods that are needed to address complex nutrition interventions which are often studied using observational research.[8] Therefore, further research is needed to evaluate whether the gaps in the topics covered by RCTs included in systematic reviews apply also to non-randomised studies.

Reporting of funding source and investigators' conflicts of interest

We found that about 20% of the studies did not report funding sources, although disclosure rates increased over time. The low proportion of food industry sponsored studies in our sample could be due to a lack of reporting of industry sponsorship. This phenomenon has already been reported in other fields; for example, the tobacco industry funded institutes and organisations that hid the true extent of industry involvement in their projects.[40]

We also found a low rate of reporting of investigators' conflicts of interest. Although a recent study found that all core clinical journals require disclosure of author financial conflicts of interest[41], these disclosure policies are still not enforced across all journals. The failure to comply with the current conflicts of interest disclosure requirements has been reported in several studies [42-44], therefore it is likely that the disclosures we relied on did not give an accurate assessment of authors' conflicts of interest.

A recent call for disclosure of funding sources and authors' conflicts of interest in all abstracts listed in PubMed could improve reporting across all journals.[45] If funding sources and investigator conflicts of interest are not reported or only partially reported, differences in the design, conduct and publication of industry compared to non-industry sponsored studies cannot be empirically investigated. Readers will not be able to determine whether an area of research has been funded

only by certain stakeholders and might be left unsure about how to interpret the likelihood of bias related to funding source.[46] This reporting gap may also have important research and policy implications by making it difficult to estimate the impact of funding sources on the studies included in systematic reviews and, consequently, public health guidelines and regulations. A recent revision of the methodological standards for Cochrane Reviews requires that funding sources for included studies be listed in the included studies table.[47] However, most Cochrane Reviews do not currently contain these disclosures.[46]

Limitations

Our study has several limitations. First, we searched the *Cochrane Database of Systematic Reviews* using the following terms: obesity AND (nutrition* OR diet*). It is possible that this search strategy might have missed potentially eligible reviews. However, the search strategy is very broad and the large number of reviews identified that did not meet our inclusion criteria suggests that our initial search was sensitive rather than specific.

Another limitation is that we analysed only RCTs included in Cochrane Reviews. However, Cochrane Reviews cover a broad range of interventions targeted at adults, children or both, involve a comprehensive search for evidence, and their topics are often driven by the availability of original research. Thus, the studies included in the Cochrane Reviews are likely a good representation of the type of RCTs that have been conducted on nutrition interventions to reduce obesity. In addition, we focused on obesity because it is a complex health condition that could be addressed by a wide variety of nutrition interventions. Our findings may be different if we focused on other harm outcomes, such as cardiovascular disease, or the beneficial effects of foods.

Another challenge of this study was the development of a taxonomy able to capture the complexity of research topics examined in nutrition intervention studies. Moreover, we relied only on the

intervention description provided in the publications. Sometimes the quality of the description was poor or not detailed so we might have missed important aspects of the intervention. Accurate and complete descriptions of complex interventions are crucial to ensuring not only the evaluation of interventions but also their replicability. [48] The low proportion of food industry sponsored studies compared to non-food industry sponsored studies may explain why we did not observe statistically significant differences between funding sources. Food industry sponsorship may have been underreported.

CONCLUSION

Our findings show a gap in the research topics covered by RCTs of nutrition interventions to address obesity and suggest that the research agenda may be influenced by industry interests. The predominance of nutrient-specific topics in the nutrition research agenda could limit the public health relevance of rigorous evidence available for systematic reviews and dietary guidelines. More independent funding of nutrition research could address some of the imbalance in the research agenda. Effective nutrition policies need to be informed by evidence on a wider variety of interventions.

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Figure 1. Flow chart of study selection

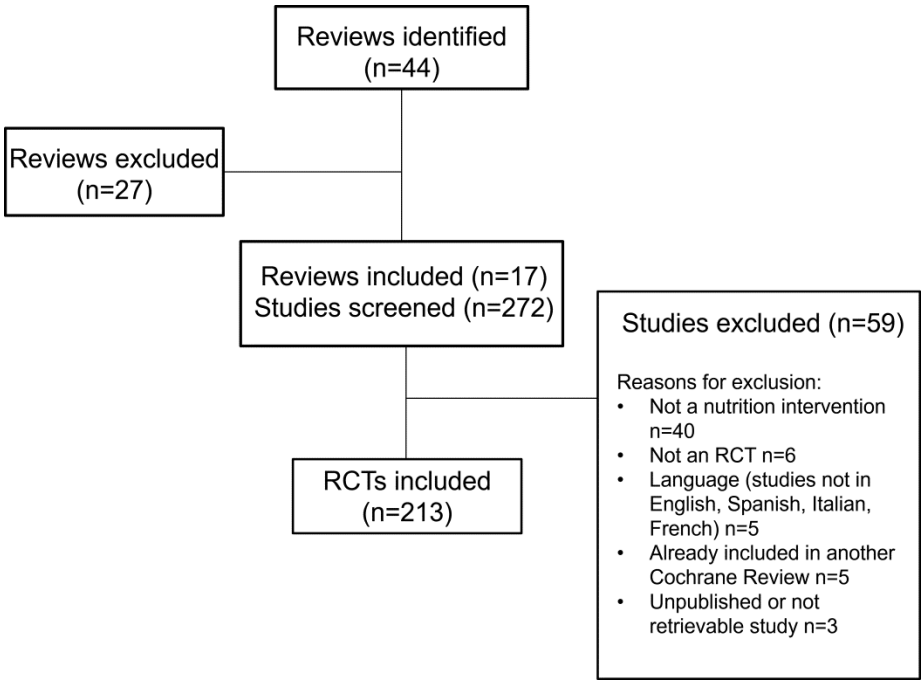

Table 1. Location of study site by WHO Regions (n= 213)

Location	**N of RCTs**	**% of RCTs**
Africa	1	0.5
America	126	59.1
Europe	60	28.1
Eastern Mediterranean	0	0
South-East Asia	1	0.5
Western Pacific Region	23	10.8
Not clear	2	1
Total	213	100%

Table 2. Categories of funding sources for studies disclosing a sponsor (n= 175)

Funding source	**Frequency**	**Percent**
Governmental agencies	65	37.1%
Non profit	28	16.0%
Pharmaceutical industry	12	6.9%
Food industry	8	4.6%
Mixed funding sources (without industry)	34	19.4%
Mixed funding sources (with food industry)	16	9.1%
Mixed funding sources (with pharmaceutical industry)	9	5.1%
Unknown	3	1.7%
Total	175	100%

Table 3. Nutrition research topics in randomized controlled trials (n = 213)

		n	**%**
Level of dietary composition	Energy	16	7.5
	Nutrient (n=21) Nutrient + Energy (n=73)	94	44.2
	Food (n=16) Food + Energy (n=8)	24	11.3
	Nutrient/Food (n=24) Nutrient/Food + Energy (n=34)	58	27.2
	Dietary pattern	2	0.9
	Not applicable	19	8.9
Level of food processing	Yes	57	26.8
	No	156	73.2
Dietary behaviours	Yes	121	56.8
	No	92	43.2

Table 4. Research topics by funding sources (n=151)

		Food industry n=24	**Non-Food industry n=127**	**P value**
		n (%)	**n (%)**	
Level of dietary composition	Energy	2 (8.3)	10 (7.9)	0.083
	Nutrient Nutrient + Energy	16 (66.7)	45 (35.4)	
	Food Food + Energy	1 (4.2)	17 (13.4)	
	Nutrient/Food Nutrient/Food + Energy	5 (20.8)	42 (33.1)	
	Dietary pattern	0 (0)	2 (1.6)	
	Not applicable	0 (0)	11 (8.7)	
Level of food processing	Yes	6 (25)	40 (31.5)	0.526
	No	18 (75)	87 (68.5)	
	Yes	8 (33.3)	85 (66.9)	0.002

Dietary behaviours	No	16 (66.7)	42 (33.1)	

Column percents are calculated

Supplementary File 1. List of included and excluded Cochrane Reviews

Included Cochrane Reviews

First author	Title	Number of studies	Publication date
Adegboye	Diet or exercise, or both, for weight reduction in women after childbirth	Studies included in the review:14 Studies included in our analysis:10	July 2013
Adeniyi	Weight loss interventions for chronic asthma1423	Studies included in the review:4 Studies included in our analysis:2	July 2012
Cheng	Calorie controlled diet for chronic asthma	Studies included in the review:1 Studies included in our analysis:1	April 2003
Faulkner	Interventions to reduce weight gain in schizophrenia	Studies included in the review:23 Studies included in our analysis:10	January 2007
Jull	Chitosan for overweight or obesity	Studies included in the review:15 Studies included in our analysis:14	July 2008
Luttikhuis	Interventions for treating obesity in children	Studies included in the review:64 Studies included in our analysis:60	January 2009
Martin	Lifestyle intervention for improving school achievement in overweight or obese children and adolescents	Studies included in the review:6 Studies included in our analysis:5	March 2014
Mastellos	Transtheoretical model stages of change for dietary and physical exercise	Studies included in the review:3	February 2014

	modification in weight loss management for overweight and obese adults	Studies included in our analysis:3	
Moran	Lifestyle changes in women with polycystic ovary syndrome	Studies included in the review:6 Studies included in our analysis:4	July 2011
Norris	Long-term non-pharmacological weight loss interventions for adults with type 2 diabetes mellitus	Studies included in the review:24 Studies included in our analysis:23	April 2005
Norris	Long-term non-pharmacological weight loss interventions for adults with prediabetes	Studies included in the review:9 Studies included in our analysis:7	April 2005
Orozco	Exercise or exercise and diet for preventing type 2 diabetes mellitus	Studies included in the review:8 Studies included in our analysis:7	July 2008
Peng	Weight reduction for non-alcoholic fatty liver disease	Studies included in the review:7 Studies included in our analysis:5	June 2011
Thomas	Low glycaemic index or low glycaemic load diets for overweight and obesity	Studies included in the review:6 Studies included in our analysis: 6	July 2007
Tian	Chromium picolinate supplementation for overweight or obese adults	Studies included in the review:9 Studies included in our analysis:9	November 2013
Waters	Interventions for preventing obesity in children	Studies included in the review:55 Studies included in our analysis:31	December 2011

Wieland	Interactive computer-based interventions for weight loss or weight maintenance in overweight or obese people	Studies included in the review:18 Studies included in our analysis:16	August 2012

Excluded Cochrane Reviews

First author	Title	Publication date	Reason for exclusion
Barrett	Probiotics for preventing gestational diabetes	February 2014	The included population is not relevant to our study.
Barley	Interventions to encourage uptake of cancer screening for people with severe mental illness	July 2013	The studied intervention is not a nutrition intervention to address obesity or overweight.
Buckley	Service organisation for the secondary prevention of ischaemic heart disease in primary care	March 2010	The studied intervention is not a nutrition one.
Christie	Workplace-based organisational interventions to prevent and control obesity by improving dietary intake and/or increasing physical activity	June 2010	The review is relevant to our study. However, only the protocol is available.
Colquitt	Surgery for weight loss in adults	August 2014	The studied intervention is not a nutrition one.
Curioni	Rimonabant for overweight or obesity	October 2006	The studied intervention is not a nutrition one.
Ebrahim	Multiple risk factor interventions for primary prevention of coronary heart disease	January 2011	The considered outcomes are not relevant to our study.

Ells	Surgery for the treatment of obesity in children and adolescents	June 2015	The studied intervention is not a nutrition one.
El Dib	Zinc supplementation for the prevention of type 2 diabetes mellitus in adults with insulin resistance	May 2015	There are no obesity related outcomes.
Fernandes	Intragastric balloon for obesity	January 2007	The studied intervention is not a nutrition one.
Furber	Antenatal interventions for reducing weight in obese women for improving pregnancy outcome	January 2013	The included population is not relevant to our study.
Flodgren	Interventions to change the behaviour of health professionals and the organisation of care to promote weight reduction in overweight and obese adults	March 2010	The studied intervention is not a nutrition one.
Kramer	Optimal duration of exclusive breastfeeding	August 2012	For the purpose of this study, we did not consider breastfeeding as a nutrition intervention.
Han	Interventions for pregnant women with hyperglycaemia not meeting gestational diabetes and type 2 diabetes diagnostic criteria	January 2012	The included population is not relevant to our study.
Kramer	Energy/protein restriction for high weight-for-height or weight gain during pregnancy	October 1996	The review is withdrawn.
Jefferys	Deflation of gastric band balloon in pregnancy for improving outcomes	April 2013	The studied intervention is not a nutrition one.

Middleton	Different intensities of glycaemic control for pregnant women with pre-existing diabetes	August 2012	The included population is not relevant to our study.
Milne	Protein and energy supplementation in elderly people at risk from malnutrition	April 2009	The included population is not relevant to our study.
Opray	Directed preconception health programs and interventions for improving pregnancy outcomes for women who are overweight or obese	July 2015	The included population is not relevant to our study.
Saenz	Metformin monotherapy for type 2 diabetes mellitus	July 2005	The studied intervention is not a nutrition one.
Saraswat	Carbohydrate or fat-restricted diets for obesity	August 2012	This protocol was withdrawn.
Shaw	Exercise for overweight or obesity	October 2006	The studied intervention is not a nutrition one.
Siebenhofer	Long-term effects of weight-reducing drugs in hypertensive patients	March 2013	The studied intervention is not a nutrition one.
Summerbell	Advice on low-fat diets for obesity	July 2008	The review is withdrawn.
Thomas	Exercise for type 2 diabetes mellitus	July 2006	The studied intervention is not a nutrition one.
Tieu	Interconception care for women with a history of gestational diabetes for improving maternal and infant outcomes	June 2013	The included population is not relevant to our study.
Williams	Strategies for enhancing the implementation of school-based	May 2015	Only the protocol is available.

	policies or practices targeting risk factors for chronic disease		

APPENDIX ii

Study Sponsorship and the Nutrition Research Agenda:

Analysis of cohort studies examining the association between nutrition and obesity

(Public Health nutrition 2017; https://doi.org/10.1017/S1368980017002178)

Alice Fabbri[1,2], Nicholas Chartres[2], Lisa A Bero[2]

[1]Centre for Research in Medical Pharmacology, University of Insubria, Varese, Italy

[2]Charles Perkins Centre and Faculty of Pharmacy, The University of Sydney, Australia

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Conflict of interest: None.

Authorship: AF, NC, LAB conceived the study and designed the data collection tool. AF, NC collected the data. AF, NC, LAB analysed the data. AF wrote the first draft of the paper. NC, LAB contributed to the writing of the paper and approved the final version.

Abstract

Objective To categorize the research topics covered by a sample of cohort studies exploring the association between nutrition and obesity; to describe their funding sources; to explore the association between funding sources and research topics.

Design Cross-sectional study.

Subjects Cohort studies retrieved from Medline and Pubmed published between 2010 and 2016.

Results One hundred twenty-one studies were included. Funding source and conflicts of interest were disclosed in 95.0% and 90.1% of the studies, respectively. Food industry sponsorship was disclosed in 8.3% of the studies. Half of the studies analysed the consumption of a single food or food groups, 18.2% included an analysis of dietary patterns and 17.4% focused on specific nutrients. Highly processed foods were considered in 48.8% of the studies and 27.3% considered dietary behaviours (e.g. eating away from home). No statistically significant differences in research topics were observed between industry and non-industry funded studies.

Conclusions Cohort studies focused on more complex exposures (e.g. food or dietary patterns) rather than single nutrients. No significant differences in the research agenda by funding sources were observed. The analysis was limited by the low proportion of studies with disclosed food industry sponsorship.

INTRODUCTION

A recent analysis of internal industry documents revealed that decades of research on the link between nutrition and cardiovascular disease have been shaped by the sugar industry with the aim of deflecting attention away from sucrose as a potential risk factor.(1) This new case study bolsters previous concerns about the potential manipulation of the research agenda (namely the questions being studied) by corporate interests across different fields.(2) For example, cigarette companies deflected attention from the hazards of second hand smoke by funding studies suggesting that other indoor air pollutants were more harmful than tobacco.(3)

A systematic review published in 2016 has found that few studies have examined potential biases in nutrition research. The 12 studies included in the review focused on the effect of food industry sponsorship on the results, conclusions and methodological quality of nutrition research,(4) while potential biases in the nutrition research agenda have not been comprehensively assessed. Apart from case studies based on the analysis of internal sugar industry documents (1, 5) and investigative journalism reports that exposed the attempts of a multinational soda company to influence the obesity research agenda,(6) a systematic analysis examining whether food industry sponsorship influences the nutrition research agenda has not been done.

We previously conducted a study to explore the association between funding sources and research topics in a sample of randomized controlled trials (RCTs) assessing nutrition interventions to address obesity. We found that most of the food industry sponsored studies involved manipulation of specific nutrients, while less attention was paid to food level and dietary pattern level interventions.(7) This supports the hypothesis that a reductive focus on nutrients might be strategic for the industry as it can produce results that will allow food companies to market ultra-processed foods using nutrient content claims.(8)

However, complex diet-disease relationships cannot always be studied with RCTs. Dietary interventions can manipulate only limited components of diet, and are sometimes considered unethical or unfeasible to answer questions about the association of diet and diseases.(9, 10) Therefore long term observational studies play a fundamental role in nutrition research and have led to important findings about the complex interrelations between diet and diseases.(11) An analysis of 330 papers published in five nutrition journals between January-June 2007 found that observational designs were more frequent than experimental ones (68.2% versus 31.8%).(12) In addition, evidence from observational studies currently informs the development of dietary guidelines.(13) Cohort studies are a common and rigorous type of observational study design. Compared with case-control studies, cohort studies can test hypotheses regarding the association between an exposure and multiple outcomes and avoid some of the biases, such as recall bias, that might affect other observational studies.(14)

In light of these considerations, the aim of this study is to evaluate whether the association of research topics and funding sources previously observed in RCTs also applies to observational cohort studies. The specific objectives are:

4. To categorize the research topics covered by a sample of cohort studies exploring the association between nutrition and obesity;
5. To describe their funding sources;
6. To explore the association between funding sources and research topics.

METHODS

Study selection

We included published cohort studies examining the association between dietary exposures and overweight or obesity. We included studies where the primary or secondary outcomes were BMI score or other measures of overweight and obesity (eg. waist circumference, fat mass). We included studies published in English, Spanish, French and Italian.

We searched Medline (2010-2016) and PubMed (2010-2016) on July 29th 2016. The search strategy is shown in Supplementary File 1. We used a broad search strategy as our analysis was not designed to provide a clinical answer to a particular question (e.g. the association between a specific nutrition exposure and obesity) but to categorize the research topics across a sample of nutrition research studies addressing outcomes relevant to obesity. We restricted our search to studies published from 2010 as international standards on disclosure of funding sources and investigators' conflicts of interest have been mostly developed since that time (15, 16) and journals' disclosure policies have gradually become more stringent and widespread.(17) Thus, as our objective was to explore the association between funding sources and nutrition research topics, we focused on articles that were likely to have funding and conflicts of interest disclosures.

One investigator screened the titles and abstracts for obvious exclusions. When a study could not be rejected with certainty, the decision was made with a second investigator.

Data extraction

The full text was retrieved for each included study and the following data were collected:

- study characteristics: population studied, location, year of publication;

- disclosed funding source(s). These were classified as: food industry, pharmaceutical industry, other for profit entities, governmental agencies, not for profit, mixed funding sources, unknown (when the funding source was disclosed in the article, but information about the sponsor could not be retrieved from the Internet), or no funding disclosed. The food industry category could include transnational food corporations (e.g. Coca Cola), primary producers (e.g. dairy industry), food processing companies (e.g. meat packing industry), wholesale, distribution and retail companies (e.g. supermarkets, grocery chains), and trade associations (e.g. American Beverage Association);
- disclosure of investigators' conflicts of interest as stated in the publications;
- research topics as classified below.

The taxonomy we used to code research topics was inspired by a framework for food classification (8) and has already been extensively described elsewhere.(7) We coded research topics by:

1. Level of dietary composition

We assessed whether the study focused on:

- energy level: focus on caloric restriction;
- nutrient level: focus on the intake of specific nutrients, micronutrients, compounds (e.g. fat, protein, carbohydrates, vitamin B);
- food level: focus on the consumption of a single food or food groups (e.g. vegetables, fruit, grain foods, meats, fish, eggs, or processed foods such as sugar-sweetened beverages, high-energy snacks, fast foods etc);
- dietary pattern level: focus on the overall dietary pattern or cuisine (e.g. the Mediterranean diet);
- not applicable: when the article did not fit in any of the above categories.

To determine the level of dietary composition we extracted the hypothesis of the study. If the hypothesis was not clearly framed, we extracted information on how the authors defined the dietary exposure in the methods and results sections. Each article could fit more than one of the above categories, however, we coded the studies according to the most complex level. Each level can therefore include a combination of the lower levels; for example a study in the food category could include analysis of certain foods (e.g. fruit and vegetable) and studies focusing on a combination of foods and nutrients (e.g. fruit, vegetable and fiber).

Our *a priori* hypothesis was that the food industry is more likely to fund nutrient level studies compared to other sponsors in order to generate evidence in support of its nutritional claims on food products.(8)

2. Level of food processing

A study was rated as 'yes' if it explored the association between the consumption of highly processed foods, defined as foods that are constructed primarily out of processed-reconstituted and refined-extracted materials (eg. sugar-sweetened beverages, fried fast foods, breakfast cereals, confectionaries) and obesity-related outcomes. When we pilot tested the taxonomy, we found that many studies mentioned highly processed foods as one of the many food items that were part of the dietary assessment. Therefore, in order to be specific rather than sensitive, we decided to code as "yes" only the studies that mentioned highly processed foods in their primary hypothesis or that reported an adiposity measure related to the consumption of highly processed foods, whether as a single item or as the main components of a dietary pattern. Our *a priori* hypothesis was that little research focuses on evaluating the effects of the levels of food processing and that the food industry is less likely to sponsor such studies compared to other funding sources.(8, 18)

3. Dietary behaviours

A study was coded as 'yes' if it explored the association between certain dietary behaviours (e.g. meal skipping, eating away from home, eating while watching television, eating dinner together as a family, parental feeding practices) and obesity-related outcomes. Our *a priori* hypothesis was that the food industry is less likely to fund studies that address dietary behaviours compared to other sponsors.

Double coding

For the analysis of the nutrition research topics, 30% of the publications were randomly selected to be coded independently by two reviewers and any disagreement was resolved by consensus. As the percentage of agreement between the two coders was 92.5%, the rest of the sample was single coded.

Analysis

Categorical variables were described using frequency tables. Cross tabulations were performed for evaluating possible associations between the funding sources and the research topics using the chi-square test. All analyses were performed using SPSS Version 22.

RESULTS

Study selection

As shown in Figure 1, 1573 studies were identified and 121 met the inclusion criteria. Apart from one retrospective cohort study, all the included studies were prospective cohort studies. They targeted children/adolescents (n=49; 40.5%), adults (n=63; 52.1%) or both (n=9; 7.4%). The majority of the studies were conducted in Europe (n=56, 46.3%) and the United States (n=31, 25.6%). The length of observation varied: in 14 studies it was less than one year, in 55 studies 1-5 years, in 30 studies 5-10

years and in 22 studies more than 10 years. Five studies looked specifically at how the interaction between genetic variants and weight is mediated by diet.

Disclosure of funding source and investigators' conflicts of interest

Of the 121 included studies, 95.0% (n=115) disclosed their funding source. Of these, 112 studies disclosed the presence of one or multiple sponsors while in 3 cases the authors received no specific funding for conducting the study. As Table 1 shows, 40.5% (n=49) of the studies were funded by governmental, intergovernmental agencies or other public bodies, 36.4% (n=44) by mixed funding sources without any industry involvement, while food industry sponsorship (alone or with other sponsors) was disclosed in 8.3% (n=10) of the studies.

Of the 121 included studies, 90.1% (n=109) contained a conflicts of interest disclosure. In 9 studies (7.4%) the authors disclosed a conflict of interest with the food industry.

Research topics

Table 2 shows the research topics explored in the included cohort studies. With regard to the level of dietary composition:

- 3 studies (2.5%) focused on energy intake (e.g. *"this study aimed to assess associations between baseline objectively measured activity intensity, dietary energy density (DED) and 4-year change in adiposity");*
- 21studies (17.4%) focused on nutrients (e.g. *"the objective of the present study is to investigate the relationship between the macronutrient composition of the usual diet and weight change after 5 years on average"*);
- 61 studies (50.4%) analysed the consumption of a single food/food groups or a combination of nutrients, energy and foods (e.g. *"our aims were to determine the effects of total and full-*

and reduced-fat dairy intake in children at 10 y of age on risk of excess total body fat mass (TBFM) and overweight at age 13 y");

- 22 studies (18.2%) included an analysis of dietary patterns (e.g. *"we assessed the association between the adherence to the Mediterranean dietary pattern (MDP), prospective weight change, and the incidence of overweight or obesity"*);
- 14 studies (11.6%) did not fit any of the categories related to the level of dietary composition; those 14 articles addressed dietary behaviours instead.(see below)

Highly processed foods were considered in 48.8% (n=59) of the studies (e.g. *"we examined the association of SCB* (sugar-containing beverages) *intake at 13 months with BMI development until 6 years and body composition at age 6 years"*) and 27.3% (n=33) considered dietary behaviours (e.g. *"we assessed the association between breakfast skipping and body mass index (BMI) among young Chinese children in Hong Kong"*).

Research topics by funding sources

The results of the analysis of nutrition research topics by funding sources are presented in Table 3. To test our hypotheses, we compared the research topics of food industry and non-food industry sponsored studies. Considering the low proportion of food industry sponsored studies in our sample, we grouped studies sponsored solely by the food industry (n=1), studies with mixed food industry and other funding (n=9), and studies that did not disclose food industry funding but had authors who disclosed a conflict of interest with the food industry or personal support from industry (n=6). The non-food industry category includes studies funded by governmental agencies, non-profit sector and mixed funding sources without the presence of food industry and the studies that did not receive specific funding (n=96). We did not include in this analysis the studies funded by pharmaceutical companies and the ones with undisclosed funding sources, therefore the total number of included studies is 112.

As shown in Table 3, the most represented category in food industry sponsored studies was the nutrient level (37.5%) followed by the food level (31.3%). Most of the non-food industry funded studies addressed foods (52.1%) and 20.8% analysed dietary patterns (chi-square test: p=0.050). No statistically significant differences were observed between the two categories of funding sources with regard to the level of food processing and the dietary behaviours (chi-square test: p=0.643 and p=0.862 respectively).

DISCUSSION

Study sponsorship and the nutrition research agenda

Our *a priori* hypothesis that there would be statistically significant differences in the research topics funded by the food industry compared to other funders was not confirmed. Our focus on articles published from 2010 did maximise the proportion of studies (95.0%) with disclosed funding sources. Nevertheless, the analysis of the research topics by funding source was limited by the low proportion of studies with disclosed food industry sponsorship. One explanation could be the possible underreporting of industry sponsorship or authors' conflicts of interest as has been described in previous studies.(19) As the current system for disclosure has flaws, valid methodologies need to be developed to assess the accuracy of disclosed information. Information on conflicts of interests could be sought directly from authors of published studies, but, in our experience this is time consuming and yields little additional information. Another alternative is the creation of a centralized, publicly accessible registry for conflicts of interest disclosures that would aggregate information from different sources (e.g., published articles, internal registries of funding agencies).(20) This could be an important source of standardized conflicts of interest information for journal editors, researchers and readers of the scientific literature.

Another reason that we did not see a significant association between funding source and research topics could be that we focused on studies examining the relationship between diet and obesity. Food industry sponsors may not fund nutrition-related research and focus on other topics instead. For example, investigative journalism reports have exposed the attempts of Coca Cola to influence the obesity research agenda by funding studies that highlighted the role of physical activity in maintaining a healthy body weight, thus deflecting attention from nutrition and particularly from the harmful food commodities that the company markets.(6) Clearly one case study cannot be generalized to all food companies, but similar distracting techniques have already extensively been described across other industry sectors.(3)

We observed that the most represented category in food industry sponsored studies was the nutrient level immediately followed by the food level. Most of the non-industry funded studies instead addressed foods or dietary patterns. According to some authors, food corporations have strategically exploited the reductive approach to the nutrient composition of diets in order to market highly processed foods using nutrient content claims, a phenomenon described as "corporate capture of nutritionism".(8)

The level of food processing was taken into consideration in around half of the cohort studies. Although food processing is a fundamental determinant of the overall diet quality and a fundamental driver in the global obesity epidemics,(21) it still seems to be an overlooked factor in nutrition science.(22) Some researchers have pointed out the risks associated with this approach. For example, unprocessed whole grain foods and highly processed breakfast cereals could be classified together within the food group of cereals. This has resulted in calls for the adoption of new food classifications based on the extent of industrial processing.(22, 23) The 2015 Brazilian dietary guidelines are among the few guidelines that explicitly take this issue into account and recommend to limit the intake of processed foods and avoid those that are ultra-processed.(24)

Comparison of the research agenda studied in RCTs and observational studies

Our analysis shows that cohort studies focused on examining complex exposures (e.g. foods or dietary patterns) rather than single nutrients or dietary behaviours. In addition, highly processed foods were analysed in about half of the studies. In contrast, our previous study on nutrition interventions to address obesity, showed that the majority of the included RCTs involved manipulations of specific nutrients in a context of reduced caloric intake (44.2%), while there was a gap in the research agenda examining food-level (11.3%) and dietary pattern-level (0.9%) interventions. Highly processed foods were analysed in less than one-third of the interventions and slightly more than half of the RCTs addressed dietary behaviours.(7)

The gap in the research agenda and particularly the nutritional reductionism that was found in our previous study on RCTs was not so evident in the current sample of cohort studies. One explanation for these differences in level of dietary composition studied could be that cohort studies may be more likely than trials to focus on complex exposures in real word scenarios rather than a single nutrient's manipulation under ideal conditions. Another explanation could be that research topics have changed over time. The cohort analysis included only studies published between 2010-2016 while the RCT sample covered the period 1978-2013. The increasing focus on higher levels of dietary composition (e.g. foods and dietary patterns) might be the result of the numerous calls that have been made for an alternative approach to nutrition research, namely a "top-down" approach that starts from diet patterns and then works backward to smaller units of analysis (e.g. nutrients). (25, 26)

Limitations

Our study has several limitations. Firstly, we searched only two databases. However, the search strategy was broad and the large number of studies that did not meet our inclusion criteria suggests that the search was sensitive rather than specific. Also, we were not attempting to identify every study relevant to a clinical question but to identify a sample of cohort studies analysing the association between dietary exposures and obesity. Secondly, we excluded articles published in languages other than English, Spanish, French and Italian. Thirdly, we relied only on the information reported in the publications and did not contact the authors, therefore important aspects of the studies such as details of exposures studied or undisclosed conflicts of interest, might have been missed.

CONCLUSION

Cohort studies exploring the association between a dietary exposure and obesity outcomes focus on more complex exposures such as foods or dietary patterns rather than single nutrients. No statistically significant differences in the research topics by funding sources were observed, however the analysis was limited by the low proportion of studies with disclosed food industry sponsorship.

The low proportion of food industry sponsored studies suggests that a different approach might be needed to explore corporate interests' influence on the research agenda. To characterize the research agenda of the food industry, one option could be to analyse the research projects that food companies disclose on their websites or in annual reports. Another option could be to focus on a different research area as previous investigations have shown how some food and beverage companies have funded studies on topics that could distract from the harmful effects of their products.(5, 6) The involvement of food companies in sponsoring research on non-nutrition related

topics could therefore be another interesting area for future research. Lastly, identification of undisclosed conflicts of interest in nutrition research would support analyses of differences between industry and non-industry supported research.

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Figure 1. Flow chart of study selection

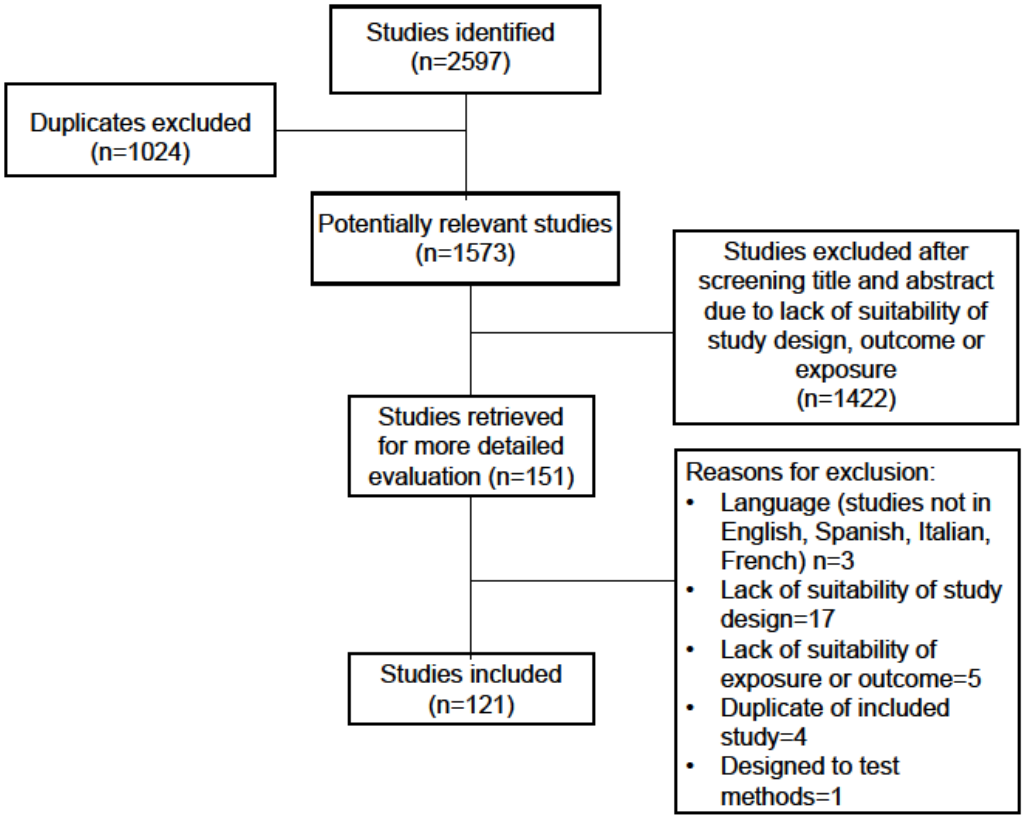

Table 1. Categories of funding sources (n= 121)

Funding source	**Frequency**	**Percent**
Governmental agencies	49	40.5%
Mixed funding sources (without industry)	44	36.4%
Mixed funding sources (with food industry)	7	5.8%
Non profit	5	4.1%
No funding disclosed	6	5.0%
Mixed funding sources (with pharmaceutical industry)	4	3.3%
No funding for study received	3	2.5%
Mixed funding sources with food and pharmaceutical industries	2	1.7%
Food industry	1	0.8%
Total	121	100%

Table 2. Nutrition research topics in cohort studies (n=121)

		n	%
Level of dietary composition*	Energy	3	2.5
	Nutrient	21	17.4
	Food	61	50.4
	Dietary pattern	22	18.2
	Not applicable	14	11.6
Level of food processing	Yes	59	48.8
	No	62	51.2
Dietary behaviours	Yes	33	27.3
	No	88	72.7

*For the analysis we grouped the studies according to the higher level of dietary composition in our taxonomy. Each level can therefore include a combination of the lower levels (e.g. the food category includes studies examining only certain foods and studies focusing on a combination of foods, nutrients and energy).

Table 3. Research topics by funding sources for studies that disclosed a sponsor (n=112)

		Food industry n=16	**Non Food industry n=96**	**P value**
		n (%)*	**n (%)***	
Level of dietary composition**	Energy	1 (6.3)	1 (1.0)	0.050
	Nutrient	6 (37.5)	14 (14.6)	
	Food	5 (31.3)	50 (52.1)	
	Dietary pattern	1 (6.3)	20 (20.8)	
	Not applicable	3 (18.8)	11 (11.5)	
Level of food processing	Yes	7 (43.8)	48 (50.0)	0.643
	No	9 (56.3)	48 (50.0)	
Dietary behaviours	Yes	4 (25.0)	26 (27.1)	0.862
	No	12 (75.0)	70 (72.9)	

* Column percents are calculated

**For the analysis we grouped the studies according to the higher level of dietary composition in our taxonomy. Each level can therefore include a combination of the lower levels (e.g. the food category includes studies examining only certain foods and studies focusing on a combination of foods, nutrients and energy).

APPENDIX iii

Reporting bias in the literature on the associations of health-related behaviors and statins with cardiovascular disease and all-cause mortality.

(PLoS biology. 2018;16(6):e2005761. doi: 10.1371/journal.pbio.2005761)

Leandro Fórnias Machado de Rezende[1], Juan Pablo Rey-López[3], Thiago Hérick de Sá[4], Nicholas Chartres[5], Alice Fabbri[5], Lauren Powell[3], Emmanuel Stamatakis[#2 3], Lisa Bero[#*5].

[1] Departamento de Medicina Preventiva, Faculdade de Medicina FMUSP, Universidade de São Paulo, São Paulo, São Paulo, Brasil

[2] Charles Perkins Centre, Epidemiology Unit, The University of Sydney, Sydney, Australia

3 Prevention Research Collaboration, School of Public Health, The University of Sydney, Sydney, Australia

[4] Núcleo de Pesquisas Epidemiológicas em Nutrição e Saúde, Universidade de São Paulo, São Paulo, São Paulo, Brasil

[5] Charles Perkins Centre, Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia.

Author summary

In the scientific literature, reporting bias occurs when communication and publication of results are influenced by the direction of findings. Reporting bias distorts the completeness of the scientific evidence and may misguides clinical and public health guidance. Our study provided an assessment of the degree of reporting bias in the literature on the associations of health-related behaviors (smoking, alcohol, diet, physical activity, sedentary behavior) and statins with cardiovascular disease and all-cause mortality. We selected 49 systematic reviews (111 meta-analyses) published recently (2010-2016). Most of the systematic reviews (90%) had a high risk of bias related to study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. We found evidence of reporting bias in about one-fifth of health-related behavior meta-analyses, but none of the statins meta-analyses. Readers should be aware of the extent of reporting bias in these research areas while interpreting meta-analytical results. Development of reproducible research practices to reduce reporting bias are needed.

ABSTRACT

Reporting bias in the literature occurs when there is selective revealing or suppression of results influenced by the direction of findings. We assessed the risk of reporting bias in the epidemiological literature on health-related behaviors (tobacco, alcohol, diet, physical activity, and sedentary behavior) and cardiovascular disease mortality and all-cause mortality**;** and provided a comparative assessment of reporting bias between health-related behaviors and statins (in primary prevention) meta-analyses. We searched Medline, Embase, Cochrane Methodology Register Database, and Web of Science for systematic reviews synthesizing the associations of health-related behaviors and statins with cardiovascular disease mortality and all-cause mortality published between 2010 and 2016. Risk of bias in systematic reviews was assessed using the ROBIS tool. Reporting bias in the literature was evaluated via small study effect and excess significance tests. We included 49 systematic reviews in our study. The majority of these reviews exhibited a high overall risk of bias, with a higher extent in health-related behaviors reviews, relative to statins. We re-performed 111 meta-analyses conducted across these reviews, of which 65% had statistically significant results ($P<0.05$). Around 22% of health-related behaviors meta-analyses showed small study effect, as compared to none of statins meta-analyses. Physical activity and the smoking research areas had more than 40% of meta-analyses with small study effect. We found evidence of excess significance in 26% of health-related behaviors meta-analyses, as compared to none of statins meta-analysis. Half of the meta-analyses from physical activity, 26% from diet, 18% from sedentary behavior, 14% for smoking, and 12% from alcohol showed evidence of excess significance bias. These biases may be distorting the body of evidence available by providing inaccurate estimates of preventive effects on cardiovascular and all-cause mortality.

INTRODUCTION

The literature on the association between behavioral risk factors (*e.g.*, smoking, alcohol, physical inactivity, and unhealthy diet) and cardiovascular diseases – the single largest cause of death globally[1] – has grown exponentially in the last decades[2-39]. Observational epidemiological studies are the dominant design assessing these associations, since clinical trials cannot always be ethically or logistically conducted[40]. Systematic review methods are used to synthesize and evaluate this growing body of evidence. It is important to evaluate the methodological risks of bias in systematic reviews [41], as well as the impact that reporting bias can have on the findings of reviews [42, 43].

Reporting bias is one of the most common biases identified in the literature. It includes selective publication of studies or outcomes of studies[44, 45] based on factors other than the study quality, such as nominally statistical significance results ($P<0.05$)[46, 47] or authors "pedigree"[44, 45, 48]. These practices threaten the completeness and validity of scientific evidence[46] by distorting the estimates of causal effects of interventions or exposures on diseases[49]. The extent of reporting bias could differ between bodies of evidence consisting of randomized trials, such as drug studies, compared to observational studies, such as studies of health behaviors. Different levels of reporting bias in the literature on health behaviors may lead to inaccurate estimates of preventive effects on cardiovascular and all-cause mortality, and therefore offer incorrect guidance for policymaking.

To gain a better understanding of the potential reporting bias in the literature on health-related behaviors and cardiovascular disease mortality and all-cause mortality, we examined reporting and other risks of bias in a sample of systematic reviews published between 2010 to 2016. Our analysis also provided a comparative assessment of the reporting bias between health-related behaviors and statins used in primary prevention.

RESULTS

Of the 5,511 records identified searching the databases, we selected 49 systematic reviews. All research areas (tobacco, alcohol, diet, physical activity, sedentary behavior, and statins) presented less than 20 eligible systematic reviews, therefore we included all the systematic reviews within each area that met our inclusion criteria (Fig 1). List of excluded reviews and reasons for exclusions are described in S1 Table and S2 Table. Studies were excluded most frequently because they did not include one of the exposures (28%) or outcomes (29%) of interest and for utilizing clinical samples (16%).

Fig 1. Flowchart for systematic review selection by research area.

Most of the included systematic reviews (n=35, 7%) analyzed only one outcome eligible for our study (cardiovascular disease mortality and all-cause mortality), whereas 17 (18%), 40 (8%), and 28 (2%) analyzed two, three, and four outcomes, respectively. All-cause mortality (69%), cardiovascular disease mortality (29%) and stroke mortality (14%) were the most frequent outcomes investigated (Table 1).

Table 1. Risk of bias in systematic reviews of the associations of health-related behaviors and statins with cardiovascular and all-cause mortality - ROBIS assessment.

First author, year (Reference)	Exposures	Outcomes (mortality)	ROBIS Assessment			
			1. Study eligibility criteria	2. Identification and selection of studies	3. Data collection and study appraisal	4. Synthesis and findings
Physical activity						
Kelly, 2014[2]	Walking; Cycling	ACM	low risk	high risk	high risk	high risk
Samitz, 2011[3]	Total leisure-time; Exercise; Walking; Commuting; Daily activities	ACM	low risk	low risk	high risk	high risk
Woodcock, 2011[4]	Non-vigorous; Walking	ACM	high risk	high risk	unclear risk	low risk
Hupin, 2015[5]	Low-dose physical activity	ACM	low risk	high risk	unclear risk	low risk
Sedentary behavior						
Biswas, 2015[6]	Sedentary time	CVD, ACM	low risk	high risk	low risk	high risk
Chau, 2013[7]	Sedentary time	ACM	high risk	high risk	low risk	high risk
Grontved, 2011[8]	Television viewing	ACM	low risk	high risk	high risk	high risk
Wilmot, 2012[9]	Sedentary time	CVD, ACM	high risk	high risk	low risk	high risk
Ford, 2012[10]	Sitting time; Screen-time	CVD	high risk	high risk	high risk	high risk
Pandey, 2016[11]	Sedentary time	CVD	high risk	high risk	unclear risk	unclear risk
Sun, 2015[12]	Television viewing	ACM	high risk	unclear risk	high risk	high risk
Alcohol						
Costanzo, 2011[13]	Wine, Beer, Spirits	CHDM, CVD, ACM	high risk	high risk	unclear risk	high risk
Jayasekara, 2014[14]	Alcohol intake	ACM	low risk	high risk	high risk	high risk
Roerecke, 2011[15]	Alcohol intake	IHD	low risk	high risk	high risk	low risk
Roerecke, 2014 [16]	Heavy drinking	IHD	low risk	high risk	high risk	high risk
Ronksley, 2011[17]	Alcohol intake	CVD, CHD, Stroke, ACM	low risk	low risk	high risk	low risk
Park, 2015[18]	Moderate alcohol intake	ACM	high risk	high risk	high risk	high risk
Stockwell, 2016[19]	Low-alcohol intake	ACM	low risk	high risk	unclear risk	low risk
Zheng, 2015[20]	Alcohol intake	ACM, Cardiac death	high risk	low risk	low risk	low risk
Roerecke, 2010[21]	Alcohol intake	IHD	high risk	high risk	high risk	high risk
Roerecke, 2014[22]	Alcohol intake	IHD	low risk	high risk	high risk	high risk
Smoking						

Gellert, 2012[23]	Current smoking; Former smoker	ACM	low risk	unclear risk	unclear risk	unclear risk
Lv, 2015[24]	Second hand smoking	ACM, CVD	low risk	high risk	unclear risk	high risk
Sinha, 2016[25]	Second hand smoking	ACM, IHD, Stroke	low risk	high risk	high risk	high risk
Diet						
Farvid, 2014[26]	Dietary linoleic acid	ACM	low risk	high risk	high risk	high risk
Graudal, 2014[27]	Sodium	ACM	low risk	high risk	high risk	high risk
Hu, 2014[28]	Fruits and vegetables	Stroke	low risk	high risk	high risk	high risk
Li, 2012[29]	Salt intake	Stroke	high risk	high risk	high risk	high risk
Musa-Veloso, 2011[30]	Long-chain n-3 fatty acid	Sudden cardiac, Coronary event	high risk	high risk	high risk	high risk
Pan, 2012[31]	α-linolenic acid	CVD	high risk	high risk	low risk	high risk
Poggio, 2015[32]	Sodium	CVD	low risk	high risk	high risk	low risk
Schwingshackl, 2014[33]	MUFA; MUFA:SFA ratio, olive oil	ACM, CVD	low risk	low risk	high risk	high risk
Wang, 2014[34]	Fruits and vegetables	ACM, CVD	low risk	high risk	low risk	high risk
Chen, 2016[35]	Long-chain n-3 polyunsaturated; EPA; DHA	ACM	low risk	low risk	low risk	low risk
Cheng, 2015[36]	Long chain n-3 PUFA intake	Stroke	low risk	high risk	low risk	high risk
Cheng, 2016[37]	Dietary saturated fat	Stroke	low risk	high risk	low risk	high risk
De Souza, 2015[38]	Saturated fat; total trans-fat; industrial trans-Fat; Ruminants' trans-fat	CHD	low risk	high risk	high risk	low risk
Narain, 2016[39]	Artificially sweetened beverage	ACM	low risk	low risk	high risk	low risk
Statins						
Bukkapatnam, 2010[50]	Statin	ACM	high risk	high risk	high risk	high risk
Kizer, 2010[51]	Statin	ACM	low risk	high risk	high risk	high risk
Kostis, 2012[52]	Statin	ACM	high risk	high risk	high risk	low risk
Lv, 2014[53]	Statin	ACM, CVD	high risk	high risk	high risk	low risk
Ray, 2010[54]	Statin	ACM	high risk	high risk	high risk	high risk
Savarese, 2013[55]	Statin	CVD, ACM	low risk	high risk	low risk	low risk
Taylor, 2011[56]	Statin	CHD, CVD, ACM	low risk	low risk	low risk	low risk
Tonelli, 2011[57]	Low-dose statin; High-dose statin	ACM	low risk	high risk	low risk	high risk
Chou, 2016[58]	Statin	ACM	low risk	high risk	low risk	low risk
Preiss, 2015[59]	Statin	Heart failure	low risk	high risk	high risk	low risk
Teng, 2015[60]	Statin	Stroke, MI, ACM	low risk	high risk	low risk	low risk

Legend: low risk = low risk of bias; high risk = high risk of bias; unclear risk = unclear risk of bias

Abbreviation: ACM: all-cause mortality; CHD: coronary heart disease; CVD: cardiovascular disease; MI: myocardial infarction; MUFA: Monounsaturated fatty acids; SFA: saturated Fatty acids; PUFA: Polyunsaturated fatty acids;

Risk of bias in systematic reviews – ROBIS results

The majority of the systematic reviews exhibited a high overall risk of bias (n=44, 90%) (Fig 2). Among the four ROBIS domains, domain 1 (study eligibility criteria) presented the best scores, with 32 (65%) out of 49 reviews showing a low risk of bias. In domain 2 (identification and selection of studies), 2 (4%) reviews were scored as unclear, 40 (82%) showed a high risk and 7 (14%) a low risk of bias. Whereas, in domain 3 (data collection and study appraisal), 7 (14%) reviews were scored as unclear, 28 (57%) scored with high risk and 14 (29%) with low risk of bias. Finally, in domain 4 (synthesis and findings), 1 (2%) review was scored as unclear, 30 (61%) with high risk and 17 (35%) with low risk of bias (Fig 2 and S3 Table).

Fig 2. Risk of bias in systematic reviews of the associations of health behaviors and statins with cardiovascular disease mortality and all-cause mortality – ROBIS results.
Underlying data can be found in S1 Data.

Comparing risk of bias in the reviews across research areas, sedentary behavior performed worse in domain 1 (study eligibility criteria) (70% reviews were regarded as having high risk of bias). All research areas performed poorly in domain 2 (identification and selection of studies), with high risk of bias ranging from 70% in smoking reviews to 90% in both sedentary behavior and statins reviews. Alcohol (70%) and diet (60%) reviews presented high risk of bias in domain 3 (data collection and study appraisal). Sedentary behavior (90%), smoking (70%) and diet (70%) reviews presented high risk of bias in domain 4 (synthesis and findings). Overall, statin reviews presented the best scores in the ROBIS assessment compared to other research areas. Among all statin reviews: a low risk of bias was identified in 60% in domain 1, 10% in domain 2, 50% in domain 3, and 60% in domain 4 (Table 1 and Fig 3).

Fig 3. Risk of bias in systematic reviews of the associations of health behaviors and statins with cardiovascular disease mortality and all-cause mortality, by research area – ROBIS results.

Risk of bias in systematic reviews on the associations of physical activity (A), smoking (B), sedentary behavior (C), diet (D), alcohol (E) and statins (F) with cardiovascular disease and mortality. Underlying data can be found in S1 Data.

Risk of reporting bias in the body of evidence

We identified 111 meta-analyses (exposure-outcomes associations) that were performed across the 49 included reviews. On average, each meta-analysis synthesized results from nine primary studies (ranging from 2 to 81), including 331,688 participants (ranging from 595 to 3,674,042) and 19,012 deaths (ranging from 33 to 320,252) (Table 2 and S4 Table). 72 (65%) out of 111 meta-analyses showed a nominally statistically significant result at $P<0.05$.

Nominally statistically significant results ($P<0.05$) was found in 92% of the meta-analyses from sedentary behavior and 100% of the meta-analyses from physical activity and smoking. Alcohol and statin reviews had 38% and 45% of meta-analyses with $P<0.05$ results, respectively (Table 2 and S4 Table).

Table 2. Relative and absolute frequency of meta-analyses with nominally statistically significant results, small-study effect, and excess significance, by research area.

Research area	Total number of meta-analysis	Meta-analysis with P<0.05[#]		Small-study effect			Excess significance				
								O>E			
	N	n	%	N*	n	%	N**	n	%	n with P<0.05	%
Physical Activity	12	12	100	12	5	42	12	8	67	6	50
Sedentary behavior	12	11	92	11	1	9	11	7	64	2	18
Alcohol	24	9	38	18	3	17	17	10	59	2	12
Smoking	7	7	100	7	3	43	7	3	43	1	14
Diet	36	24	67	31	5	16	31	16	52	8	26
Statin	20	9	45	17	0	0	17	9	53	0	0
Overall	111	72	65	96	17	18	95	53	56	19	20

Abbreviation: O>E: meta-analyses with number of observed primary studies with P<0.05 beyond expected;

*N: Numbers of meta-analysis with enough primary studies to perform the small study effect test (≥3)

**N: Numbers of meta-analysis with enough primary studies (≥3) and available data to perform the excess significance test.

[#] P-value of the summary random effects estimate.

Small Study effect

Indication of small study effect was found in 17 (18%) of the 96 meta-analyses. Physical activity and the smoking research areas had more than 40% of meta-analyses with small study effect. Sedentary behavior had less than 10% of meta-analysis with small study effect (Table 2 and S4 Table). Overall, 17 (22%) out of 79 meta-analyses of health-related behaviors presented small study effect, as compared to zero statins meta-analysis.

Excess significance

More than half (56%; 53/95) of the meta-analyses displayed a greater number of observed primary studies (O) with P<0.05 results than the number expected (E). Of those, 19 meta-analyses (20% of the total meta-analyses and 36% of the meta-analyses with O>E) showed evidence of excess significance bias (P<0.10). Half of the meta-analyses from physical activity, 26% from diet, 18% from sedentary behavior, 14% from smoking, and 12% from alcohol showed evidence of excess significance (Table 2 and S4 Table). Overall, 24% of the meta-analyses of health-related behaviors showed excess significance, as compared to zero statin meta-analysis.

Sensitivity analyses

We conducted a sensitivity analysis by restricting the sample in each research area to meta-analyses with ≥10 primary studies. In this subsample (n=29), 86.2% of the meta-analyses showed statistically significant results at P<0.05, as compared to 65% in the entire sample of meta-analyses. These results varied by research area, ranging from 60% in statins meta-analyses to 100% in physical activity, sedentary behavior, and smoking meta-analyses (Table 3).

Small study effect was present in 31% of the meta-analyses. The proportions of meta-analyses in the sensitivity analysis with small study effect were 85% for physical activity, 50% for sedentary behavior, 29% for alcohol, and 33% for smoking. Diet and statins meta-analyses had no

evidence of small study effect. Around 38% of the health-related behaviors meta-analyses with ≥10 primary studies presented small-study effect, as compared to zero in statins meta-analyses (Table 3).

Excess significance was identified in 27% of the meta-analyses with ≥10 primary studies: 100% of the meta-analyses for sedentary behavior, 50% for diet, 40% for physical activity, 20% for alcohol, and 17% for smoking. Around 33% of the health-related meta-analyses with ≥10 primary studies showed evidence of excess significance, as compared to zero in statins meta-analyses (Table 3).

Overall, after excluding small individual studies (with less than < 200 deaths) from meta-analyses, results from small study effect and excess significance tests did not change (S5

Table 3. Sensitivity analysis: Relative and absolute frequency of meta-analyses with ≥10 primary studies showing nominally statistical significant results, small-study effect, and excess significance, by research area.

Research area	Total number of meta-analysis	Meta-analysis with P<0.05[#]		Small-study effects			Excess significance				
							O>E				
	N	n	%	N*	n	%	N**	n	%	n with P<0.05	%
Physical Activity	5	5	100	5	4	80	5	2	40	2	40
Sedentary behavior	2	2	100	2	1	50	1	1	100	1	100
Alcohol	7	6	86	7	2	29	5	2	40	1	20
Smoking	6	6	100	6	2	33	6	3	50	1	17
Diet	4	3	75	4	0	0	4	3	75	2	50
Statin	5	3	60	5	0	0	5	4	80	0	0
Overall	29	25	86	29	9	31	26	15	58	7	27

Abbreviation: O>E: meta-analyses with number of observed primary studies with P<0.05 beyond expected;

*N: Numbers of meta-analysis with enough primary studies to perform the small study effect test (≥10)

**N: Numbers of meta-analysis with enough primary studies (≥10) and available data to perform the excess significance test.

[#] P-value of the summary random effects estimate.

DISCUSSION

This study aimed to assess the extent of reporting bias among recent meta-analyses that examined the associations of health behaviors and statins with cardiovascular and all-cause mortality. We found evidence of reporting bias across all health-related behavior areas. The degree of reporting bias varied by the method used to assess it. Reporting bias was present in 20% (according to excess significance test) or 18% (according to small study effect test) of all meta-analyses included (health behaviors and statins). Evidence of reporting bias was found in between a quarter and one-fifth of health-related behavior meta-analyses (22% small study effect and 24% excess significance), but in none of the statins meta-analyses (0%).

In lifestyle epidemiology, the interpretation of evidence for researchers and policymakers is challenging for several reasons[61]. As observational studies are the dominant designs in this area, spurious associations can arise due to confounding or several sources of bias. The impact of such biases on statistical findings and interpretation of findings has been poorly reported and discussed[62]. Therefore, meta-analytical synthesis of the evidence in lifestyle health behavior epidemiology may provide precise but spurious results[63].

Reporting bias is a major threat to the validity of the relevant body of evidence. Our results suggest that around 20% of the meta-analyses on health-related behaviors and cardiovascular disease mortality and all-cause mortality may be susceptible to reporting biases. The existence of reporting bias in the literature has several explanations. Failure to submit manuscripts of analyses that did not produce statistically significant results ("the file-drawer problem"[46]), and the low likelihood of publication of small studies (regardless of statistical significance)[44] are two possible reasons. The selective reporting of certain analyses with statistically significant results is another likely source of reporting bias [44, 46, 47]. Each of the research areas we examined is likely to be linked to variable levels of reporting bias due

to the different economics, dynamics, and conflicts of interest in each discipline[64, 65]. Interpreting the literature as a whole is challenging considering the numerous biases that may affect the reliability and integrity of the scientific enterprise[66, 67].

To obtain a complete picture of the evidence (*i.e.*, without reporting bias), it is important to know the results from all conducted studies on a given research question[68]. In our study, results from meta-analyses of health-related behavior and cardiovascular disease mortality and all-cause mortality were more likely to be affected by reporting bias compared to statin meta-analyses (22%-24% vs 0%, respectively). The literature of health-related behaviors is almost exclusively composed by observational studies, whereas statins are most often studied using randomized controlled trials. Reporting bias may be less frequent among trials than observational studies because several efforts to increase transparency and reproducibility of results have been adopted over the history of randomized controlled trials[69]. These include the mandatory registration of all clinical trials in humans and disclosure of all results[70]. As of more recently, data sharing statements of clinical trials are also required[71]. Observational epidemiologic studies should embrace these reproducible research practices to reduce reporting bias in the literature[68-70, 72]. These practices could involve key elements of the scientific process, including: a) methods (*e.g.*, rigorous training in statistics), b) reporting and dissemination (*e.g.*, disclosure of conflicts of interest), c) reproducibility (*e.g.*, open data), d) evaluation (*e.g.*, pre and post-publication peer review), and e) incentives (*e.g.*, funding replication studies)[72]. Improving methodological training involves aspects of both research design and statistical analyses. For example, correct interpretation of P values[73], acknowledging the importance of statistical power, and improving the accuracy of effect sizes[72]. Protecting against cognitive biases is another major issue that has been overlooked[72]. Protecting against conflict of interests, especially financial-related, is an imperative to achieve reproducible science. In addition to disclosure of potential conflicts of interest, promoting pre-registration of study procedures and analytical plan may prevent

reporting bias favoring positive results[72]. Funding replication of studies, and encouraging openness in science and reproducibility practices by making datasets, scripts, and software publicly available may increase transparency and credibility of scientific claims[72]. For instance, food industry-sponsored studies are more likely to report conclusions favorable to the sponsors[74], but frequently lack transparency on acknowledgment of the funding source [75]. Further examples of reproducibility practices have been described and discussed by Munafò et al[72].

To our knowledge, our analysis is the first comparative assessment of reporting bias across different fields of health-related behaviors and statins. Our findings were based on well-established statistical tests developed to detect different aspects of reporting bias, as well as a complementary assessment of the risk of bias of systematic reviews using the ROBIS tool. We selected the ROBIS tool as it has greater specification to assess risk of bias compared to other tools. For instance, the "Assessing the Methodological Quality of Systematic Reviews" (AMSTAR) that has been used to evaluate the methodological quality of systematic reviews has constructs which are more related to quality of reporting than risk of bias[76, 77]. Risk of bias is linked to methodological quality of systematic reviews but provides further evaluation on how methodological limitations were considered to form conclusions. In this sense, the ROBIS tool is increasingly being used to assess risk of bias not only in systematic reviews [41, 76, 78] but also in guideline committees that evaluate evidence level (*e.g.*, Australian Government, National Health and Medical Research Council). Our ROBIS tool results showed that most of the systematic reviews had high risk of bias. Similar findings have been observed in previous studies appraising risk of bias in other research areas using ROBIS tool[76, 78]. For instance, 18 (58%) out 31 systematic reviews evaluating the effectiveness of intra-articular hyaluronic acid injection in treating knee osteoarthritis had high (n=16) or unclear (n=2) risk of bias [74]. Another survey assessing systematic reviews about psoriasis found that most reviews (86%) were classified as high risk

of bias [75]. It is noteworthy that high risk of bias was found even for systematic reviews exhibiting high methodological quality as assessed through AMSTAR.

Our ROBIS assessment indicated that identification and selection of studies (*i.e.*, appropriate range of databases, terms and filters used, and efforts to minimize errors in selection of studies) are major concerns. These biases in the review process could explain, at least in part, reporting bias results obtained from small study effect and excess significance tests. The synthesis and findings domain also revealed potential risk of bias due to insufficient inclusion of studies and appropriate synthesis of estimates. This domain also reflects between-study variation, robustness of findings (*e.g.*, sensitivity analyses) and biases in synthesis findings (*i.e.*, if evaluated by systematic reviews).

We used small study effect and excess significance tests to appraise reporting bias in the literature which are the most commonly recommended and used methods[79]. However, results from these tests might also reflect methodological and clinical heterogeneity, or even chance[42]. In fact, most meta-analyses contained moderate to high heterogeneity (based on I^2 statistic; S4 Table). Results from Egger's test (small study effect) can give spurious false positive results due to correlation between log of effect size and its variance, especially in the presence of heterogeneity between studies in a meta-analysis. An alternative better performing test has been proposed by Peters to identify reporting bias in meta-analysis, but it requires data from 2x2 table[80]. Such data were rarely reported in individual studies in the meta-analyses of observational studies. As also noted by Tsilidis et al.,[81] meta-analyses commonly use maximally-adjusted relative risks rather than unadjusted relative risks calculated from 2x2 tables. For such data the use of Egger test is appropriate.

Egger test and excess significance test have low power to detect reporting bias and do not give indication about what is the sources of bias. Therefore, we performed sensitivity analysis retaining only meta-analyses with ≥10 individual studies. In this sub-sample of meta-analyses, evidence of reporting

bias was higher than the entire sample (Small study effect: 31% vs 18%; Excess significance: 27% vs 20%). Differences between primary results and sensitivity analyses are likely related to low power of reporting bias tests, which could lead to false negative results in the former group of meta-analysis. Therefore, our estimates of reporting bias in the meta-analyses is possibly conservative. The ranking of research areas according to levels of reporting bias was also different between the main analysis and the sensitivity analysis (*i.e.*, meta-analyses with ≥10 individual studies). For instance, meta-analyses of sedentary behavior appeared most sensitive to this restriction as estimates proportion of reporting bias increased when calculated with either the small study effects (from 9% to 50%) or excess significance tests (from 18% to 100%). A possible explanation could be the small fraction of meta-analysis with ≥10 individual studies (2 out of 12) in this relatively new research field[82].

It is important to acknowledge that certain methodological decisions we made may have introduced bias in the sample of reviews selected or may compromise the generalizability of our findings. We excluded systematic reviews on alcohol published in Chinese language (n=2), which potentially have high risk of bias[83]. In addition, we restricted our analyses to systematic reviews published in this decade only (2010-2016), which explains the small number of included meta-analyses in some research areas. This may have limited comparisons of the extent of reporting bias between research areas investigated. Our results may not provide a complete historical assessment of reporting bias in these areas. Nevertheless, our results reflect reporting bias in the literature of recent and relevant public health topics and from a time period when reporting standards have been improving due to *e.g.* the widespread use of various manuscript reporting checklists[84]. Recent systematic reviews contain a higher number of primary studies than older systematic reviews and synthesize evidence of emerging fields that have flourished only recently (*i.e.*, sedentary behavior).

In conclusion, we found evidence of reporting bias in approximately one-fifth of recent meta-analyses of observational studies of health-related behaviors (physical activity, sedentary behavior, smoking, alcohol

consumption, diet) and cardiovascular and all-cause mortality. Such a level of reporting bias may, to some extend at least, distort conclusions arising from this body of evidence. Contrarily, we found no evidence of reporting bias in meta-analyses of randomized controlled trials of statins.

MATERIAL AND METHODS

Identification and selection of relevant systematic reviews

We searched Medline (trough PubMed), Embase (*i.e.*, excluding Medline), Cochrane Methodology Register Database, and Web of Science for systematic reviews published between 2010 and 2016. We restricted our search to recent systematic reviews for several reasons. These systematic reviews belong to a "birth cohort" of systematic reviews published after the launch of the MOOSE (Meta-analysis of Observational Studies in Epidemiology)[85] and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[86] guidelines and are expected to have lower risk of bias. As we were interested in comparing levels of bias across different research areas, this restriction may have reduced confounding due to date of publication. We restricted the search, as well as the successive phases of our study, to systematic reviews aiming to investigate the associations of health-related behaviors [tobacco, alcohol, diet (fat, fruits and vegetables, salt, and sugar), physical activity, and sedentary behavior] and statins with cardiovascular disease mortality (overall cardiovascular mortality and cause-specific deaths from cardiovascular disease) and all-cause mortality. We accepted any definition for the exposures and the outcomes as defined in the original systematic reviews. The keywords used in the search are described in S1 Text and files exported from databases during search strategy with all studies screened and selected are available at https://osf.io/wpb69/.

Systematic reviews were screened and selected (by two reviewers, and disagreements solved by a third reviewer) based on the following eligibility criteria: (i) sought to investigate an exposure-outcome

association in a non-clinical population; (ii) systematically-searched for primary studies and performed a meta-analysis (*i.e.*, weighted summary effect size) using results from primary studies; (iii) selected only observational studies (cohort and case-control studies) if a health-related behavior review; and only randomized controlled trials if a statin review; (v) reported data from each primary study included in the meta-analysis (S1 Text).

We decided a priori that a random sample of up to 20 systematic reviews per research area (tobacco, alcohol, diet, physical activity, sedentary behavior, and statins) would be included to compare levels of reporting bias in the relevant literature. If our search retrieved fewer than 20 meta-analyses in a given research area, we included them all. A similar study selection strategy was recently used in a study evaluating publication bias in meta-analyses of individual studies[87]. These methods were decided a priori as described in the analysis plan available at https://osf.io/wpb69/ (not published prior to the identification and selection of systematic reviews).

Risk of bias in systematic reviews

Reporting bias could be related to overall risk of bias in a review. Therefore, four reviewers (JPRL NC, AF, LP), working in pairs, independently assessed the risk of bias in the included systematic reviews using the ROBIS tool[41]. ROBIS comprises 3 phases: 1) assess relevance; 2) identify concerns with review process; 3) judge risk of bias in the review. To assess relevance, we extracted the target question from each review using PICOS acronym (participants, interventions, comparisons, outcomes) or equivalents for etiological questions (participants, exposure, comparisons, outcomes). In phase 2, we assessed the risk of bias in four domains related to the review process: (1) study eligibility criteria; (2) identification and selection of studies; (3) data collection and study appraisal; and (4) synthesis and findings. Questions included in each of the four domains are available in S3 Table. Questions were answered as

"Yes", "Probably Yes", "Probably No", "No" and "No Information", with "Yes" indicating low risk of bias. In phase 3, we summarized the concerns identified in each domain during the phase 2 and risk of bias in the review as: low, high, or unclear. Further details on the ROBIS tool are described elsewhere[41].

Risk of reporting bias in the body of evidence

For each meta-analysis performed in the selected systematic reviews, we assessed the extent of reporting bias in the included literature via small study effect[42] and excess significance tests [88]. To perform these tests, we extracted necessary data [*e.g.*, effect size, confidence intervals, sample size, and number of events (deaths)] for each primary study included in the main meta-analysis performed in the systematic reviews. We also used these data to re-perform the meta-analyses (*i.e.*, using random effect models, which was used in the majority of the original meta-analyses). We did this to describe the number of meta-analyses with nominally statistical significant results at P<0.05 (S1 Text).

Small study effect test (also known as regression asymmetry test proposed by Egger et al.) evaluates whether smaller studies tend to overestimate the effect size estimates compared to larger studies. For this matter, the test evaluates whether the association between effect size (*e.g.*, relative risk, odds ratio) and precision (standard error) is greater than might be expected by chance. We considered a P value <0.10 as a statistical significance threshold for small study effect bias (*i.e.,* suggesting evidence of reporting bias), as initially proposed by Egger et al.[42, 89] and consistently used in the literature[42, 66, 81, 87, 90, 91].

Excess significance test evaluates whether the number of observed (O) studies with statistically significant results differs from the number of studies expected (E) in a given body of evidence with no reporting biases. The E in each meta-analysis was obtained from the sum of power estimates of each primary study. The power estimate of each primary study depends on the plausible causal effect of each

research area (*e.g.,* smoking and cardiovascular mortality), which was assumed to be the effect of the most precise individual study (smaller standard error) in each meta-analysis[88]. We considered P<0.10 (one-side P <0.05 for O>E) as a statistical significance threshold for excess significance bias[43, 88]. The excess significance is reported as a proportion of studies, with the higher proportion indicating more excess significance (O>E), and, thus, more evidence of reporting bias.

Due to low power of these bias tests, we performed a sensitivity analysis excluding meta-analysis with less than 10 studies to analyze the impact in the results. We also performed a sensitivity analysis excluding small individual studies (less than 200 deaths) within meta-analysis to evaluate whether results reflect reporting bias among small studies only. We performed all statistical analyses using Stata version 15.0 (College Station, TX).

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SUPPORTING MATERIAL

MATERIAL AND METHODS

We searched Medline, Embase, Cochrane Methodology Register Database, PsycINFO, and Web of Science for systematic reviews published between 2010 and 2016. We restricted our search to recent systematic reviews for several reasons. These systematic reviews belong to a "birth cohort" of systematic reviews published after the launch of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and are expected to have lower risk of bias. As we were interested in comparing levels of reporting bias across different research areas, this restriction may have reduced confounding due to date of publication.

We restricted the search, as well as the successive phases of our study, on systematic reviews aiming to investigate the associations of key health-related behaviors [physical activity, and sedentary behavior, alcohol, smoking, diet (fat, fruits and vegetables, salt, and sugar)] and statins with cardiovascular and all-cause mortality. We used the following keywords to search the literature, filtering by study design ("systematic reviews" AND "meta-analysis"):

Physical Activity:

(((“physical inactivity” OR “physical activity” OR motor activity OR “physical exercise” OR exercise OR MVPA OR walking OR cycling OR “aerobic exercise”))) AND (((death) OR cardiovascular mortality) OR all-cause mortality);

Sedentary Behavior:

(((sedentary behavior OR sedentary behaviour OR sedentary lifestyle OR “sedentary time” OR “sitting time” OR “television viewing” OR “TV” OR “screen time” OR driving OR "screen based" OR “video game” OR computer))) AND (((death) OR cardiovascular mortality) OR all-cause mortality);

Alcohol Intake:

((“ethanol” OR “alcohol” OR “alcoholic beverages” OR “drinking behaviour” OR “alcohol drinking” OR “drink*” OR “liquor*” OR “ethanol intake” OR “alcohol* drink*” OR “ethanol drink*”)) AND (((death) OR cardiovascular mortality) OR all-cause mortality);

Smoking:

((tobacco OR smoking OR cigarette)) AND (((death) OR cardiovascular mortality) OR all-cause mortality);

Diet:

Fat Intake: (((dietary fat OR omega 6 OR omega 3 OR fat intake OR fat OR saturated fat OR trans-fat OR monounsaturated fat OR polyunsaturated))) AND (((death) OR cardiovascular mortality) OR all-cause mortality)

Sugar Intake: ((“sugar-sweetened beverages” OR "sugar*" OR sucrose OR fructose OR "dietary sucrose" OR "soft drink*" OR "refined sugar")) AND (((death) OR cardiovascular mortality) OR all-cause mortality).

Salt Intake: ((Salt intake OR sodium intake OR na intake OR high salt diet)) AND (((death) OR cardiovascular mortality) OR all-cause mortality)

Fruit and Vegetables: ((Fruit OR Citrus OR Vegetables OR fruit* OR vegetable* OR orange* OR apple* OR pear OR pears OR grape or grapes OR banana* OR berry or berries OR citrus OR carrot* OR greens OR cabbage* OR brassica* OR blackberr* OR blueberr* OR cranberr* OR guava* OR kiwi* OR lingonberr* OR mango* OR melon* OR papaya* OR pineapple* OR raspberr* OR strawberr* OR tomato* OR potato* OR

onion* OR grapefruit* OR mandarin* OR satsuma* OR tangerine* OR plum OR plums OR apricot* OR cherry OR cherries OR nectarine* OR peach OR peaches)) AND (((death) OR cardiovascular mortality) OR all-cause mortality);

Statin:

((statins OR statin OR “lipid lowering” OR Pravastatin OR Atorvastatin OR Lipitor OR Torvast OR Fluvastatin OR “Hydroxymethylglutaryl-CoA Reductase Inhibitors" OR Simvastatin OR Rosuvastatin OR Lovastatin OR Mevastatin OR Cerivastatin)) AND (((death) OR cardiovascular mortality) OR all-cause mortality).

We imported all the studies retrieved into the EndNote X7 to remove duplicates. Two reviewers independently (LFMR and JPRL) examined the title and abstract of all records and disagreements were settled by a third reviewer (THS). The same scheme was used to check for the eligibility criteria in the full-text of the selected records in the previous stage.

To be included in the final sample systematic reviews had to meet the following eligibility criteria:

(i) Sought to investigate an exposure-outcome association in a general healthy adult population. Exposures-outcome associations were restricted to studies on (physical activity OR sedentary behavior OR alcohol OR smoking OR diet OR statins) AND (cardiovascular mortality OR all-cause mortality). We excluded reviews of prognostic studies with diseased population. For statins only, we included systematic reviews of adult’s population with CVD risk factors, but not for those with history of CVD. Use of statins is recommend for the primary prevention in adults with the following conditions: 1) 40 to 75 years; 2) One or more CVD risk factors (*i.e.*, dyslipidemia, diabetes, hypertension, or smoking); 3) with calculated 10-year risk of a cardiovascular event of 10% or

greater (https://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement175/statin-use-in-adults-preventive-medication1)

(ii) Searched individual studies through a systematic-search of literature and performed a meta-analysis (*i.e.*, weighted summary effect size) using results from individual studies; We excluded narrative reviews, systematic reviews without meta-analysis, network meta-analysis, and individual patient data meta-analyses because these sorts of reviews did not provide data required to perform tests to identify bias in the body of the evidence.

(iii) Selected only observational studies (cohort and case-control studies) if a health-related behavior meta-analysis, otherwise only randomized controlled trials if a statins meta-analysis; Since RCT cannot always be ethically or logistically conducted, we restricted to systematic reviews of observational studies assessing associations between health-related behavior and cardiovascular and all-cause mortality. On the other hand, meta-analyses for statins were restricted to RCT.

(iv) Reported data from each individual study included in the meta-analysis; Several data (see data extraction section below) regarding the primary studies included in the meta-analyses are needed to evaluate the risk of bias the body of evidence via small study effects and excess significance tests. We excluded systematic reviews that did not report at least the maximally adjusted effect size with its respective 95% CI for each primary study included in the main meta-analysis.

We included only systematic reviews in English, Portuguese, and Spanish language.

Data extraction

For each systematic review, we extracted the following information: first author, year of publication, exposure-outcome association, number of included studies, sum of total sample size and

number of events (sum of all primary studies included) and weighted summary effect size with its 95% confidence intervals (95% CI).

We also extracted the following information from each primary study included in the meta-analyses: study design (RCT, cohort, or case-control), number of events and total sample size (for cohort and RCT studies), number of cases and controls (for case-control studies), maximally adjusted effect size (reported as odds ratio for case-control studies and hazard ratio or mortality ratio for cohort and RCT) with its respectively 95% CI and P values. To obtain these data we first searched in the systematic review. If these data were not available, we contacted the first author of the systematic review and, if necessary, extracted data from the original studies. In case of lack of clarity in the information presented in a meta-analysis, authors were directly contacted to resolve any unclear points. Data extraction was performed by trained research assistants and reviewed by one investigator (LR).

Data Analysis

We re-performed each meta-analysis (*i.e.*, using random effect models) conducted in the systematic reviews in order to estimate summary effect measures and its 95% confidence intervals. We included only one estimate per primary study in the meta-analysis. Whenever effects were not available for the total sample size of the primary study (*e.g.*, relative risks and 95% CI were provided separated by sex), we performed a meta-analysis using fixed effect models within stratum-categories. Finally, RR and 95% CI from fixed effect models were included in the meta-analysis.

Table S1: List of excluded studies and reasons for exclusion, by research area.

Reference	Reason for exclusion
Physical activity	
Dahabreh IJ, Paulus JK. Association of episodic physical and sexual activity with triggering of acute cardiac events: systematic review and meta-analysis. JAMA 2011;305(12):1225-33. doi: 10.1001/jama.2011.336	Other exposure
Kivimaki M, Nyberg ST, Fransson EI, et al. Associations of job strain and lifestyle risk factors with risk of coronary artery disease: a meta-analysis of individual participant data. CMAJ. 2013;185(9):763-9. doi: 10.1503/cmaj.121735	Other exposure
Zhang Y, Hu G. Dietary Pattern, Lifestyle Factors, and Cardiovascular Diseases. Current Nutrition Reports 2012;1(2):64-72.	Other exposure
Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. The Lancet 2016;388(10051):1302-10.	Other exposure
Reimers CD, Knapp G, Reimers AK. Does physical activity increase life expectancy? A review of the literature. Journal of Aging Research 2012;2012(243958)	Not systematic review
Oja P, Titze S, Bauman A, et al. Health benefits of cycling: a systematic review. Scandinavian Journal of Medicine & Science in Sports 2011;21(4):496-509. doi: 10.1111/j.1600-0838.2011.01299.x	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Li J, Loerbroks A, Angerer P. Physical activity and risk of cardiovascular disease: what does the new epidemiological evidence show? Current Opinion in Cardiology 2013;28(5):575-83. doi: 10.1097/HCO.0b013e328364289c	Other outcome
Koba S, Tanaka H, Maruyama C, et al. Physical Activity in the Japan Population: Association with Blood Lipid Levels and Effects in Reducing Cardiovascular and All-Cause Mortality. Journal of Atherosclerosis and Thrombosis 2011;18(10):833-45.	Not systematic review

Fogelholm M. Physical activity, fitness and fatness: relations to mortality, morbidity and disease risk factors. A systematic review. Obesity Reviews 2010;11(3):202-21. doi: 10.1111/j.1467-789X.2009.00653.x	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Hartley L, Lee MS, Kwong JSW, et al. Qigong for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2015(6) doi: 10.1002/14651858.CD010390.pub2	Other outcome
Milton K, Macniven R, Bauman A. Review of the epidemiological evidence for physical activity and health from low-and middle-income countries. Global Public Health 2014;9(4):369-81. doi: 10.1080/17441692.2014.894548	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Zheng G, Huang M, Liu F, et al. Tai Chi Chuan for the primary prevention of stroke in middle-aged and elderly adults: A systematic review. Evidence-based Complementary and Alternative Medicine 2015;2015(742152)	Other outcome
Hartley L, Flowers N, Lee MS, et al. Tai chi for primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2014; (4). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010366.pub2/abstract.	Other outcome
Goodman JM, Burr JF, Banks L, et al. The Acute Risks of Exercise in Apparently Healthy Adults and Relevance for Prevention of Cardiovascular Events. Canadian Journal of Cardiology 2016;32(4):523-32. doi: 10.1016/j.cjca.2016.01.019	Other exposure
Yerrakalva D, Mullis R, Mant J. The associations of "fatness," "fitness," and physical activity with all-cause mortality in older adults: A systematic review. Obesity 2015;23(10):1944-56. doi: 10.1002/oby.21181	Other exposure
Liu B, Hu X, Zhang Q, et al. Usual walking speed and all-cause mortality risk in older people: A systematic review and meta-analysis. Gait and Posture 2016;44:172-77.	Other exposure
Hartley L, Dyakova M, Holmes J, et al. Yoga for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2014;5:Cd010072. doi: 10.1002/14651858.CD010072.pub2 [published Online First: 2014/05/16]	Other outcome
Sedentary behavior	
Rhodes RE, Mark RS, Temmel CP. Adult sedentary behavior: a systematic review. Am J Prev Med 2012;42(3):e3-28. doi: 10.1016/j.amepre.2011.10.020	Other outcome

Rezende LFM, de Sa TH, Mielke GI, et al. All-Cause Mortality Attributable to Sitting Time Analysis of 54 Countries Worldwide. American Journal of Preventive Medicine 2016;51(2):253-63. doi: 10.1016/j.amepre.2016.01.022	Not systematic review
Kivimaki M, Nyberg ST, Fransson EI, et al. Associations of job strain and lifestyle risk factors with risk of coronary artery disease: a meta-analysis of individual participant data. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 2013;185(9):763-9. doi: 10.1503/cmaj.121735	Other exposure
Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet (London, England) 2016;388(10051):1302-10. doi: 10.1016/s0140-6736(16)30370-1	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
van Uffelen JG, Wong J, Chau JY, et al. Occupational sitting and health risks: a systematic review. Am J Prev Med 2010;39(4):379-88. doi: 10.1016/j.amepre.2010.05.024	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Rezende LF, Rey-Lopez JP, Rodrigues Matsudo VK, et al. Sedentary behavior and health outcomes among older adults: a systematic review. BMC public health 2014;14 doi: 10.1186/1471-2458-14-333	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Proper KI, Singh AS, van Mechelen W, et al. Sedentary behaviors and health outcomes among adults: a systematic review of prospective studies. Am J Prev Med 2011;40(2):174-82. doi: 10.1016/j.amepre.2010.10.015	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Thorp AA, Owen N, Neuhaus M, et al. Sedentary behaviors and subsequent health outcomes in adults a systematic review of longitudinal studies, 1996-2011. Am J Prev Med 2011;41(2):207-15. doi: 10.1016/j.amepre.2011.05.004	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Biddle SJ, Bennie JA, Bauman AE, et al. Too much sitting and all-cause mortality: is there a causal link? BMC public health 2016;16:635. doi: 10.1186/s12889-016-3307-3	Not systematic review
Alcohol	
Liu PM, Dosieah S, Zheng HS, et al. [Alcohol consumption and coronary heart disease in Eastern Asian men: a meta-analysis of prospective cohort studies]. Zhonghua xin xue guan bing za zhi 2010;38(11):1038-44	Chinese language

Liu PM, Dosieah S, Luo NS, et al. [Alcohol intake and stroke in Eastern Asian men:a systemic review and meta-analysis of 17 prospective cohort studies]. Zhonghua yi xue za zhi 2010;90(40):2834-8.	Chinese language
Costanzo S, Di Castelnuovo A, Donati MB, et al. Alcohol Consumption and Mortality in Patients With Cardiovascular Disease A Meta-Analysis. Journal of the American College of Cardiology 2010;55(13):1339-47.	Clinical population
Jin M, Cai S, Guo J, et al. Alcohol drinking and all cancer mortality: a meta-analysis. Annals of Oncology 2013;24(3):807-16. doi: 10.1093/annonc/mds508	Other outcome
Branas CC, Han S, Wiebe DJ. Alcohol Use and Firearm Violence. Epidemiologic Reviews 2016;38(1):32-45. doi: 10.1093/epirev/mxv010	Other outcome
Roerecke M, Rehm J. Alcohol use disorders and mortality: a systematic review and meta-analysis. Addiction 2013;108(9):1562-78. doi: 10.1111/add.12231	Clinical population
Darvishi N, Farhadi M, Haghtalab T, et al. Alcohol-Related Risk of Suicidal Ideation, Suicide Attempt, and Completed Suicide: A Meta-Analysis. Plos One 2015;10(5) doi: 10.1371/journal.pone.0126870	Other outcome
Huang C, Zhan J, Liu YJ, et al. Association between alcohol consumption and risk of cardiovascular disease and all-cause mortality in patients with hypertension: a meta-analysis of prospective cohort studies. Mayo Clinic proceedings 2014;89(9):1201-10. doi: 10.1016/j.mayocp.2014.05.014	Clinical population
McQueen J, Howe TE, Allan L, et al. Brief interventions for heavy alcohol users admitted to general hospital wards. Cochrane Database of Systematic Reviews 2011;(8).http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD005191.pub3/abstract.	Clinical population
Fernandez-Sola J. Cardiovascular risks and benefits of moderate and heavy alcohol consumption. Nature Reviews Cardiology 2015;12(10):576-87. doi: 10.1038/nrcardio.2015.91	Not systematic review
Crippa A, Discacciati A, Larsson SC, et al. Coffee consumption and mortality from all causes, cardiovascular disease, and cancer: a dose-response meta-analysis. American journal of epidemiology 2014;180(8):763-75. doi: 10.1093/aje/kwu194	Other exposure
Zhang Y, Hu G. Dietary Pattern, Lifestyle Factors, and Cardiovascular Diseases. Current Nutrition Reports 2012;1(2):64-72. doi: 10.1007/s13668-012-0009-z	Not systematic review
Zhang XY, Shu L, Si CJ, et al. Dietary Patterns, Alcohol Consumption and Risk of Coronary Heart Disease in Adults: A Meta-Analysis. Nutrients 2015;7(8):6582-605. doi: 10.3390/nu708530	Other outcome

Calabria B, Degenhardt L, Hall W, et al. Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. Drug and alcohol review 2010;29(3):318-30. doi: 10.1111/j.1465-3362.2009.00149.x	Other exposure
Wang C, Xue H, Wang Q, et al. Effect of drinking on all-cause mortality in women compared with men: a meta-analysis. Journal of women's health (2002) 2014;23(5):373-81. doi: 10.1089/jwh.2013.4414	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Probst C, Roerecke M, Behrendt S, et al. Gender differences in socioeconomic inequality of alcohol-attributable mortality: A systematic review and meta-analysis. Drug and alcohol review 2015;34(3):267-77. doi: 10.1111/dar.12184	Other exposure
McCambridge J, Hartwell G. Has industry funding biased studies of the protective effects of alcohol on cardiovascular disease? A preliminary investigation of prospective cohort studies. Drug and alcohol review 2015;34(1):58-66. doi: 10.1111/dar.12125	Not systematic review
Hansel B, Kontush A, Bruckert E. Is a cardioprotective action of alcohol a myth? Current Opinion in Cardiology 2012;27(5):550-55. doi: 10.1097/HCO.0b013e328356dc30	Other outcome
Rehm J, Shield KD, Roerecke M, et al. Modelling the impact of alcohol consumption on cardiovascular disease mortality for comparative risk assessments: an overview. BMC public health 2016;16 doi: 10.1186/s12889-016-3026-9	Not systematic review
Colpani V, Baena C, Jaspers L, et al. Modifiable risk factors for prevention of cardiovascular disease and mortality in middle-aged women: Systematic review and meta-analysis. Circulation 2015;131	Abstract only
Uthman OA, Hartley L, Rees K, et al. Multiple risk factor interventions for primary prevention of cardiovascular disease in low- and middle-income countries. Cochrane Database of Systematic Reviews 2015; (8). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011163.pub2/abstract.	Other outcome
Grosso G, Yang J, Marventano S, et al. Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiologic studies. American Journal of Clinical Nutrition 2015;101(4):783-93. doi: 10.3945/ajcn.114.099515	Other outcome
Roerecke M, Gual A, Rehm J. Reduction of Alcohol Consumption and Subsequent Mortality in Alcohol Use Disorders: Systematic Review and Meta-Analyses. Journal of Clinical Psychiatry 2013;74(12):E1181-U102. doi: 10.4088/JCP.13r08379	Clinical population

Laramee P, Leonard S, Buchanan-Hughes A, et al. Risk of All-Cause Mortality in Alcohol-Dependent Individuals: A Systematic Literature Review and Meta-Analysis. Ebiomedicine 2015;2(10):1394-404. doi: 10.1016/j.ebiom.2015.08.040	Clinical population
Shield KD, Rehm J. Russia-specific relative risks and their effects on the estimated alcohol-attributable burden of disease. BMC public health 2015;15 doi: 10.1186/s12889-015-1818-y	Not systematic review
Roerecke M, Rehm J. The cardioprotective association of average alcohol consumption and ischaemic heart disease: a systematic review and meta-analysis. Addiction 2012;107(7):1246-60. doi: 10.1111/j.1360-0443.2012.03780.x	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Smoking	
Mons U, Muezzinler A, Gellert C, et al. Impact of smoking and smoking cessation on cardiovascular events and mortality among older adults: meta-analysis of individual participant data from prospective cohort studies of the CHANCES consortium. Bmj-British Medical Journal 2015;350 doi: 10.1136/bmj.h1551	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Murakami Y. Meta-analyses using individual participant data from cardiovascular cohort studies in Japan: current status and future directions. Journal of epidemiology / Japan Epidemiological Association 2014;24(2):96-101.	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Colpani V, Baena C, Jaspers L, et al. Modifiable risk factors for prevention of cardiovascular disease and mortality in middle-aged women: Systematic review and meta-analysis. Circulation 2015;131	Abstract only
Woodcock J, Franco OH, Orsini N, et al. Non-vigorous physical activity and all-cause mortality: Systematic review and meta-analysis of cohort studies. International Journal of Epidemiology 2011;40(1):121-38.	Other exposure
Sinha DN, Palipudi KM, Gupta PC, et al. Smokeless tobacco use: A meta-analysis of risk and attributable mortality estimates for India. Indian Journal of Cancer 2014;51(5):73-77. doi: 10.4103/0019-509x.147477	Not systematic review
Silva Vde L, Cesse EA, de Albuquerque Mde F. Social determinants of death among the elderly: a systematic literature review. Revista brasileira de epidemiologia. 2014;17 Suppl 2:178-93	Other exposure

Chang CM, Corey CG, Rostron BL, et al. Systematic review of cigar smoking and all cause and smoking related mortality. BMC public health 2015;15 doi: 10.1186/s12889-015-1617-5	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Lee PN. The effect of reducing the number of cigarettes smoked on risk of lung cancer, COPD, cardiovascular disease and FEV1 - A review. Regulatory Toxicology and Pharmacology 2013;67(3):372-81. doi: 10.1016/j.yrtph.2013.08.016	Not systematic review
Waziry R, Jawad M, Ballout RA, et al. The effects of waterpipe tobacco smoking on health outcomes: an updated systematic review and meta-analysis. Int J Epidemiol 2016 doi: 10.1093/ije/dyw021	Other outcome
Diet	
Aburto NJ, Ziolkovska A, Hooper L, et al. Effect of lower sodium intake on health: Systematic review and meta-analyses. BMJ (Online) 2013;346(7903)	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Schwab U, Lauritzen L, Tholstrup T, et al. Effect of the amount and type of dietary fat on cardiometabolic risk factors and risk of developing type 2 diabetes, cardiovascular diseases, and cancer: a systematic review. Food & nutrition research 2014;58 doi: 10.3402/fnr.v58.25145	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Harcombe Z, Baker JS, Davies B. Evidence from prospective cohort studies did not support the introduction of dietary fat guidelines in 1977 and 1983: a systematic review. Br J Sports Med 2016 doi: 10.1136/bjsports-2016-096409	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Grosso G, Marventano S, Yang J, et al. A Comprehensive Meta-analysis on Evidence of Mediterranean Diet and Cardiovascular Disease: Are Individual Components Equal? Critical reviews in food science and nutrition 2015:0. doi: 10.1080/10408398.2015.1107021	Other exposure
Mayhew AJ, de Souza RJ, Meyre D, et al. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. Br J Nutr 2016;115(2):212-25. doi: 10.1017/s0007114515004316	Other exposure
Wu YH, Qian YF, Pan YW, et al. Association between dietary fiber intake and risk of coronary heart disease: A meta-analysis. Clinical Nutrition 2015;34(4):603-11. doi: 10.1016/j.clnu.2014.05.009	Other exposure

Rizos EC, Ntzani EE, Bika E, et al. Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: A systematic review and meta-analysis. JAMA - Journal of the American Medical Association 2012;308(10):1024-33	Clinical population
Li F, Hou LN, Chen W, et al. Associations of dietary patterns with the risk of all-cause, CVD and stroke mortality: A meta-Analysis of prospective cohort studies. British Journal of Nutrition 2015;113(1):16-24.	Other exposure
Hunter JE, Zhang J, Kris-Etherton PM. Cardiovascular disease risk of dietary stearic acid compared with trans, other saturated, and unsaturated fatty acids: a systematic review. Am J Clin Nutr 2010;91(1):46-63. doi: 10.3945/ajcn.2009.27661	Other outcome
Gan Y, Tong XY, Li LQ, et al. Consumption of fruit and vegetable and risk of coronary heart disease: A meta-analysis of prospective cohort studies. International Journal of Cardiology 2015;183:129-37. doi: 10.1016/j.ijcard.2015.01.077	Other outcome
Brennan SF, Woodside JV, Lunny PM, et al. Dietary fat and breast cancer mortality: a systematic review and meta-analysis. Critical reviews in food science and nutrition 2015 doi: 10.1080/10408398.2012.724481	Other outcome
Kim Y, Je Y. Dietary fiber intake and total mortality: A meta-analysis of prospective cohort studies. American journal of epidemiology 2014;180(6):565-73.	Other exposure
Hartley L, May MD, Loveman E, et al. Dietary fibre for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2016; (1). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011472.pub2/abstract.	Other exposure
Zhang XY, Shu L, Si CJ, et al. Dietary Patterns, Alcohol Consumption and Risk of Coronary Heart Disease in Adults: A Meta-Analysis. Nutrients 2015;7(8):6582-605. doi: 10.3390/nu7085300	Other exposure
Marik PE, Flemmer M. Do Dietary Supplements Have Beneficial Health Effects in Industrialized Nations: What Is the Evidence? Journal of Parenteral and Enteral Nutrition 2012;36(2):159-68. doi: 10.1177/0148607111416485	Not systematic review
Sonestedt E, Overby NC, Laaksonen DE, et al. Does high sugar consumption exacerbate cardiometabolic risk factors and increase the risk of type 2 diabetes and cardiovascular disease? Food & nutrition research 2012;56 doi: 10.3402/fnr.v56i0.19104	Not systematic review
Aburto NJ, Hanson S, Gutierrez H, et al. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. Bmj-British Medical Journal 2013;346 doi: 10.1136/bmj.f1378	Other exposure

Mozaffarian D, Micha R, Wallace S. Effects on coronary heart disease of increasing polyunsaturated fat in place of saturated fat: a systematic review and meta-analysis of randomized controlled trials. PLoS medicine 2010;7(3):e1000252. doi: 10.1371/journal.pmed.1000252	Clinical population
Bloomfield HE, Koeller E, Greer N, et al. Effects on Health Outcomes of a Mediterranean Diet With No Restriction on Fat Intake: A Systematic Review and Meta-analysis. Ann Intern Med 2016;165(7):491-500. doi: 10.7326/m16-0361	Other exposure
Shin JY, Xun P, Nakamura Y, et al. Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis. American Journal of Clinical Nutrition 2013;98(1):146-59. doi: 10.3945/ajcn.112.051318	Other exposure
Zhao LG, Sun JW, Yang Y, et al. Fish consumption and all-cause mortality: a meta-analysis of cohort studies. European Journal of Clinical Nutrition 2016;70(2):155-61. doi: 10.1038/ejcn.2015.72	Other exposure
Aucoin M, Cooley K, Knee C, et al. Fish-Derived Omega-3 Fatty Acids and Prostate Cancer: A Systematic Review. Integrative cancer therapies 2016 doi: 10.1177/1534735416656052	Other outcome
O'Sullivan TA, Hafekost K, Mitrou F, et al. Food sources of saturated fat and the association with mortality: a meta-analysis. American journal of public health 2013;103(9):e31-42. doi: 10.2105/ajph.2013.301492	Other exposure
Pedersen AN, Kondrup J, Borsheim E. Health effects of protein intake in healthy adults: a systematic literature review. Food & nutrition research 2013;57 doi: 10.3402/fnr.v57i0.21245	Other exposure
Wang Q, Afshin A, Yakoob MY, et al. Impact of Nonoptimal Intakes of Saturated, Polyunsaturated, and Trans Fat on Global Burdens of Coronary Heart Disease. Journal of the American Heart Association 2016;5(1) doi: 10.1161/jaha.115.002891	Not systematic review
Hartley L, Igbinedion E, Holmes J, et al. Increased consumption of fruit and vegetables for the primary prevention of cardiovascular diseases. Cochrane Database Syst Rev 2013;6:Cd009874. doi: 10.1002/14651858.CD009874.pub2	Other outcome
Pimpin L, Wu JHY, Haskelberg H, et al. Is butter back? A systematic review and meta-analysis of butter consumption and risk of cardiovascular disease, diabetes, and total mortality. PLoS ONE 2016;11(6)	Other exposure

Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J, et al. Long chain omega-3 fatty acids and cardiovascular disease: A systematic review. British Journal of Nutrition 2012;107(SUPPL. 2):S201-S13.	Clinical population
D'Alessandro A, De Pergola G, Silvestris F. Mediterranean Diet and cancer risk: an open issue. International Journal of Food Sciences and Nutrition 2016;67(6):593-605. doi: 10.1080/09637486.2016.1191444	Other outcome
Rees K, Hartley L, Flowers N, et al. 'Mediterranean' dietary pattern for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013;8:Cd009825. doi: 10.1002/14651858.CD009825.pub2	Other exposure
Soedamah-Muthu SS, Ding EL, Al-Delaimy WK, et al. Milk and dairy consumption and incidence of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. Am J Clin Nutr 2011;93(1):158-71. doi: 10.3945/ajcn.2010.29866	Other exposure
Ramsden CE, Hibbeln JR, Majchrzak SF, et al. N-6 Fatty acid-specific and mixed polyunsaturate dietary interventions have different effects on CHD risk: A meta-analysis of randomised controlled trials. British Journal of Nutrition 2010;104(11):1586-600.	Clinical population
Luo C, Zhang Y, Ding Y, et al. Nut consumption and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis. Am J Clin Nutr 2014;100(1):256-69. doi: 10.3945/ajcn.113.076109	Other exposure
Grosso G, Yang J, Marventano S, et al. Nut consumption on all-cause, cardiovascular, and cancer mortality risk: A systematic review and meta-analysis of epidemiologic studies. American Journal of Clinical Nutrition 2015;101(4):783-93.	Other exposure
Kotwal S, Jun M, Sullivan D, et al. Omega 3 fatty acids and cardiovascular outcomes: Systematic review and meta-analysis. Circulation: Cardiovascular Quality and Outcomes 2012;5(6):808-18.	Clinical population
Al-Khudairy L, Hartley L, Clar C, et al. Omega 6 fatty acids for the primary prevention of cardiovascular disease. Cochrane Database of Systematic Reviews 2015; (11). http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011094.pub2/abstract.	Other outcome
Kruse LG, Ogletree RL, Jr. Omega-3 fatty acids and cardiovascular risk. Journal of the Mississippi State Medical Association 2013;54(6):156-7.	Clinical population
Price HC, Simmons RK. Primary prevention of CVD: diet. BMJ clinical evidence 2011;2011	Not systematic review

Larsson SC, Orsini N. Red Meat and Processed Meat Consumption and All-Cause Mortality: A Meta-Analysis. American journal of epidemiology 2014;179(3):282-89. doi: 10.1093/aje/kwt261	Other exposure
Adler AJ, Taylor F, Martin N, et al. Reduced dietary salt for the prevention of cardiovascular disease. Cochrane Database Syst Rev 2014;12:Cd009217. doi: 10.1002/14651858.CD009217.pub3	Clinical population
Hooper L, Summerbell CD, Thompson R, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Cochrane Database of Systematic Reviews 2012(5) doi: 10.1002/14651858.CD002137.pub3	Clinical population
Hooper L, Martin N, Abdelhamid A, et al. Reduction in saturated fat intake for cardiovascular disease. Cochrane Database Syst Rev 2015(6):Cd011737. doi: 10.1002/14651858.cd011737	Clinical population
van den Brandt PA, Schouten LJ. Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: a cohort study and meta-analysis. Int J Epidemiol 2015;44(3):1038-49. doi: 10.1093/ije/dyv039	Other exposure
Lorente-Cebrian S, Costa AG, Navas-Carretero S, et al. Role of omega-3 fatty acids in obesity, metabolic syndrome, and cardiovascular diseases: a review of the evidence. Journal of physiology and biochemistry 2013;69(3):633-51. doi: 10.1007/s13105-013-0265-4	Not systematic review
Engell RE, Sanman E, Lim SS, et al. Seafood omega-3 intake and risk of coronary heart disease death: an updated meta-analysis with implications for attributable burden. Lancet (London, England) 2013;381:45-45.	Abstract only
Sethi A, Bajaj A, Khosla S, et al. Statin use mitigate the benefit of omega-3 fatty acids supplementation - A meta-regression of randomized trials. American Journal of Therapeutics 2016;23(3):e737-e48.	Other exposure
Zhang C, Qin YY, Wei X, et al. Tea consumption and risk of cardiovascular outcomes and total mortality: a systematic review and meta-analysis of prospective observational studies. European Journal of Epidemiology 2015;30(2):103-13. doi: 10.1007/s10654-014-9960-x	Other exposure
Elwood PC, Pickering JE, Givens DI, et al. The Consumption of Milk and Dairy Foods and the Incidence of Vascular Disease and Diabetes: An Overview of the Evidence. Lipids 2010;45(10):925-39. doi: 10.1007/s11745-010-3412-5	Other exposure

The role of Mediterranean type of diet on the development of cancer and cardiovascular disease, in the elderly: a systematic review	Other exposure
Johnson C, Raj TS, Trieu K, et al. The Science of Salt: A Systematic Review of Quality Clinical Salt Outcome Studies June 2014 to May 2015. Journal of Clinical Hypertension 2016;18(9):832-39.	Other outcome
Lippi G, Mattiuzzi C, Franchini M. Vegetables intake and venous thromboembolism: a systematic review. Blood Coagulation & Fibrinolysis 2016;27(3):242-45. doi: 10.1097/mbc.0000000000000427	Other outcome
Elamin MB, Abu Elnour NO, Elamin KB, et al. Vitamin D and cardiovascular outcomes: A systematic review and meta-analysis. Journal of Clinical Endocrinology and Metabolism 2011;96(7):1931-42.	Other exposure
Wei HL, Gao Z, Liang R, et al. Whole-grain consumption and the risk of all-cause, CVD and cancer mortality: a meta-analysis of prospective cohort studies. British Journal of Nutrition 2016;116(3):514-25. doi: 10.1017/s0007114516001975	Other exposure
Statin	
Alberton M, Wu P, Druyts E, et al. Adverse events associated with individual statin treatments for cardiovascular disease: an indirect comparison meta-analysis. QJM : monthly journal of the Association of Physicians 2012;105(2):145-57. doi: 10.1093/qjmed/hcr158	Other outcome
Silverman MG, Ference BA, Im K, et al. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. Jama 2016;316(12):1289-97. doi: 10.1001/jama.2016.13985	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Danaei G, Tavakkoli M, Hernan MA. Bias in Observational Studies of Prevalent Users: Lessons for Comparative Effectiveness Research From a Meta-Analysis of Statins. American journal of epidemiology 2012;175(4):250-62. doi: 10.1093/aje/kwr301	Clinical population
Hourcade-Potelleret F, Laporte S, Lehnert V, et al. Clinical benefit from pharmacological elevation of high-density lipoprotein cholesterol: meta-regression analysis. Heart (British Cardiac Society) 2015;101(11):847-53. doi: 10.1136/heartjnl-2014-306691	Clinical population
Naci H, Brugts JJ, Fleurence R, et al. Comparative benefits of statins in the primary and secondary prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. European journal of preventive cardiology 2013;20(4):641-57. doi: 10.1177/2047487313480435	Data Extraction: did not provide data from individual studies or did not perform meta-analysis

Cifkova R, Krajcoviechova A. Dyslipidemia and Cardiovascular Disease in Women. Current Cardiology Reports 2015;17(7)	Not systematic review
Thomopoulos C, Skalis G, Michalopoulou H, et al. Effect of low-density lipoprotein cholesterol lowering by ezetimibe/simvastatin on outcome incidence: Overview, meta-analyses, and meta-regression analyses of randomized trials. Clinical Cardiology 2015;38(12):763-69.	Other outcome
Fulcher J, O'Connell R, Voysey M, et al. Efficacy and safety of LDL-lowering therapy among men and women: Meta-analysis of individual data from 174 000 participants in 27 randomised trials. The Lancet 2015;385(9976):1397-405.	Not systematic review
Lu Y, Cheng Z, Zhao Y, et al. Efficacy and safety of long-term treatment with statins for coronary heart disease: A Bayesian network meta-analysis. Atherosclerosis 2016;254:215-27.	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet (London, England) 2010;376(9753):1670-81. doi: 10.1016/s0140-6736(10)61350-5	Not systematic review
Koduri H, Kanmanthareddy A, Akinapelli A, et al. Efficacy of ezetimibe and statin versus statin: A meta-analysis of randomized controlled trials. Journal of the American College of Cardiology 2016;67(13 SUPPL. 1):1884.	Abstract only
Bruckert E, Ferrieres J. Evidence supporting primary prevention of cardiovascular diseases with statins: Gaps between updated clinical results and actual practice. Archives of cardiovascular diseases 2014;107(3):188-200. doi: 10.1016/j.acvd.2014.01.011	Not systematic review
Takagi H, Matsui M, Umemoto T. High-density lipoprotein-dependent effects of statins on the risk of coronary heart disease deaths and events. International Journal of Cardiology 2011;152(3):377-79. doi: 10.1016/j.ijcard.2011.07.071	Not systematic review
Ribeiro RA, Ziegelmann PK, Duncan BB, et al. Impact of statin dose on major cardiovascular events: a mixed treatment comparison meta-analysis involving more than 175,000 patients. Int J Cardiol 2013;166(2):431-9. doi: 10.1016/j.ijcard.2011.10.128	Data Extraction: did not provide data from individual studies or did not perform meta-analysis

Mills EJ, O'Regan C, Eyawo O, et al. Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. Eur Heart J 2011;32(11):1409-15. doi: 10.1093/eurheartj/ehr035	Clinical population
Chan DKY, O'Rourke F, Shen Q, et al. Meta-analysis of the cardiovascular benefits of intensive lipid lowering with statins. Acta Neurologica Scandinavica 2011;124(3):188-95. doi: 10.1111/j.1600-0404.2010.01450.x	Other outcome
Liu G, Zheng XX, Xu YL, et al. Meta-analysis of the effect of statins on mortality in patients with preserved ejection fraction. American Journal of Cardiology 2014;113(7):1198-204.	Clinical population
Hansen MR, Pottegard A, Hrobjartsson A, et al. Modelling of endpoint postponement for all-cause mortality in statin trials. Pharmacoepidemiology and Drug Safety 2015;24:1.	Abstract only
Karlson BW, Palmer MK, Nicholls SJ, et al. Predicting the reduction in risk of cardiovascular events with high-intensity statin treatment: A voyager analysis. Atherosclerosis 2015;241(1):e202-e03.	Abstract only
Sethi A, Bajaj A, Khosla S, et al. Statin use mitigate the benefit of omega-3 fatty acids supplementation - A meta-regression of randomized trials. American Journal of Therapeutics 2016;23(3):e737-e48.	Clinical population
Beri A, Contractor T, Khasnis A, et al. Statins and the reduction of sudden cardiac death: Antiarrhythmic or anti-ischemic effect? American Journal of Cardiovascular Drugs 2010;10(3):155-64.	Not systematic review
Squizzato A, Romualdi E, Dentali F, et al. Statins for acute ischemic stroke. Cochrane database of systematic reviews (Online) 2011(8):CD007551.	Clinical population
Minder CM, Blumenthal RS, Blaha MJ. Statins for primary prevention of cardiovascular disease: The benefits outweigh the risks. Current Opinion in Cardiology 2013;28(5):554-60.	Not systematic review
Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet (London, England) 2012;380(9841):581-90. doi: 10.1016/s0140-6736(12)60367-5	Data Extraction: did not provide data from individual studies or did not perform meta-analysis
Briel M, Vale N, Schwartz GG, et al. Updated evidence on early statin therapy for acute coronary syndromes: meta-analysis of 18 randomized trials involving over 14,000 patients. Int J Cardiol 2012;158(1):93-100. doi: 10.1016/j.ijcard.2011.01.033	Clinical population

Table S2: Summary of reasons for excluding studies during full-text screening, by research area.

	Did not include the exposure of interest	Did not include cardiovascular disease mortality or all-cause mortality outcomes	Did not provide data from individual studies or did not perform meta-analysis	Did not published full-text (abstract only)	Chinese language	Clinical population	It was not a systematic review of literature
Physical activity	41%	29%	18%	-	-	-	12%
Sedentary Behavior	11%	11%	56%	-	-	-	22%
Alcohol	12%	27%	8%	4%	8%	23%	19%
Smoking	22%	11%	33%	11%	-	-	22%
Diet	49%	17%	6%	2%	-	17%	9%
Statins	-	12%	20%	12%	-	28%	28%
Overall	28%	19%	15%	4%	1%	16%	17%

ROBIS: Tool to assess risk of bias in systematic reviews

Phase 2: Identifying concerns with the review process

DOMAIN 1: STUDY ELIGIBILITY CRITERIA	
Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI
Concerns regarding specification of study eligibility criteria	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES	
Describe methods of study identification and selection (e.g. number of reviewers involved):	
2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify relevant reports?	Y/PY/PN/N/NI
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Y/PY/PN/N/NI
2.4 Were restrictions based on date, publication format, or language appropriate?	Y/PY/PN/N/NI
2.5 Were efforts made to minimise error in selection of studies?	Y/PY/PN/N/NI
Concerns regarding methods used to identify and/or select studies	LOW/HIGH/UNCLEAR
Rationale for concern:	

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL	
Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:	
3.1 Were efforts made to minimise error in data collection?	Y/PY/PN/N/NI
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Y/PY/PN/N/NI
3.3 Were all relevant study results collected for use in the synthesis?	Y/PY/PN/N/NI
3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Y/PY/PN/N/NI
3.5 Were efforts made to minimise error in risk of bias assessment?	Y/PY/PN/N/NI
Concerns regarding methods used to collect data and appraise studies Rationale for concern:	LOW/HIGH/UNCLEAR

DOMAIN 4: SYNTHESIS AND FINDINGS	
Describe synthesis methods:	
4.1 Did the synthesis include all studies that it should?	Y/PY/PN/N/NI
4.2 Were all pre-defined analyses reported or departures explained?	Y/PY/PN/N/NI
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Y/PY/PN/N/NI
4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Y/PY/PN/N/NI
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Y/PY/PN/N/NI
4.6 Were biases in primary studies minimal or addressed in the synthesis?	Y/PY/PN/N/NI
Concerns regarding the synthesis and findings Rationale for concern:	LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Phase 3: Judging risk of bias

Summarize the concerns identified during the Phase 2 assessment:

Domain	Concern	Rationale for concern
1. Concerns regarding specification of study eligibility criteria		
2. Concerns regarding methods used to identify and/or select studies		
3. Concerns regarding used to collect data and appraise studies		
4. Concerns regarding the synthesis and findings		

RISK OF BIAS IN THE REVIEW	
Describe whether conclusions were supported by the evidence:	
A. Did the interpretation of findings address all of the concerns identified in Domains 1 to 4?	Y/PY/PN/N/NI
B. Was the relevance of identified studies to the review's research question appropriately considered?	Y/PY/PN/N/NI
C. Did the reviewers avoid emphasizing results on the basis of their statistical significance?	Y/PY/PN/N/NI
Risk of bias in the review	RISK: LOW/HIGH/UNCLEAR

Y=YES, PY=PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

Table S3: Risk of bias in systematic reviews of physical activity, sedentary behaviour, diet, alcohol, smoking and statins using ROBIS tool.

	DOMAIN 1: STUDY ELIGIBILITY						DOMAIN 2: IDENTIFICATION AND SELECTION						DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL						DOMAIN 4: SYNTHESIS AND FINDINGS						
Study	1.1	1.2	1.3	1.4	1.5	Concerns eligibility criteria	2.1	2.2	2.3	2.4	2.5	Concerns selection studies	3.1	3.2	3.3	3.4	3.5	Concerns collection of data	4.1	4.2	4.3	4.4	4.5	4.6	Concerns synthesis
Physical activity																									
Kelly, 2014[1]	Y	PY	Y	Y	PY	LOW	Y	Y	Y	N	Y	HIGH	N	Y	Y	Y	Y	HIGH	Y	Y	PN	Y	PY	Y	HIGH
Samitz, 2011[2]	PY	Y	Y	Y	Y	LOW	Y	Y	Y	Y	PY	LOW	Y	Y	Y	N	N	HIGH	Y	NI	Y	Y	PY	N	HIGH
Woodcock, 2011[3]	PY	Y	Y	PN	Y	HIGH	Y	Y	N	Y	PY	HIGH	NI	PY	Y	Y	NI	UNCLEAR	Y	NI	Y	Y	Y	Y	LOW
Hupin, 2015[4]	PY	Y	Y	PY	PY	LOW	Y	Y	PN	N	PY	HIGH	NI	Y	Y	Y	NI	UNCLEAR	Y	NI	Y	Y	Y	PY	LOW
Sedentary behaviour																									
Biswas, 2015[5]	PY	Y	Y	Y	PY	LOW	Y	Y	Y	N	PY	HIGH	PY	Y	Y	Y	Y	LOW	Y	NI	N	Y	N	N	HIGH
Chau, 2013[6]	PY	Y	Y	PN	PY	HIGH	Y	Y	PN	N	NI	HIGH	PY	Y	Y	PY	Y	LOW	Y	NI	Y	Y	N	Y	HIGH
Grontved, 2011[7]	PY	PY	PY	Y	Y	LOW	Y	Y	PY	N	NI	HIGH	PY	Y	Y	N	NI	HIGH	Y	NI	Y	Y	Y	N	HIGH
Wilmot, 2012[8]	PY	PN	PN	Y	PY	HIGH	Y	Y	N	N	Y	HIGH	PY	Y	Y	Y	Y	LOW	Y	NI	N	Y	PN	N	HIGH
Ford, 2012[9]	PY	PN	PN	Y	PY	HIGH	N	Y	Y	N	NI	HIGH	Y	Y	PN	N	N	HIGH	NI	NI	N	Y	N	N	HIGH
Pandey, 2016[10]	PY	PN	PN	Y	PY	HIGH	Y	Y	PN	N	Y	HIGH	Y	Y	Y	Y	NI	UNCLEAR	Y	NI	Y	Y	Y	Y	UNCLEAR
Sun, 2015[11]	PY	PN	PN	Y	NI	HIGH	Y	Y	Y	NI	NI	UNCLEAR	PY	Y	Y	N	NI	HIGH	Y	NI	Y	Y	Y	N	HIGH
Alcohol																									
Costanzo, 2011[12]	PY	PN	PN	PY	PY	HIGH	PY	Y	PN	N	Y	HIGH	NI	Y	Y	Y	NI	UNCLEAR	Y	NI	Y	Y	Y	PN	HIGH
Jayasekara, 2014[13]	PY	PN	PN	PY	PY	LOW	Y	N	Y	N	N	HIGH	PY	Y	Y	N	N	HIGH	Y	NI	Y	Y	Y	N	HIGH
Roerecke, 2011[14]	PY	Y	Y	Y	PY	LOW	Y	Y	Y	N	N	HIGH	NI	Y	Y	N	NI	HIGH	Y	NI	Y	Y	PY	N	LOW
Roerecke, 2014 [15]	Y	Y	Y	PY	PY	LOW	Y	Y	Y	N	N	HIGH	N	Y	Y	N	N	HIGH	Y	Y	Y	Y	PY	N	HIGH
Ronksley, 2011[16]	PY	PY	PY	Y	Y	LOW	Y	Y	Y	Y	Y	LOW	PY	PN	Y	PY	NI	HIGH	Y	PY	Y	Y	Y	PY	LOW
Park, 2015[17]	N	N	PN	NI	NI	HIGH	Y	Y	N	NI	PY	HIGH	NI	PN	PN	Y	Y	HIGH	Y	NI	PN	Y	PN	Y	HIGH

Stockwell, 2016[18]	Y	Y	Y	Y	PY	LOW	Y	Y	Y	N	PY	HIGH	Y	Y	Y	PY	NI	UNCLEAR	Y	Y	Y	Y	Y	Y	LOW
Zheng, 2015[19]	PY	PN	PN	PY	Y	HIGH	Y	Y	Y	Y	PY	LOW	Y	Y	Y	Y	Y	LOW	Y	NI	Y	Y	Y	Y	LOW
Roerecke, 2010[20]	PY	PN	PN	Y	PY	HIGH	Y	Y	Y	N	N	HIGH	NI	Y	Y	N	N	HIGH	Y	NI	Y	Y	PY	N	HIGH
Roerecke, 2014[21]	Y	Y	Y	Y	PY	LOW	Y	Y	Y	N	NI	HIGH	N	Y	Y	N	N	HIGH	Y	Y	Y	Y	Y	N	HIGH
Smoking																									
Gellert, 2012[22]	PY	Y	Y	Y	Y	LOW	Y	Y	PN	NI	PY	UNCLEAR	PY	Y	Y	Y	NI	UNCLEAR	Y	NI	Y	Y	Y	Y	UNCLEAR
Lv, 2015[23]	PY	Y	Y	Y	PY	LOW	Y	Y	Y	N	Y	HIGH	Y	PN	Y	Y	NI	UNCLEAR	Y	NI	Y	PY	Y	N	HIGH
Sinha, 2016[24]	PY	Y	Y	PY	PY	LOW	Y	Y	Y	N	PY	HIGH	PY	PN	Y	N	Y	HIGH	Y	NI	PN	Y	PN	N	HIGH
Diet																									
Farvid, 2014[25]	PY	Y	PY	Y	Y	LOW	Y	Y	Y	Y	N	HIGH	Y	Y	PY	N	N	HIGH	Y	NI	PY	Y	Y	N	HIGH
Graudal, 2014[26]	Y	Y	Y	Y	Y	LOW	Y	Y	PY	Y	NI	HIGH	Y	NI	Y	N	NI	HIGH	NI	NI	PY	PY	N	N	HIGH
Hu, 2014[27]	Y	Y	PY	PY	Y	LOW	Y	Y	N	Y	NI	HIGH	NI	Y	Y	Y	NI	HIGH	Y	NI	PY	PY	PY	N	HIGH
Li, 2012[28]	Y	PY	N	PN	PN	HIGH	Y	Y	PN	N	N	HIGH	Y	Y	Y	N	N	HIGH	Y	NI	N	Y	PY	N	HIGH
Musa-Veloso, 2011[29]	Y	PY	PY	Y	N	HIGH	Y	PY	PY	PY	NI	HIGH	Y	Y	PY	N	N	HIGH	Y	NI	Y	N	N	N	HIGH
Pan, 2012[30]	Y	Y	Y	Y	N	HIGH	Y	Y	Y	N	N	HIGH	Y	Y	Y	Y	Y	LOW	Y	NI	N	PY	PY	N	HIGH
Poggio, 2015[31]	Y	Y	PY	Y	Y	LOW	Y	Y	N	Y	Y	HIGH	NI	Y	Y	Y	Y	HIGH	Y	NI	Y	Y	Y	Y	LOW
Schwingshackl, 2014[32]	Y	PY	PY	Y	Y	LOW	Y	Y	PY	Y	PY	LOW	NI	Y	Y	Y	N	HIGH	PY	NI	Y	Y	PN	Y	HIGH
Wang, 2014[33]	Y	Y	Y	Y	Y	LOW	Y	Y	N	Y	Y	HIGH	Y	Y	Y	Y	PY	LOW	Y	NI	Y	Y	Y	Y	HIGH
Chen, 2016[34]	Y	Y	Y	Y	Y	LOW	Y	Y	PY	Y	Y	LOW	Y	Y	PY	Y	Y	LOW	Y	NI	Y	Y	Y	Y	LOW
Cheng, 2015[35]	Y	Y	Y	Y	Y	LOW	Y	Y	PY	Y	N	HIGH	Y	Y	Y	Y	Y	LOW	Y	NI	Y	Y	Y	NI	HIGH
Cheng, 2016[36]	Y	Y	Y	Y	Y	LOW	Y	Y	PN	Y	N	HIGH	Y	Y	Y	Y	Y	LOW	Y	NI	Y	Y	Y	N	HIGH
De Souza, 2015[37]	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	N	HIGH	Y	Y	PY	Y	N	HIGH	PY	NI	Y	Y	Y	Y	LOW
Narain, 2016[38]	Y	Y	Y	Y	Y	LOW	Y	Y	PY	Y	Y	LOW	Y	Y	Y	N	Y	HIGH	Y	NI	Y	Y	Y	Y	LOW
Statins																									
Bukkapatnam, 2010[39]	Y	Y	Y	PN	N	HIGH	Y	N	PN	N	N	HIGH	Y	Y	Y	N	N	HIGH	Y	NI	Y	Y	Y	N	HIGH
Kizer, 2010[40]	Y	Y	Y	PY	Y	LOW	Y	Y	PN	N	N	HIGH	N	Y	N	N	N	HIGH	N	NI	Y	PY	PY	N	HIGH

Kostis, 2012[41]	Y	Y	Y	N	Y	HIGH	Y	N	Y	Y	Y	HIGH	N	Y	NI	Y	N	HIGH	Y	NI	Y	PY	PY	Y	LOW
Lv, 2014[42]	Y	PN	Y	PY	Y	HIGH	Y	Y	PN	Y	N	HIGH	Y	Y	PY	Y	N	HIGH	Y	NI	PY	Y	Y	PY	LOW
Ray, 2010[43]	PN	PN	PN	Y	Y	HIGH	Y	Y	N	PY	N	HIGH	Y	Y	Y	N	N	HIGH	Y	NI	Y	Y	Y	N	HIGH
Savarese, 2013[44]	Y	Y	Y	Y	Y	LOW	Y	N	Y	Y	Y	HIGH	Y	Y	Y	Y	Y	LOW	Y	NI	Y	Y	Y	Y	LOW
Taylor, 2011[45]	Y	Y	PY	Y	Y	LOW	Y	Y	Y	Y	Y	LOW	Y	Y	Y	Y	Y	LOW	Y	NI	Y	Y	Y	Y	LOW
Tonelli, 2011[46]	Y	Y	Y	Y	Y	LOW	Y	Y	Y	N	Y	HIGH	Y	Y	Y	Y	Y	LOW	Y	NI	Y	Y	Y	PN	HIGH
Chou, 2016[47]	Y	Y	Y	Y	Y	LOW	Y	Y	Y	N	Y	HIGH	Y	Y	PY	Y	Y	LOW	Y	NI	Y	Y	Y	PY	LOW
Preiss, 2015[48]	Y	Y	Y	PY	Y	LOW	Y	N	PN	N	Y	HIGH	Y	Y	Y	N	N	HIGH	PY	NI	Y	Y	Y	PY	LOW
Teng, 2015[49]	Y	Y	Y	Y	Y	LOW	Y	Y	Y	N	Y	HIGH	Y	Y	PY	Y	Y	LOW	Y	NI	Y	Y	PY	PY	LOW

Y=YES, PY= PROBABLY YES, PN=PROBABLY NO, N=NO, NI=NO INFORMATION

S4 Table. Meta-analyses of cardiovascular disease and all-cause mortality by research area.

First author, year (Reference)	Exposure-outcome association	Number of Estimates	Sample size	Number of Cases	Largest study, RR (95% CI)*	Random Effect, RR (95% CI)**	Random Effects, P#	I^2 (95% CI)	Egger's P†	Excess Significance		
										O	E‡	P-value‡
Physical Activity												
Kelly, 2014[1]	walking and all-cause mortality	14	279231	21119	0.89(0.84,0.95)	0.87 (0.8 ,0.95)	2.79E-03	86.8 (79.6 ,90.6)	0.32	3	6.71	NP
Kelly, 2014[1]	cycling and all-cause mortality	7	188539	20607	0.88(0.84,0.93)	0.91 (0.88 ,0.94)	1.27E-08	0 (0 ,58.5)	0.58	2	5.42	NP
Samitz, 2011[2]	total physical activity and all-cause mortality	23	395382	34274	0.61(0.57,0.65)	0.63 (0.56 ,0.69)	2.86E-18	85.8 (80.1 ,89.2)	0.09	18	20.21	NP
Samitz, 2011[2]	leisure-time physical activity and all-cause mortality	41	551110	61465	0.67(0.62,0.72)	0.73 (0.69 ,0.77)	1.44E-31	71.1 (59.3 ,78.2)	0.03	30	37.63	NP
Samitz, 2011[2]	leisure-time physical activity and all-cause mortality	6	384672	28607	0.99(0.99,1.00)	0.95 (0.93 ,0.98)	4.67E-05	96.9 (95.6 ,97.6)	0.21	5	0.39	<0.01
Samitz, 2011[2]	exercise and all-cause mortality	8	396431	16481	0.95(0.92,0.97)	0.91 (0.87 ,0.94)	4.73E-07	83.2 (65.8 ,89.8)	0.06	8	1.77	<0.01
Samitz, 2011[2]	walking and all-cause mortality	10	148627	7044	0.99(0.98,1.00)	0.97 (0.94 ,0.99)	3.35E-03	78.1 (55.5 ,86.6)	<0.01	5	0.52	<0.01
Samitz, 2011[2]	physical activity for transportation and all-cause mortality	6	203914	14253	0.99(0.98,1.00)	0.97 (0.94 ,1)	2.51E-02	76.2 (29.5 ,87.6)	0.15	2	0.34	0.04
Samitz, 2011[2]	routine activities of daily living and all-cause mortality	4	99618	4161	0.98(0.98,0.99)	0.96 (0.93 ,0.98)	1.36E-03	94.7 (90.2 ,96.6)	0.32	3	0.26	<0.01
Woodcock, 2011[3]	moderate non-vigorous physical activity and all-cause mortality	22	975227	64970	1.01(0.97,1.06)	0.8 (0.76 ,0.85)	1.35E-13	88.8 (84.8 ,91.3)	0.07	18	1.4	<0.01
Woodcock, 2011[3]	walking and all-cause mortality	5	217042	11383	0.95(0.90,1.01)	0.89 (0.82 ,0.96)	1.58E-03	75.9 (12.7 ,88.3)	0.70	3	1.25	0.10
Hupin, 2015 [4]	high dose physical activity and all-cause mortality	9	122417	18122	0.75(0.70,0.80)	0.65 (0.61 ,0.7)	2.45E-33	61.1 (0 ,79.5)	0.16	9	8.31	1.00
Sedentary Behavior												
Biswas, 2015[5]	sedentary time and all-cause mortality	12	836491	15644	1.05(1.03,1.07)	1.19 (1.11 ,1.27)	3.86E-07	89.8 (84.5 ,92.7)	0.02	11	1.86	<0.01
Biswas, 2015[5]	sedentary time and cvd mortality	6	528440	4383	1.23(1.14,1.32)	1.18 (1.11 ,1.26)	4.05E-07	35.6 (0 ,73.5)	0.16	5	3.57	0.41
Biswas, 2015[5]	high physical activity, high sedentary time and all-cause mortality	6	741588	14394	1.12(1.03,1.22)	1.17 (1.01 ,1.36)	3.36E-02	81.1 (51.1 ,89.6)	0.96	5	3.92	0.67
Biswas, 2015[5]	low physical activity, high sedentary time and all-cause mortality	6	741588	14394	1.29(1.20,1.38)	1.46 (1.29 ,1.65)	1.18E-09	86.9 (71.7 ,92.2)	0.50	6	5.15	1.00
Chau, 2013[6]	sedentary time and all-cause mortality	6	595186	29162	1.02(1.02,1.03)	1.02 (1.01 ,1.03)	8.59E-05	84.3 (63.1 ,91)	0.24	5	0.69	<0.01
Grontved, 2011[7]	television viewing and all-cause mortality	3	26509	1879	1.14(1.06,1.23)	1.13 (1.07 ,1.18)	4.75E-06	0 (0 ,72.9)	0.61	2	1.15	0.56
Wilmot, 2012[8]	sedentary time and all-cause mortality	8	497211	44998	1.81(1.74,1.88)	1.66 (1.5 ,1.83)	1.08E-22	79.3 (53.7 ,87.9)	0.38	8	8	NP
Wilmot, 2012[8]	sedentary time and cvd mortality	8	421921	13023	1.95(1.82,2.10)	1.94 (1.66 ,2.26)	2.78E-17	62.7 (0 ,80.8)	0.82	6	7.92	NP
Ford, 2012 [9]	sitting time and cvd mortality	2	364035	11053	1.05(1.03,1.08)	1.03 (0.99 ,1.08)	1.36E-01	86 (0 ,0)	NA	1	1.14	NP
Ford, 2012 [9]	screen-time and cvd mortality	4	270560	5521	1.17(1.13,1.21)	1.17 (1.13 ,1.21)	5.24E-21	0 (0 ,67.9)	0.94	2	1.88	1.00

Pandey, 2016[10]	sedentary time and cvd mortality	5	579948	19723	1.23(1.14,1.32)	1.17 (1.08 ,1.26)	7.18E-05	52.6 (0 ,80.6)	0.54	4	4.85	NP
Sun, 2015[11]	television viewing and all-cause mortality	10	536683	50456	1.61(1.47,1.76)	1.33 (1.2 ,1.47)	4.19E-08	66.7 (20.2 ,81.3)	0.74	7	8.72	NP
Alcohol												
Costanzo, 2011[12]	wine intake and all-cause mortality	5	56610	11905	1.81(1.5,2.18)	1.16 (0.74 ,1.82)	5.26E-01	87.6 (70.7 ,92.9)	0.84	1	5	NP
Costanzo, 2011[12]	wine intake and chd mortality	2	60773	1335	1.08(0.61,1.91)	0.92 (0.6 ,1.42)	7.16E-01	0 (0 ,0)	NA	0	0.38	NP
Costanzo, 2011[12]	wine intake and cvd mortality	3	41401	1113	0.67(0.45,1)	0.72 (0.49 ,1.06)	9.66E-02	0 (0 ,72.9)	0.14	0	2.61	NP
Costanzo, 2011[12]	beer intake and all-cause mortality	2	15545	8338	1.15(1.04,1.28)	1.16 (1.05 ,1.29)	5.03E-03	0 (0 ,0)	NA	1	1.2	NP
Costanzo, 2011[12]	beer intake and cvd mortality	2	39573	866	0.74(0.37,1.48)	0.92 (0.54 ,1.57)	7.63E-01	0 (0 ,0)	NA	0	1.59	NP
Costanzo, 2011[12]	spirits intake and all-cause mortality	2	15517	8338	1.12(0.94,1.34)	1.12 (0.94 ,1.32)	1.95E-01	0 (0 ,0)	NA	0	1.11	NP
Costanzo, 2011[12]	spirits intake and cvd mortality	2	39573	866	0.88(0.47,1.64)	1.47 (0.51 ,4.19)	4.74E-01	77.7 (0 ,0)	NA	1	0.45	040
Jayasekara, 2014[13]	alcohol intake of >=60 g/day and all-cause mortality	3	23599	3040	2.44(1.93,3.08)	1.52 (0.78 ,2.98)	2.19E-01	89.5 (62.9 ,94.8)	0.54	1	3	NP
Roerecke, 2011[14]	alcohol intake and ischemic heart disease mortality in men	14	8038	408	1.08(0.92,1.26)	1.29 (1.15 ,1.44)	8.71E-06	26.4 (0 ,60.5)	0.23	0	0.28	NP
Roerecke, 2011[14]	alcohol intake and ischemic heart disease mortality in women	10	0	0	1.09(0.97,1.22)	1.54 (1.17 ,2.03)	1.90E-03	71.1 (34.5 ,83.3)	0.07	NA	NA	NP
Roerecke, 2014[15]	heavy drinkers and ischemic heart disease mortality	2	80233	862	1.06(0.76,1.48)	1.07 (0.78 ,1.48)	6.61E-01		NA	0	0.2	NP
Ronksley, 2011 [16]	alcohol consumption and cvd mortality	22	1176623	15628	0.71(0.68,0.75)	0.75 (0.7 ,0.8)	1.23E-17	72.2 (55 ,80.9)	0.72	14	17.37	NP
Ronksley, 2011 [16]	alcohol consumption and chd mortality	30	1924612	47245	0.82(0.79,0.86)	0.75 (0.68 ,0.81)	6.08E-11	87.9 (84.2 ,90.4)	0.56	18	17.79	1.00
Ronksley, 2011 [16]	alcohol consumption and stroke mortality	10	723551	5171	0.76(0.67,0.87)	1.07 (0.89 ,1.27)	4.87E-01	73.1 (40.8 ,84.2)	0.17	4	6.63	NP
Ronksley, 2011 [16]	alcohol consumption and all-cause mortality	31	844127	96807	0.81(0.76,0.86)	0.87 (0.83 ,0.92)	1.40E-07	68.9 (53.1 ,77.7)	0.90	9	24.35	NP
Park, 2015[17]	mild alcohol consumption and all-cause mortality	5	964893	18359	0.89(0.86,0.92)	0.76 (0.59 ,0.97)	2.74E-02	85.5 (62.7 ,92)	0.31	3	2.27	0.66
Stockwell, 2016 [18]	low alcohol consumption and all-cause mortality	81	3674042	320252	0.95(0.91,0.99)	0.86 (0.83 ,0.88)	4.71E-22	63 (52 ,70.4)	0.04	35	18.48	<0.01
Zheng, 2015[19]	alcohol intake and all-cause mortality in men	9	88239	5409	1.09(1.01,1.17)	1 (0.81 ,1.22)	9.63E-01	91.4 (86.4 ,93.9)	0.66	4	2.38	0.26
Zheng, 2015[19]	alcohol intake and all-cause mortality in women	9	100150	4503	1.07(0.96,1.19)	1.2 (0.99 ,1.46)	6.01E-02	68.6 (21.5 ,82.7)	0.56	3	1.93	0.41
Zheng, 2015[19]	alcohol intake and cardiac death in men	4	51386	6230	1.15(1.02,1.28)	0.93 (0.7 ,1.23)	6.09E-01	86.9 (61.6 ,93.1)	0.74	2	1.38	0.61
Zheng, 2015[19]	alcohol intake and cardiac death in women	4	67977	8553	0.88(0.8,0.97)	1.04 (0.74 ,1.46)	8.24E-01	48.1 (0 ,81.3)	0.53	1	1.37	NP
Roerecke, 2010[20]	alcohol consumption and ischemic heart disease mortality	5	595	115	1.4(1.15,1.72)	1.63 (1.28 ,2.09)	8.12E-05	25.4 (0 ,72.4)	0.01	5	1.54	<0.01
Roerecke, 2014[21]	alcohol consumption and ischemic heart disease mortality - reference group lifetime abstainers	4	34234	618	0.74(0.56,0.97)	1.05 (0.76 ,1.46)	7.70E-01	69 (0 ,87.1)	0.25	2	1.89	1.00

Roerecke, 2014[21]	alcohol consumption and ischemic heart disease mortality - reference group current abstainers	7	39461	818	0.92(0.84,1)	0.9 (0.72 ,1.12)	3.46E-01	67.5 (0 ,83.5)	0.59	1	0.55	0.43
Smoking												
Gellert, 2012[22]	current smokers and all-cause mortality	16	1194293	191660	2.48(2.47,2.5)	1.88 (1.61 ,2.18)	3.55E-16	97.7 (97.3 ,98)	0.02	16	16	NP
Gellert, 2012[22]	former smokers and all-cause mortality	19	1220691	213874	1.22(1.16,1.28)	1.33 (1.26 ,1.4)	3.28E-25	60.4 (16 ,76.5)	0.61	11	10.79	1.00
Lv, 2015[23]	second hand smoking and all-cause mortality	11	939163	27228	1.1(1.03,1.18)	1.18 (1.1 ,1.27)	1.54E-05	69.7 (33.8 ,82.2)	0.12	6	6.15	NP
Lv, 2015[23]	second hand smoking and cardiovascular mortality	16	1367710	16738	1.02(0.98,1.07)	1.16 (1.08 ,1.24)	2.66E-05	67.1 (37.9 ,79.2)	<0.01	7	2.91	0.02
Sinha, 2016[24]	smokeless tobacco use and all-cause mortality	12	1099896	87321	0.89(0.84,0.93)	1.22 (1.09 ,1.37)	5.44E-04	95.3 (93.8 ,96.3)	0.75	10	10.42	NP
Sinha, 2016[24]	smokeless tobacco use and ischemic heart disease mortality	13	909495	17746	1(0.92,1.08)	1.1 (1.05 ,1.15)	1.06E-05	8.1 (0 ,52.6)	0.18	4	3.5	0.76
Sinha, 2016[24]	smokeless tobacco use and stroke mortality	8	873754	6123	1.46(1.31,1.64)	1.39 (1.29 ,1.5)	2.29E-18	0 (0 ,56.3)	0.07	4	7.44	NP
Diet												
Farvid, 2014[25]	dietary linoleic acid and chd mortality	11	270280	5882	0.77(0.63,0.94)	0.79 (0.71 ,0.88)	4.51E-05	0 (0 ,51.2)	0.29	3	6.42	NP
Graudal, 2014[26]	high sodium and all-cause mortality	8	37618	8573	1(0.94,1.06)	0.94 (0.87 ,1.03)	1.76E-01	53.7 (0 ,77.3)	0.91	3	0.4	0.01
Hu, 2014[27]	fruits and vegetables and stroke mortality	6	388003	4615	0.76(0.69,0.83)	0.74 (0.62 ,0.88)	5.82E-04	34.1 (0 ,73)	0.43	3	4.83	NP
Li, 2012[28]	salt intake and stroke mortality	5	183532	4086	1.22(1.05,1.4)	1.28 (1.1 ,1.5)	1.44E-03	57.9 (0 ,82.3)	0.24	3	3.38	NP
Li, 2012[28]	salt intake and isquemic stroke mortality	2	72085	647	2.04(1.41,2.94)	2.16 (1.53 ,3.05)	1.13E-05	0 (0 ,0)	NA	2	2	NP
Musa-Veloso, 2011[29]	long-chain n-3 fatty acid and sudden cardiac death	3	35443	499	0.64(0.47,0.86)	0.65 (0.54 ,0.79)	9.80E-06	1.4 (0 ,73.3)	0.43	2	2.62	NP
Musa-Veloso, 2011[29]	long-chain n-3 fatty acid and fatal coronary events	5	161708	1805	1.05(0.87,1.28)	0.83 (0.68 ,1.03)	8.46E-02	66 (0 ,84.9)	0.24	2	0.42	0.06
Pan, 2012[30]	dietary a-linolenic acid intake and risk of CVD death	6	150438	3370	1.02(0.73,1.44)	0.8 (0.65 ,0.98)	3.46E-02	18.6 (0 ,67.8)	0.77	1	0.34	0.30
Pan, 2012[30]	a-linolenic acid biomarker concentration and risk of CVD death	3	3668	1144	1.23(1,1.52)	1.06 (0.64 ,1.75)	8.23E-01	49.2 (0 ,84.3)	0.38	0	0.98	NP
Poggio, 2015[31]	sodium intake and cvd mortality	11	199785	9346	1.05(0.96,1.15)	1.16 (1.03 ,1.31)	1.70E-02	68.4 (29.7 ,81.6)	0.63	5	1.3	0.01
Schwingshackl, 2014[32]	MUFA and all-cause mortality	5	183956	20685	0.97(0.9,1.05)	1 (0.93 ,1.08)	9.32E-01	21.6 (0 ,71.3)	0.67	0	0.84	NP
Schwingshackl, 2014[32]	MUFA:SFA ratio and all-cause mortality	10	246390	19410	0.98(0.91,1.06)	0.9 (0.82 ,1)	4.40E-02	58.5 (0 ,77.7)	0.15	3	0.74	0.03
Schwingshackl, 2014[32]	olive oil and all-cause mortality	4	73665	3446	0.77(0.68,0.87)	0.77 (0.7 ,0.85)	4.86E-07	0 (0 ,67.9)	0.86	2	3.34	NP
Schwingshackl, 2014[32]	MUFA and cvd mortality	8	255053	4967	0.97(0.89,1.06)	0.96 (0.89 ,1.04)	3.69E-01	7 (0 ,59.3)	0.65	0	0.56	NP
Schwingshackl, 2014[32]	MUFA:SFA and cvd mortality	4	103788	2346	0.92(0.81,1.04)	0.91 (0.83 ,0.99)	3.34E-02	0 (0 ,67.9)	0.38	0	0.76	NP
Schwingshackl, 2014[32]	olive oil and cvd mortality	5	98252	1260	0.61(0.46,0.81)	0.7 (0.48 ,1.03)	7.05E-02	71.4 (0 ,86.7)	0.87	3	4.64	NP
Wang, 2014[33]	fruits and vegetables and all-cause mortality	7	553698	42219	0.99(0.98,0.99)	0.95 (0.92 ,0.98)	6.64E-04	82.4 (60.6 ,89.8)	0.01	5	0.49	<0.01

Wang, 2014[33]	fruits and all-cause mortality	7	660186	40192	0.99(0.98,1)	0.94 (0.9 ,0.98)	2.07E-03	77.4 (42.5 ,87.5)	0.02	4	0.48	<0.01
Wang, 2014[33]	vegetables and all-cause mortality	7	660186	40192	0.97(0.96,0.98)	0.95 (0.92 ,0.99)	6.40E-03	86.1 (71.7 ,91.5)	0.36	4	1.48	0.04
Wang, 2014[33]	fruits and vegetables and cardiovascular mortality	4	469551	6893	0.98(0.96,0.99)	0.96 (0.92 ,0.99)	1.65E-02	42.4 (0 ,79.8)	0.08	2	0.3	0.03
Wang, 2014[33]	fruits and cardiovascular mortality	6	677674	9744	1(0.97,1.02)	0.95 (0.91 ,1)	3.41E-02	70.7 (0.5 ,85.5)	0.40	3	0.3	<0.01
Wang, 2014[33]	vegetables and cardiovascular mortality	6	677674	9744	0.93(0.91,0.96)	0.96 (0.93 ,0.99)	1.26E-02	62.7 (0 ,82.6)	0.77	3	1.91	0.39
Chen, 2016[34]	long-chain n-3 polyunsaturated x all cause mortality	6	361273	27621	0.94(0.86,1.03)	0.9 (0.83 ,0.97)	9.56E-03	69 (0 ,84.9)	0.59	2	3.42	NP
Chen, 2016[34]	EPA x all cause mortality	3	6410	3205	0.83(0.71,0.98)	0.74 (0.6 ,0.9)	3.11E-03	55.1 (0 ,85.6)	0.37	2	1.88	1.00
Chen, 2016[34]	DHA x all cause mortality	3	6410	3205	0.8(0.67,0.94)	0.78 (0.64 ,0.93)	6.72E-03	38.3 (0 ,82)	0.68	2	2.32	NP
Cheng, 2015[35]	Long chain n-3 PUFA intake assessment and stroke mortality	7	419938	4964	0.91(0.74,1.12)	0.84 (0.73 ,0.97)	1.79E-02	31.3 (0 ,70.3)	0.08	2	1.94	0.96
Cheng, 2016[36]	dietary saturated fat and stroke mortality	3	74060	1428	0.67(0.49,0.92)	0.71 (0.56 ,0.92)	8.16E-03	0 (0 ,72.9)	0.95	1	2.53	NP
De Souza, 2015[37]	saturated fat intake and all-cause mortality	5	99906	14305	0.95(0.89,1.01)	1.04 (0.91 ,1.19)	5.92E-01	47.9 (0 ,79.2)	0.21	1	1.27	NP
De Souza, 2015[37]	saturated fat intake and chd mortality	11	103548	3295	1.1(0.96,1.26)	1.15 (0.99 ,1.33)	7.52E-02	59.3 (0.3 ,77.5)	0.13	3	1.65	0.22
De Souza, 2015[37]	saturated fat intake and cvd mortality	3	90501	2094	1.02(0.91,1.14)	0.9 (0.7 ,1.17)	4.33E-01	39.8 (0 ,82.3)	0.04	0	0.17	NP
De Souza, 2015[37]	total trans fat and all-cause mortality	2	20346	2140	1.24(1.04,1.47)	1.42 (1.04 ,1.94)	2.69E-02	69.9 (0 ,0)	NA	2	1.65	1.00
De Souza, 2015[37]	total trans fat and CHD mortality	7	107610	3628	1.15(0.92,1.43)	1.22 (1.07 ,1.38)	2.17E-03	0 (0 ,58.5)	0.38	1	2.37	NP
De Souza, 2015[37]	industrial trans fat and CHD mortality	2	93394	3018	1.16(1,1.34)	1.18 (1.04 ,1.34)	9.24E-03	0 (0 ,0)	NA	1	1.51	NP
De Souza, 2015[37]	ruminant trans fat and CHD mortality	2	93394	3018	1.23(1.03,1.46)	1.03 (0.7 ,1.51)	8.87E-01	80.5 (0 ,0)	NA	1	1.8	NP
Narain, 2016[38]	sugar-sweetened beverage and all-cause mortality	3	148800	47432	1.02(0.92,1.13)	1.03 (0.91 ,1.18)	6.19E-01	74.5 (0 ,90.3)	0.97	1	0.57	0.47
Narain, 2016[38]	artificially sweetened beverage intake and all-cause mortality	2	96216	37403	1.18(1.07,1.3)	1.09 (0.92 ,1.3)	3.15E-01	72.7 (0 ,0)	NA	1	2	NP
Statin												
Bukkapatnam, 2010[39]	statin and all-cause mortality	3	11384	79	0.98(0.83,1.17)	0.9 (0.6 ,1.35)	6.07E-01	54.1 (0 ,85.4)	0.89	1	1.1	NP
Kizer, 2010[40]	statin and all-cause mortality	11	95813	6820	0.86(0.8,0.93)	0.9 (0.84 ,0.96)	1.89E-03	30 (0 ,64.7)	0.88	2	4.32	NP
Kostis, 2012[41]	statin and all-cause mortality in men	6	42647	3995	0.87(0.79,0.95)	0.92 (0.85 ,1.01)	7.97E-02	22 (0 ,69)	0.73	1	2.21	NP
Kostis, 2012[41]	statin and all-cause mortality in women	6	26287	1496	0.94(0.79,1.13)	0.87 (0.78 ,0.97)	1.36E-02	3.2 (0 ,62.2)	0.79	1	0.49	0.40
Lv, 2014[42]	statin and all-cause mortality	3	37436	6011	0.95(0.91,0.98)	0.94 (0.9 ,0.97)	1.21E-03	11.6 (0 ,75.9)	0.24	2	0.63	0.11
Lv, 2014[42]	statin and cvd mortality	3	37436	4720	0.92(0.87,0.97)	0.91 (0.87 ,0.96)	3.16E-04	0 (0 ,72.9)	0.50	2	1.04	0.28

Ray, 2010[43]	statin and all-cause mortality	11	65229	2833	1(0.88,1.13)	0.92 (0.83 ,1.01)	6.52E-02	21.5 (0 ,61.1)	0.47	1	0.55	0.43
Savarese, 2013[44]	statin and all-cause mortality	7	31272	2511	1.01(0.89,1.15)	0.94 (0.86 ,1.04)	2.39E-01	0 (0 ,58.5)	0.24	0	0.36	NP
Savarese, 2013[44]	statin and cvd mortality	5	19103	191	1.03(0.7,1.51)	0.91 (0.69 ,1.2)	4.95E-01	0 (0 ,64.1)	0.59	0	0.26	NP
Taylor, 2011[45]	statin and all-cause mortality	8	28161	802	0.78(0.61,1.01)	0.84 (0.72 ,0.99)	3.34E-02	13.5 (0 ,61.9)	0.76	0	2.13	NP
Taylor, 2011[45]	statin and chd mortality	7	17619	186	0.73(0.48,1.1)	0.8 (0.6 ,1.06)	1.19E-01	0.6 (0 ,58.7)	0.81	0	1.01	NP
Taylor, 2011[45]	statin and cvd mortality	2	7459	131	0.68(0.48,0.98)	0.7 (0.49 ,0.98)	4.03E-02	0 (0 ,0)	NA	1	0.74	1.00
Tonelli, 2011[46]	low-dose statin and all-cause mortality	13	48307	2059	0.99(0.89,1.09)	0.9 (0.78 ,1.03)	1.32E-01	24 (0 ,60.2)	0.73	2	0.66	0.14
Tonelli, 2011[46]	high-dose statin and all-cause mortality	6	29997	878	0.8(0.67,0.96)	0.84 (0.74 ,0.96)	9.72E-03	0 (0 ,61)	0.16	1	1.66	NP
Chou, 2016[47]	statin and all-cause mortality	14	129731	2351	0.93(0.81,1.08)	0.86 (0.8 ,0.93)	2.07E-04	0 (0 ,47.4)	0.49	3	1.13	0.10
Chou, 2016[47]	statin and cvd mortality	10	110847	947	0.9(0.72,1.11)	0.69 (0.54 ,0.88)	2.66E-03	53.6 (0 ,75.6)	0.25	3	0.87	0.05
Preiss, 2015[48]	statin and heart failure death	5	47200	33	0.75(0.26,2.16)	0.75 (0.38 ,1.49)	4.12E-01	0 (0 ,64.1)	0.85	0	0.35	NP
Teng, 2015[49]	statin and all-cause mortality	7	23357	2710	1.01(0.91,1.13)	0.96 (0.88 ,1.04)	2.97E-01	0 (0 ,58.5)	0.12	0	0.36	NP
Teng, 2015[49]	statin and stroke mortality	2	6938	114	1.04(0.69,1.55)	0.74 (0.22 ,2.49)	6.26E-01	42.5 (0 ,0)	NA	0	0.11	NP
Teng, 2015[49]	statin and myocardical infarction mortality	2	6938	68	0.81(0.58,1.13)	0.42 (0.09 ,2.01)	2.78E-01	78.2 (0 ,0)	NA	1	0.21	0.20

Abbreviations: CI, confidence interval; NA, not applicable, because the numbers of studies are less than three; NP, not pertinent, because the expected number of significant studies is larger than the observed; RR, relative risk; O, Observed number of statistically significant studies; E, Expected number of statistically significant studies

** Random effects refer to summary risk ratio (95% CI) using the random-effects model.

P-value of the summary random effects estimate expressed in scientific notation.

† P-value from the Egger's regression asymmetry test.

‡ Expected number of statistically significant studies using the point estimate of the largest study (smallest SE) as the plausible effect size.

‡‡ *P*-value of the excess statistical significance test.

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Table S5: Sensitivity analysis excluding individual studies with less than 200 deaths. Relative and absolute frequencies of meta-analyses with nominally statistical significant results, small-study effects, and excess significance, by research area

Research area	Total number of meta-analysis	Meta-analysis with P<0.05 (%)		Small-study effects			Excess significance				
								O>E			
	N	n	%	N*	n	%	N**	n	%	n with P<0.05	%
Physical Activity	12	12	100	12	3	25	12	8	67	6	50
Sedentary behaviour	11	11	100	11	0	0	11	7	64	1	9
Alcohol	24	9	38	13	2	15	11	3	27	1	9
Smoking	7	7	100	7	3	43	7	4	57	0	0
Diet	36	24	67	27	4	15	27	15	56	9	33
Statin	14	5	36	8	1	13	8	4	50	0	0
Overall	104	68	65	78	13	17	76	41	54	17	22

Figure 1. Flowchart for systematic review selection by research area.

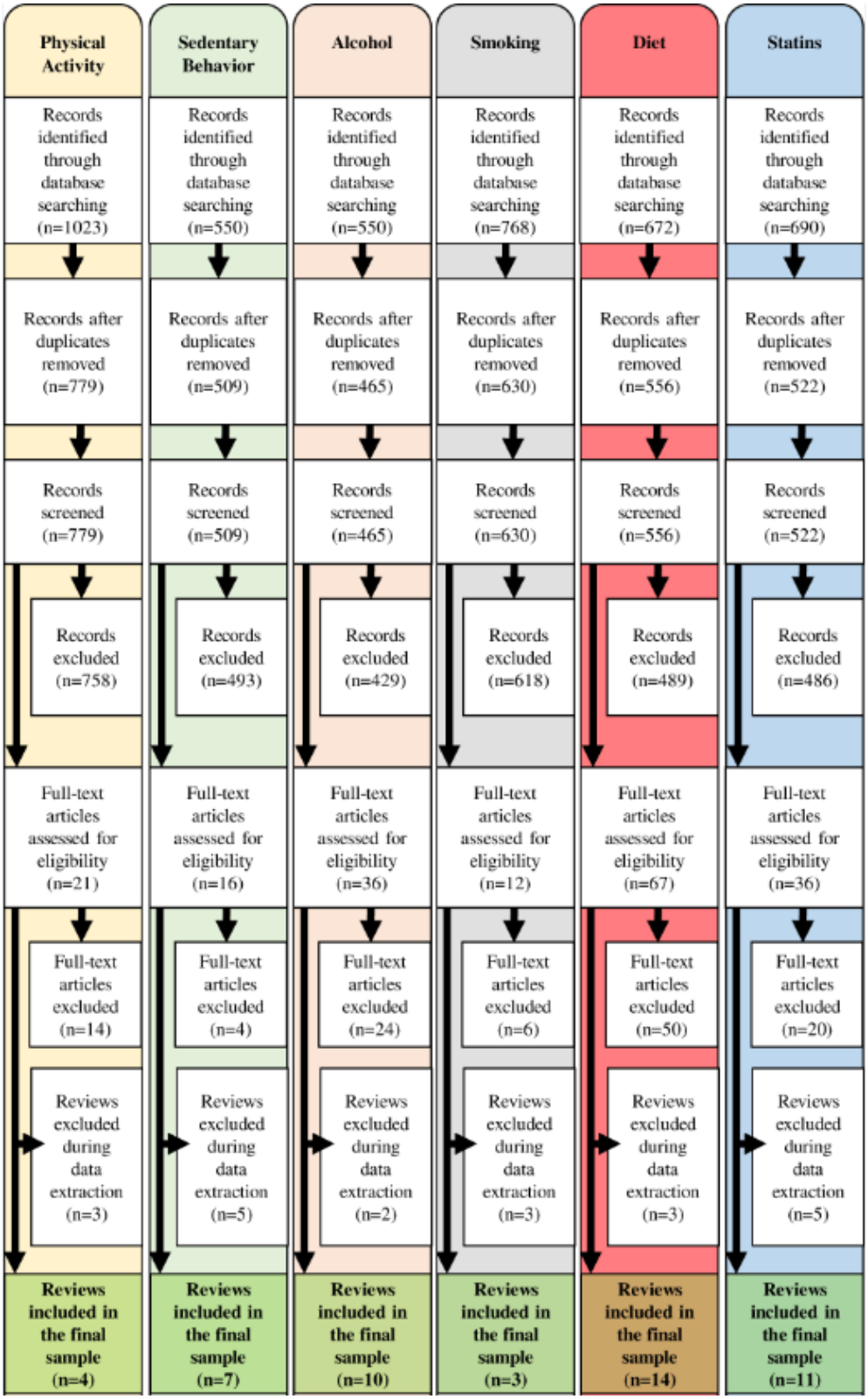


Figure 2. Risk of bias in systematic reviews of the associations of health behaviors and statins with cardiovascular disease mortality and all-cause mortality – ROBIS results

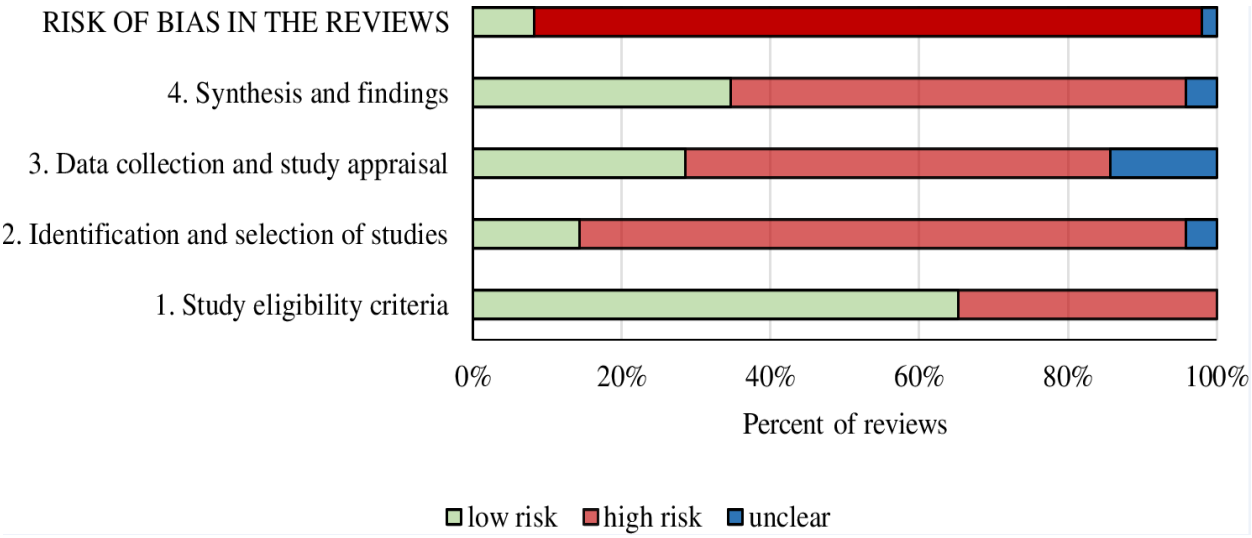
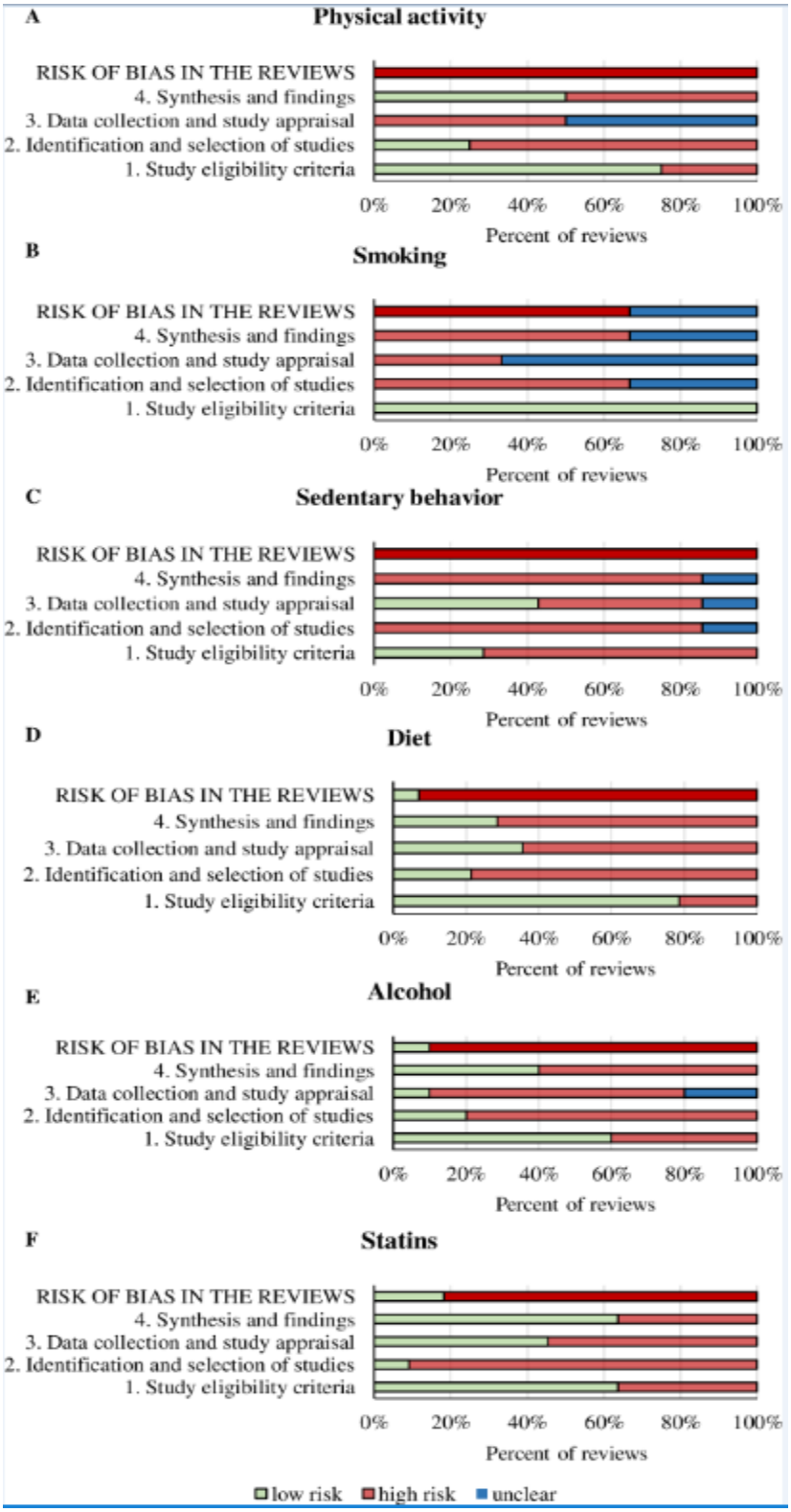


Fig 3. Risk of bias in systematic reviews of the associations of health behaviors and statins with cardiovascular disease mortality and all-cause mortality, by research area – ROBIS results.



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APPENDIX iv

The Risk of Bias in Observational Studies of Exposures (ROBINS-E) Tool:

Concerns arising from application to observational studies of exposures

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Lisa Bero*
Lisa.bero@sydney.edu.au
Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney

Nicholas Chartres
Nicholas.chartres@sydney.edu.au
Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney

Joanna Diong
Joanna.diong@sydney.edu.au
School of Medical Sciences, Faculty of Medicine and Health, The University of Sydney

Alice Fabbri
Alice.fabbri@sydney.edu.au
Charles Perkins Centre and School of Pharmacy, Faculty of Medicine and Health, The University of Sydney

Davina Ghersi
Davina.ghersi@nhmrc.gov.au
National Health and Medical Research Council

Juleen Lam
Juleen.lam@ucsf.edu
Department of Ob/Gyn & the Institute for Health Policy Studies, University of California, San Francisco and Department of Health Sciences, California State University, East Bay

Agnes Lau
Agnes.lau@ucsf.edu
School of Pharmacy, University of California, San Francisco

Sally McDonald
smcd4282@uni.sydney.edu.au
Charles Perkins Centre, The University of Sydney

Barbara Mintzes
Barbara.mintzes@sydney.edu.au
School of Pharmacy, Faculty of Medicine and Health and Charles Perkins Centre, The University of Sydney

Patrice Sutton
Patrice.sutton@ucsf.edu
University of California San Francisco

Jessica Louise Turton
jtur7823@uni.sydney.edu.au
Charles Perkins Centre, The University of Sydney

Tracey J. Woodruff
Tracey.woodruff@ucsf.edu
Department of Ob/Gyn & the Institute for Health Policy Studies, University of California, San Francisco

Abstract

Background: Systematic reviews, which assess the risk of bias in included studies, are increasingly used to develop environmental hazard assessments and public health guidelines. These research areas typically rely on evidence from human observational studies of exposures, yet there are currently no universally accepted standards for assessing risk of bias in such studies. The risk of bias in non-randomised studies of exposures (ROBINS-E) tool has been developed by building upon tools for risk of bias assessment of randomised trials, diagnostic test accuracy studies and observational studies of interventions. This paper reports our experience with the application of the ROBINS-E tool.

Methods: We applied ROBINS-E to 74 exposure studies (60 cohort studies, 14 case-control studies) in 3 areas: environmental risk, dietary exposure and drug harm. All investigators provided written feedback, and we documented verbal discussion of the tool. We inductively and iteratively classified the feedback into 7 themes based on commonalities and differences until all the feedback was accounted for in the themes. We present a description of each theme.

Results: We identified practical concerns with the premise that ROBINS-E is a structured comparison of the observational study being rated to the 'ideal' randomised controlled trial. ROBINS-E assesses 7 domains of bias, but relevant questions related to some critical sources of bias, such as exposure and funding source, are not assessed. ROBINS-E fails to discriminate between studies with a single risk of bias or multiple risks of bias. ROBINS-E is severely limited at determining whether confounders will bias study outcomes. The construct of co-exposures was difficult to distinguish from confounders. Applying ROBINS-E was time-consuming and confusing.

Conclusions: Our experience suggests that the ROBINS-E tool does not meet the need for an international standard for evaluating human observational studies for questions of harm relevant to public and environmental health. We propose that a simpler tool, based on empirical evidence of bias,

would provide accurate measures of risk of bias and is more likely to meet the needs of the environmental and public health community.

Keywords: Systematic review, Risk of bias, Quality assessment, Public health guidelines, Guidelines, GRADE, Cochrane, Nutrition, Environment, Observational study

BACKGROUND

Public health guidelines (e.g. drinking water quality, dietary, environmental hazard and risk assessments) have a direct, long-term impact on health. Systematic reviews are increasingly required for these types of guidelines [1-4]. Systematic review methods are also becoming more prevalent in research areas that rely on observational studies of exposures to assess harm [1, 2, 5-9]. In nutrition research, for example, it is not feasible to investigate the effect of a particular food or nutrient on chronic disease incidence using a controlled study design because these conditions (e.g., cardiovascular disease, bowel cancer) take several decades to develop and/or become symptomatic. In environmental health, human observational data are usually the most directly applicable data available because ethical considerations virtually preclude human randomized, controlled trials (RCTs).

A critical step in the systematic review process is the assessment of the risk of bias of included studies. Risk of bias, which is analogous to internal validity, assesses whether flaws in the design, conduct or analysis of a study may lead to biases that affect the results [10]. Since environmental and public health guidance is primarily based on evidence from human observational studies, a risk of bias tool that can be applied to such studies is needed. Although many tools exist, they have often been developed for one or a few specific systematic reviews, are inadequately described, and lack evaluation [11, 12]. There is currently no universally accepted standard or consensus about the best approach for assessing risk of bias in observational study designs. This can make both systematic reviews and public health guidelines difficult to interpret and evaluate because they use different methods.

Most of the effort to reduce bias in guideline development has focused on clinical practice guidelines and some guideline developers adopt methods used to evaluate clinical research to assess observational

studies [13]. The Cochrane tool for assessing risks of bias in randomized controlled trials is widely used for clinical systematic reviews and guideline development [14, 15]. An international group of epidemiologists, statisticians, systematic reviewers, trialists and health services researchers developed the ROBINS-I ("Risk of Bias In Non-randomized Studies of Interventions") tool building upon developments in risk of bias assessment of randomized trials and diagnostic test accuracy studies [14, 16]. ROBINS-I is based on the premise that an observational study of an intervention should be compared to a hypothetical randomized controlled trial to identify potential biases [17].

Environmental and many other public health studies, such as dietary or health behaviour studies, do not test interventions. Rather, they observe whether there is an association between an exposure not under the investigator's control and a health outcome. In these cases, it may be considered most appropriate to assess risk of bias using an appraisal tool that is specific to studies of exposures, not interventions. As part of a programme of work to adapt Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) for environmental health, an international group of researchers modified the ROBINS-I tool to develop "The Risk of Bias in Non-randomized studies of Exposures" tool, called ROBINS-E [version July 2017] [7, 18]. Like ROBINS-I, ROBINS-E compares the study being evaluated to a hypothetical, "ideal" randomized, controlled trial [19]. ROBINS-I was modified to ROBINS-E by replacing the term 'intervention' with 'exposure,' renaming of 'target trial' to 'target experiment,' adding fields to collect information on measurement of exposures and outcomes, and adding questions to assess bias in exposure measurement [19]. The ROBINS-E tool assesses 7 domains of bias: confounding, selection of participants into the study, classification of exposures, departures from intended exposures, missing data, measurement of outcomes, and selection of the reported result. Within each of these domains, "signalling questions" are asked to aid the user in making judgements.

Lastly, judgements within each domain are summarized into an overall risk of bias assessment for each study.

The ROBINS-E tool remains under development, and further refinements are not expected to change the domains of bias assessed [19]. Therefore, this is an appropriate time to gather experience with the practical application of the tool to exposure studies. Although ROBINS-I has been evaluated for intervention studies [20, 21], to our knowledge, this is the first paper summarizing user experience with ROBINS-E. As a result of our concerns, we encourage the development of a tool that incorporates existing empirical evidence on the aspects of observational study design that potentially bias outcomes.

METHODS

This paper reports our experience of the practical application of ROBINS-E [18] to 74 exposure studies in 3 areas: dietary exposure, drug harm, and environmental exposure. Twelve researchers (the authors) were convened to reflect the diverse range of backgrounds that might be found among potential users of the tool. Highest degrees included PhD, MD, PharmD, and Masters degrees in disciplines including public health, epidemiology, environmental health, nutrition, and clinical medicine. Relevant work experience ranged from 1 to 27 years. The team included researchers whose first language is not English. All authors have conducted risk of bias assessments in the context of systematic reviews and 4 authors (LB, DG, BM and TW) also have experience in conducting risk of bias assessments in the context of developing guidelines, risk assessments, or other normative guidances that include observational studies of exposures.

We conducted a pilot test of ROBINS-E [version July 2017] [18] to discuss and clarify varying interpretations of the questions. Seven of the authors (LB, NC, JD, AF, DG, AL, BM) applied ROBINS-E to

3 observational studies from different research areas relevant to meta-analyses that we were conducting: 1) a cohort study examining association of dairy consumption with cardiovascular disease [22]; 2) a nested case control study examining association of drug exposure (domperidone) with ventricular arrhythmia [23]; 3) a cross-sectional study examining the association of wind turbine noise with sleep and health outcomes [24]. Based on our experience with this pilot, we clarified questions and developed supplemental guidance for our teams of coders. For example, our supplemental guidance provided definitions for "valid and reliable" exposure and outcome measurements and indicated questions that could be ignored because they did not apply to exposure studies (e.g., regarding "intention to treat"). To promote consistency in how the questions were answered, we also created decision rules for some questions. For example, we agreed that question 7.1 regarding bias in the selection of results would be rated as low risk of bias only if a study protocol could be obtained and it could be determined that all collected results were reported.

We applied ROBINS-E [18]to studies included in systematic reviews we are conducting on nutrition, drug harm and environmental topics. Seventy-four studies were double-coded by teams of 2 authors (NC, AF, AL, BM, SM, JT). Following usual procedures for risk of bias assessment [10, 14, 17], the coders reached consensus on their judgements for each domain. If consensus could not be reached, a third author adjudicated. The assessed studies examined the association of dairy consumption with cardiovascular outcomes (n = 42; 37 cohort, 5 case control), grain consumption with cardiovascular outcomes (n = 24; 21 cohort, 3 case control) and cardiac risks of domperidone exposure (n = 8 studies with 9 analyses; 2 cohort, 4 case-control, 3 case-crossover, with one study reporting both a case-control and case-crossover analysis, each of which was assessed separately for risk of bias). Data from the risk of bias assessments were entered into a data extraction form using REDCap electronic data capture tools

hosted at The University of Sydney [25]. The risk of bias assessment for each paper will be reported in the systematic review in which it is included.

This paper reports user feedback on the ROBINS-E. After the completion of the pilot study and coding of all articles, each coder provide written feedback structured according to each question in the tool, with an additional section to collect any overall feedback. Coders were encouraged to provide specific examples from studies to supplement their feedback. In addition, the process of applying ROBINS-E was discussed in a combined face-to-face, video conference meeting among the coders and the discussion was documented in writing by LB. The discussion was structured by reviewing each question in the tool and documenting comments by questions, and then documenting overall comments on the tool. We discussed the domain elements, accuracy and clarity of each question, and the overall ease of use, including the time it took to complete the assessments. The individual comments and documented discussion were distributed to all coders as Word documents. We inductively and iteratively classified the feedback from the individual coders and group meeting into 7 themes based on commonalities and differences until all the feedback was accounted for in the themes. All authors were then given the opportunity to review the themes and suggest edits. The final themes are listed in Table 1 and summarized below.

RESULTS

Table 1 lists the 7 themes derived from the user feedback and the major concerns related to each theme. Each theme is discussed in more detail below.

1. Comparison to an "ideal" RCT

ROBINS-E, like ROBINS-I, is based on a structured comparison of the observational study being rated to a hypothetical "ideal" randomized controlled trial [26]. The process of using ROBINS-E begins with creating the ideal randomized trial specifying the population to be studied, the exposure assessed, the comparison to the exposure and the outcomes to be measured.

There are some advantages to this approach. ROBINS-E identifies key features of RCTs that reduce bias compared to observational studies and asks questions related to these key features. For example, randomisation theoretically eliminates confounding and ROBINS-E asks a series of questions to determine how likely it is that uncontrolled confounding has influenced the observational study result. Blinding in an observational exposure study minimizes observer and reporter bias in the measurement of exposure and outcome. ROBINS-E usefully assesses these biases by asking for cohort-type studies: "Were outcome assessors unaware of the exposure received by study participants?" and for case-control studies: "Was the definition of case status (and control status, if applicable) applied without knowledge of the exposure received?"

The ideal RCT is used as the comparison because it is at the top of an evidence hierarchy organized by increasing protection against bias. But, the relative value of observational and experimental studies also depends on the question [27]. Observational studies are the best design for answering questions aimed at assessing harm from exposures because real-world exposures are often complex and are never controlled by the investigator. Observational studies do not consistently find different effect estimates than RCTs, suggesting that multiple sources of bias can influence effect estimates of observational studies or RCTs [28, 29]. The ROBINS guidance indicates that the target trial "need not be feasible or ethical" [17]. In the case of studies designed to evaluate potentially harmful exposures, the target trial

could never be designed for a combination of ethical and practical reasons. For example, if a chemical is suspected of being carcinogenic, it would be unethical to randomize trial participants to exposure, and both the number of participants and duration of exposure required would make such a trial impractical. Thus, RCTs will not be available for systematic reviewers and decision makers who need to address questions of harm.

Additional limitations exist because some of the questions derived from evaluating RCTs are inappropriate or impossible to apply for observational studies. For example, ROBINS-E considers biases that arise due to departures from intended exposures as performance biases. They arise when differences occur after the start of interventions in RCTs or exposures in observational studies, but the participant continues (for analysis purposes) to be part of the intended intervention or exposure group. In randomized trials, performance bias can be minimized by blinding of participants and providers of the intervention. ROBINS-E addresses performance bias by asking questions about co-exposures, contamination, switches, and fidelity of implementation. As the exposures being measured are unintended and are not controlled by the investigator, concepts such as switching and fidelity of implementation do not generally apply to observational studies of exposure. For example, the question regarding “deviation from intended exposures” cannot be answered, as exposures are never intended. This question only makes sense in the context of an RCT of an intervention. For case-control studies, this “ideal” RCT framework is particularly unhelpful as a tool to inform risk of bias evaluations due to their retrospective study design, and the use of this design to assess infrequent serious health outcomes.

In addition, there are potential sources of bias that might afflict a particular type of observational study that are not identifiable by comparing it with a theoretical RCT. For example, failure to match by risk

set in a nested case-control study or control for confounding with the matching variable in a matched case-control study can induce bias. In addition, in an RCT, the start of exposure is clearly defined. In exposure studies, the more crucial question is whether follow-up begins at initiation of exposure and this is not assessed by ROBINS-E. These real and important sources of bias specific to aspects of observational study design cannot be detected and assessed by comparing these studies to the theoretic RCT framework of the ROBINS-E tool.

Lastly, the RCT framework does not consider advantages that an observational design can have over a randomized design. Exposure studies often include a broad gradient of exposure levels, unlike trials that are often limited to only a few comparison groups. This range of exposure levels allows dose-response relationships to be established. Dose-response relationships are an important consideration for determining true associations between exposures and health outcomes because of the improbability that bias, except due to confounding with a closely related variable, would mirror the dose-response relationship. Furthermore, ROBINS-E does not assess bias in how dose-response relationships are established because exposure levels are only considered as one aspect of whether measurements of exposure were "robust"[18].

2. Inadequate assessment of bias related to confounding

Determining if uncontrolled confounding biases outcomes

Assessing bias related to confounding is important for observational studies. Confounders are defined as factors that are associated with the exposure and prognostic for the outcome, but are not on the causal pathway [30]. ROBINS-E has limitations in determining whether confounders will bias study

outcomes. ROBINS-E rates a study as having a high risk of bias if it does not control for any or enough relevant confounders. However, there is no question in ROBINS-E regarding the potential to introduce bias through controlling for large numbers of baseline confounders unnecessarily (over-adjusting) [31].

Assessment of the risk of bias associated with confounding reflects not only whether a specific confounder such as age is included in a study, but how that confounder is modelled. Use of very broad age categories could lead to a serious risk of bias, for example, in a study that assessed cardiac risks of a specific exposure and compared groups with unequal age distributions. Additionally, many newer studies use tools such as propensity scores (or high dimensional propensity scores) to account for confounding. ROBINS-E provides inadequate guidance to assess how confounders are modelled or the application of these tools.

Identifying confounders

One of the strengths of the ROBINS-E is that prior to beginning the risk of bias assessment, the investigator is required to pre-specify relevant confounders. This means that all studies will be evaluated for methods used to control or account for the same set of confounders.

The ROBINS-E provides some guidance for identifying confounders, stating that critical confounders "are likely to be identified both through the knowledge of the subject matter experts who are members of the [systematic] review group, and through initial (scoping) reviews of the literature." The guidance should also recommend that other experts who are not part of the review group— such as epidemiologists, toxicologists, biostatisticians, systematic review experts, biologists – be consulted. This

wider consultation with experts in the field should be conducted in a systematic and comprehensive way (eg, [32]).

Ideally, confounders should be identified by searching for systematic reviews examining the association of potential confounders with relevant outcomes and assessing the quality of the reviews using a tool such as ROBIS (Risk of Bias in Systematic Reviews) [33]. This is a more rigorous method than the one recommended by ROBINS-E. However, applying this method consistently for all outcomes and bodies of observational studies would require substantial time. For our application of ROBINS-E, we consulted experts in the field relevant to each review we were conducting and identified systematic reviews that verified whether a particular variable was a confounder. See Table 2 for identification of confounders for each outcome assessed in studies evaluating the association of dairy consumption with cardiovascular disease. Although this list is based on published systematic reviews, we did not assess the risk of bias of each review identified as this would have been too time consuming. Instead, we relied on the most recent published systematic reviews that appeared to have conducted a comprehensive search. Even so, it took over 2 weeks to create and agree upon the list of confounders for the review evaluating the association of dairy consumption with cardiovascular disease. Greater resources would be needed to identify beforehand the confounders for broader questions, such as "What are the adverse health effects of living near a waste dump" or "living near a wind farm." These questions are relevant for public health guidelines, but may consider a very broad range of outcomes including developmental, psychological or clinical outcomes, and their relevant confounders. The practical limitation of using a rigorous method to identify potential confounders must be balanced against using a less rigorous method, such as expert opinion, which makes the selection of confounders more subjective.

Co-exposure vs confounding confusion

ROBINS-E defines co-exposures as "exposures that individuals might receive after or with initiation of the exposure of interest, which are related to the exposure received and which are prognostic for the outcome of interest." During our application of ROBIN-E, the term co-exposure caused confusion. In public and environmental health, most exposures are complex, so the exposure of interest is composed of multiple co-exposures. For example, fumes in a nail salon contain toluene, formaldehyde, phthalates and methylacrylates, among other chemicals. The distinction between co-exposures and confounders is less relevant in observational studies as co-exposures are usually considered as confounders and, when appropriately adjusted, can better represent real-world complex exposures. Misclassification of exposure is more of a concern in observational studies than the contamination of the different exposure groups [31]. Because ROBINS-E was derived from a tool to assess intervention studies, it does not clearly differentiate between confounders, co-exposures, and complex exposures.

Most importantly, in the context of observational studies, co-exposures may be the same as confounders. ROBINS-E distinguishes between characteristics and exposures that are present at baseline, which are defined as confounders, and additional exposures that occur at the same time or following initiation of the exposure of interest. These additional exposures are defined as co-exposures. In practice, this distinction is often arbitrary, as many exposures can be present at baseline and/or after initiation of the exposure of interest. In studies examining the association of whole grain breakfast cereal with cardiovascular outcomes, milk consumption at baseline is a confounder because it is associated with the exposure and prognostic for the outcomes, but not on the causal pathway. But, as breakfast cereal may be eaten with milk, it could also be considered a co-exposure under the ROBINS-E definition because it is received with the exposure of interest and prognostic for the outcome of

interest. For a study of cardiac harms of domperidone, exposure to another medication that prolongs the QT interval could be considered a confounder as it may be associated with exposure (e.g. domperidone-treated patients may also be more likely to receive this drug) as well as cardiac risks. However, it could also be considered a co-exposure, with additional analyses carried out to explore whether there are interaction effects. These interaction effects would not be expected to differ depending on whether the QT-prolonging medication had first been prescribed before domperidone, at the same time, or afterwards, as long as a person was exposed to the two drugs concurrently. In the case of complex exposures (such as the various nutritional components of dietary dairy exposure, or chemical mixtures) co-exposures should not be modelled separately, but would instead be a component of the description of the exposure under assessment.

Controlling for co-exposures that are not confounders, as suggested by ROBINS-E, could induce bias. When analysing presumed causes and effect, including variables that are not known to be confounders (i.e. correlated with both exposure and outcome) and controlling them as confounders could result in over-adjustment of the model, a loss of power and a bias towards the null. Likewise, inappropriately adjusting a variable that lies in the causal pathway between the exposure of interest and outcome as a confounder will bias the effect of the exposure of interest towards the null. Exclusion of cases with co-exposures can also lead to a biased effect estimate if the co-exposure is not associated with the outcome. In sum, there is no analytic reason to evaluate co-exposures if they are not associated with the outcome or can be considered as confounders.

3. **Inadequate assessment of bias related to measurement of exposure**

Determining error in the measurement of exposures and confounders is critical to assessing risk of bias in a study. The ROBINS-E tool asks investigators to specify the methods used to measure these variables and to determine if exposures and outcomes are "measured validly and reliably." We found it necessary to pre-specify the criteria we would use to rate a method as valid. For example, dietary questionnaires are frequently used to assess dietary intake as an exposure. We specified that Food Frequency Questionnaires would be considered low risk of bias for validity of measurement if the study reported that the tool was validated in another study, with the reference provided and relevant coefficients reported.

By limiting the assessment of an exposure measurement to its validity and reliability, ROBINS-E may not adequately capture other deficiencies in measurement that could contribute to bias. ROBINS-E does not assess details of exposure measurement which could be related to the outcome, including the dose, duration or developmental stage at which the exposure occurs. ROBINS-E does not consider differential biases in exposure measurement across study participant groups. Such biases in measurement of air pollution exposures, for example, could result in attenuation of the observed results. Furthermore, surrogate measures such as distance to freeway can often create systematic biases. There have been some efforts to develop instructions tailored to exposures relevant to the study question beforehand, such as for case studies involving air pollution exposures [34].

4. Inappropriate use of an overall risk of bias rating

The ROBINS- E guidance states that the overall rating for risk of bias is determined by the highest risk of bias rating for an individual domain. This rating system implies that all domains contribute equally to the risk of bias of the overall study. It also means that a study with a 'serious' risk of bias in one domain is rated similarly to another in which nearly all domains are judged to be at serious risk of bias, thus failing to discriminate between studies with different biases. Similarly, "quality scores" have not been able to distinguish between high and low risk of bias studies in meta-analyses [35] and there is no empirical evidence to support how each risk of bias item should be weighted[10, 36]. Therefore, the ratings of each domain of the tool are typically reported for each study, allowing users to clearly identify the different sources of bias in a study

5. What's missing in the ROBINS-E risk of bias assessment

The ROBINS-E tool is based on a narrow definition of bias: an error in quantitative effect estimates that may result from a methodological flaw. Non-methodological characteristics can also influence effect estimates and the inferences drawn from them. Two potential sources of bias that are important for exposure studies were not assessed with the ROBINS-E tool: funding sources and conflicts of interest of investigators. Evidence across a variety of fields shows that industry sponsorship is associated with outcomes that favour the sponsor's product, even when industry and non-industry sponsored studies have similar methodological risks of bias [37, 38]. In studies of harmful exposures, industry sponsorship is generally expected to be associated with a bias towards the null.

6. "Signalling questions" not linked to risk of bias ratings in each domain

Each domain lists "signalling questions" to facilitate judgements about the risk of bias in each domain. Our raters agreed on the domain ratings most of the time, but often disagreed on how they rated the signalling questions. Although the signalling questions are useful for making the rationale behind the assessment of each domain transparent, they do not help raters come to a consensus about what they should be considering under each domain. Our raters noted that even when they differed on their answers to the signalling questions, they could have the same rating for the bias domain. Thus, the reasoning behind their ratings was not adequately captured by the signalling questions. The manual does not indicate whether the answers to the signalling questions need to be resolved. Additionally, inadequate guidance is provided on the link between responses to multiple signalling questions within a domain and the risk of bias assessment for the domain. It was not clear to the raters whether a single signalling question indicating a high risk of bias should result in the risk of bias for the domain being rated as 'serious'. Specific issues related to answering the signalling questions for exposure studies are described in Table 3.

7. Practical considerations

Application of the ROBIN-E tool was time consuming. First, time is required to prepare for coding by developing the tables of critical confounders and agreeing on criteria for valid measurements. The amount of time varies depending on the complexity of studies, but, as noted above, it took 2 weeks to develop the table of critical confounders for one systematic review. Regardless of the level of experience of the reviewer, it took 1 to 2.5 hours to code each paper. The tool was cumbersome to use because 1) the skip patterns were difficult to follow, 2) double negatives made answering yes or no

confusing, 3) the language was often dense or overly complicated, and 4) there were inconsistencies between words used in the tool and manual.

Most of the studies we rated with ROBINS-E were cohort studies, which is the observational design most similar to the RCT. We found that the applicability of the tool was worse for case control studies. For example, the tool provides very limited guidance concerning key biases in the selection of cases and controls. Raters are asked only whether the population that gave rise to the cases was clearly defined, and not about other biases that might affect case selection, including whether there was full ascertainment, questionable exclusions, or inclusion of irrelevant cases.

We do not discuss differences in terminology which the ROBINS-E developers acknowledge and which have been discussed extensively [1].

DISCUSSION

The ROBINS-E tool has been developed by consensus of an international team of investigators and has a number of strengths including providing a structured and transparent method to assess risk of bias in observational studies. We applied the tool to over 70 observational studies and found serious limitations. The premise that observational studies should be compared to the "ideal" randomized controlled trial does not adequately capture all the sources of bias that should be considered for observational studies. Important questions related to assessing bias due to confounding and exposure assessment are missing. The ROBINS-E tool uses a rating scheme to calculate an overall risk of bias which fails to discriminate between studies with a single risk of bias or multiple risks of bias. For example, a systematic review of venous thromboembolic (VTE) risks of drospirenone-containing oral

contraceptives considered all population-based studies using administrative data to be at serious or critical risk of bias because some potential confounders, such as family history, were not recorded in administrative data [39]. These studies, which used methods considered state-of-the-art in pharmacoepidemiology, were judged to be at similar overall risk of bias to a study on a selected cohort of women that relied on initial self-report of VTE, with potential exposure recall bias and failure to exclude VTE for reasons unrelated to contraceptive use, such as surgery, cancer or pregnancy [40]. Bias related to "co-exposures" should be addressed under confounding and questions about "unintended exposures" do not make sense. Since ROBINS-E is derived from a tool for assessing studies of interventions (ROBINS-I), we noted a number of instances where the wording of the "signalling questions" used to guide judgements in each domain could not apply to exposure studies. The application of ROBINS-E was time consuming and confusing as raters could not always agree on the meaning of the questions Similarly, as noted during the development of ROBINS-E, based on the narrative responses to the signalling questions, raters reported misunderstanding the concepts in the questions and the information in the studies [19]. Although the tool is still in development and users should access the latest version [18], it is critical that concerns are addressed early in the refinement process.

Our experience in applying the ROBINS-E tool raises concerns that have also been observed by those applying the Cochrane risk of bias tool for observational studies of interventions (ROBINS-I, formerly ACROBAT-NRSI) [20, 21]. These studies have noted that the signalling questions need clarification, the application is time consuming, and the tool lacks testing for different study designs and topic areas. A recent study comparing the ROBINS-I to two other tools for assessing risk of bias in observational studies found that users of the tool rated the ROBINS-I lowest for clarity of instructions, clarity of items, discriminating between high and low risk of bias studies, and that the ROBINS-I required the most time

for training and application [41]. A strength of our study is that we report on experience applying ROBINS-E to over 70 studies of two designs (cohort and case control) over 3 topic areas.

Based on our experience, we do not recommend ROBINS-E for evaluating risk of bias in observational studies of exposures. We are concerned that the risk of bias assessments may not be useful or believable to those working with observational data, including systematic reviewers and guideline developers. The ROBINS-E has been derived from the ROBINS-I and has not been developed with input from potential users of the tool in mind. The reliability and reproducibility of the assessments is likely to be compromised because of the lack of clarity of specific components and a lengthy and complex set of instructions for use. It is also unclear whether ROBINS-E would stand up to an empirical assessment of the association between included risk of bias criteria and effects on study outcomes. This means that studies with methodological characteristics rated as high risk of bias will over- or under-estimate effects compared to studies with lower risks of bias (e.g. a lack of randomization will overestimate drug efficacy).

Exposure studies are frequently used to estimate the chance of harm occurring, for example, adverse health effects related to chemical or drug exposures. By predictably rating observational studies that inform decision making as low quality (as compared to an ideal RCT) application of ROBINS-E could question the validity of estimates of the nature and extent of potential harm. Application of ROBINS-E could bolster arguments of industries claiming that the evidence base is too weak to support regulation or policies to reduce harmful exposures, and will potentially undermine policies that can protect people from harm. Often these products are already being used in the marketplace and exposures are ongoing in the population, so delaying action will threaten public health protection.

Assessing risk of bias in observational studies of exposures is a complex topic and it may be difficult for any tool to incorporate some aspects that are essential to evaluating observational studies. Furthermore, a single tool used to address bias in different observational study designs, such as proposed by the ROBINS-E, may be unrealistic. Further study and collaboration will be required to develop a simpler, alternative tool that meets the needs of the environmental and public health community. We are not suggesting that the constraints of observational studies should lead to a lower standard in how risk of bias is assessed in observational studies compared to RCTs. We are proposing that risk of bias assessments for observational studies need to be meaningfully and rigorously aligned with the sources of bias in studies of "real-world" exposures. Selection of the items for a risk of bias tool should be informed by empirical evidence of bias and conceptual considerations. For example, randomization and blinding are part of the Cochrane risk of bias tool for randomized trials because there is evidence that inadequate application of these methods overestimates efficacy estimates [42, 43]. We recommend similar empirical tests of the association between methods and results for each risk of bias domain to be included in a tool for assessing observational studies. Thus, rather than developing a tool by modifying one for evaluating trials of interventions, development should start with systematic reviews of methodological studies assessing the association of study design characteristics with effect estimates.

An empirically based tool will be useful to systematic reviewers and public health guideline developers if it is simple to apply and developed with input from potential users. We recommend that development of an empirically based tool should involve getting feedback from a variety of stakeholders to define each item that will be included. For example, development of an empirically based tool for assessing bias in studies of harmful environmental and drug exposures should involve researchers in environmental epidemiology and pharmacoepidemiology to ensure that the language and definitions

used are consistent with these fields of research. We recommend that the questions avoid over or double counting bias domains. Lastly, we recommend that the tool and guidance for use are available for free open access to facilitate use

CONCLUSIONS

Although the ROBINS-E tool has been developed based on tools that are commonly used for assessing risk of bias in studies included in clinical systematic reviews and guidelines, our experience suggests that it does not meet the need for an international standard for evaluating human observational studies for questions of harm relevant to public and environmental health. We propose starting with an assessment of the empirical basis for items that should be included in a tool for assessing risk of bias in observational studies. This evidence could then be presented to a wide variety of stakeholders to gather further feedback on refining items for the tool. A simpler, empirically based tool is more likely to be adopted by systematic reviewers, guideline developers, journal editors, and researchers conducting observational studies of exposures.

DECLARATIONS

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

The datasets generated and/or analysed during the current study are available in the Research Data Australia data discovery service of the Australian National Data Service (ANDS). ANDS is supported by the Australian Government through the National Collaborative Research Infrastructure Strategy Program. [PERSISTENT WEB LINK TO DATASETS TO BE ADDED]

Competing interests

The authors have no competing interests.

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Authors' contributions

LB drafted the manuscript and all authors provided critical revision. All authors evaluated articles using ROBINS-E. All authors read and approved the final manuscript

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Table 1: ROBINS-E user experience themes and concerns

1. Comparison to an "ideal" randomized controlled trial (RCT)
RCTs are not available for exposure studies and, therefore, not relevant to decision makers who must rely on observational studies of exposures
Assessing observational studies based on RCTs results in a default rating of high risk of bias
Some of the questions derived from evaluating RCTs of interventions are inappropriate or impossible to apply for observational studies
Sources of bias specific to observational studies may not be captured by comparison to an RCT
2. Inadequate assessment of bias related to confounding
Does not capture bias related to over-adjustment for confounders or inappropriate modelling of confounders
Does not capture advantages of newer statistical methods used for control for confounding
Clearer guidance is needed on method for identifying confounders
Does not differentiate between confounders, co-exposures, and complex exposures
3. Inadequate assessment of bias related to measurement of exposure
Assessment is limited to validity and reliability of the measurement, and these concepts are not clearly defined
4. Use of an overall risk of bias rating
Does not distinguish between studies that have a 'serious" risk of bias in one domain and those that have multiple 'serious' risks of bias
Assumes all risk of bias domains are weighted equally
5. Additional risks of bias relevant to observational studies are not assessed (e.g., funding source)
6. Signalling questions
Do not consistently help raters come to a consensus on how to rate a bias domain
Specific questions unclear or confusing
7. Practical considerations
Time consuming to use
There are limitations of using a single tool to rate different study designs

Table 2: Table of critical confounders developed for a systematic review of studies assessing the association of dairy intake with cardiovascular outcomes

Outcome	Confounders (p/h)	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	Fibre supplement (p) Trans Fat (h) Polyunsaturated Fat (n-6) (p) Sodium (+Na) (h)	
4. CHD events	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)	
p = protective, h = harmful		

Table 3: Comments on signalling questions in the ROBINS-E risk of bias tool that were difficult to assess and often irrelevant to a particular study

Domain 1: Confounding
Signalling question 1.3: time-varying confounding: Were exposure discontinuations or switches likely to be related to factors that are prognostic for the outcome?
Cohort studies can continue over decades so changes in exposure may be related to a wide variety of factors. For example, in studies assessing dietary exposures, it is impossible to distinguish whether someone has made a change in their diet due to a diagnosis or onset of a symptom rather than personal choice or social reasoning (e.g. veganism).
1.4: baseline confounding: Did the authors use an appropriate analysis method that adjusted for all the critically important confounding areas?
Most of the studies we coded had many relevant confounders and it was rare that all confounders were controlled in every study, so we modified this question by developing decision rules around the number of confounders that were taken into account. We also determined if the study avoided adjusting for post-exposure variables. For example, in a study assessing cardiovascular disease (CVD) as an outcome, it is inappropriate to adjust for new incidence of hypertension that has occurred during the exposure period. Hypertension is not a confounder because it is on the causal pathway to CVD.
Domain 2: Bias in selection of participants
2.3 and 2.3: Were the post-exposure variables that influenced selection associated with exposure? Were the post-exposure variables that influenced eligibility selection influenced by the outcome or a cause of the outcome?
Since cohort studies are often assembled based on exposure levels, it is rare for selection to be unrelated to exposure. In exposure studies, participants are almost always selected into the study based on characteristics that are assessed after the start of exposure. For example, in a study assessing the association of an exposure with cardiovascular disease, subjects may be excluded if baseline surveys or clinical records determine they have diabetes, hypertension, or metabolic syndrome, characteristics which may be associated with exposure or outcome.
Domains 3 and 4: Exposures
2.4 Do start of follow-up and start of exposure coincide for most participants? *3.2* Did entry into the cohort begin with start of the exposure?

For many types of exposures, such as dietary exposures or various types of pollution, exposure can begin in infancy, long before entry into a cohort. Unlike interventions, exposures are not initiated by the investigators, so exposure and follow-up will rarely coincide.
4.1 Is there concern that changes in exposure status occurred among participants? *4.2* Did many participants switch to other exposures?
In exposure studies, there is always concern that changes in exposure status occurred among participants. It is rare that exposure measurements are made continuously over long periods of exposure. Techniques are used that are likely to correct for this issue, such as multiple assessments of exposure (e.g. every 2 years) and person-years adjustment. ROBINS-E terms such as "intended" exposure, "initiating and adhering to an exposure," and "switching" exposures are applicable to randomized trials, but do not apply to exposure studies where exposure is not controlled by the investigators.
Domain 5 - 7*:* bias due to missing data, bias in measurement of outcomes, and bias in the selection of reported results
Most of the questions related to these domains were applicable to observational studies. Signalling questions related to selective reporting of results (domain 7) ask whether particular outcomes are reported from multiple outcome measures, particular analyses are reported from multiple analyses, and whether data are reported for only a subset of participants. We were unable to answer these questions unless the protocol for the study was available and published protocols are rare for observational studies. Therefore, we most frequently coded this domain as "not enough information."

APPENDIX v

Associations between industry involvement and study characteristics at the time of trial registration in biomedical research

Short title: Industry involvement and study characteristics at time of trial registration

(Under Review)

Anna Lene Seidler[1], Kylie Hunter[1], Nicholas Chartres[2], Lisa Askie[1]

1 NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia

2 The University of Sydney, Sydney, Australia

Correspondence to:

Anna Lene Seidler

NHMRC Clinical Trials Centre, the University of Sydney

MAIL: Locked bag 77, Camperdown NSW 1450, Australia

PHONE: +61 2 9562 5082

EMAIL: lene.seidler@ctc.usyd.edu.au

Abstract

Background: Commercial or industry funding is associated with outcomes that favour the study funder in published studies, across various areas of research. However, it is currently unclear whether there are differences between trials with and without industry involvement at the stage of trial registration.

Objective: To determine whether industry involvement (industry sponsorship, funding, or collaboration) is associated with trial characteristics at the time of trial registration.

Methods: We conducted a cross-sectional analysis of all interventional studies registered on the Australian New Zealand Clinical Trials Registry in 2017 and classified them by industry involvement. We analysed whether there were differences in study characteristics (including type of control, sample size, study phase, randomisation, registration timing, and purpose of study) by industry involvement.

Results: Industry involvement was reported by 21% of the 1,433 included trials. Only 40% of trials with industry involvement used an active control compared to 58% of non-industry trials (OR = 0.49, 95%CI = 0.38 to 0.63), and industry trials reported smaller sample sizes ($Median(IQR)_{industry}$=45(24-100), $Median(IQR)_{non\text{-}industry}$=70(35-160)). Industry trials were more likely to be earlier phase trials ($X^2(df)=71.46(4)$, p <.001). There was no difference in use of randomisation between industry (70%) and non-industry trials (73%) (OR=0.88, 95%CI=0.67-1.20). Eighty-three percent of industry trials compared to 70% of non-industry trials were prospectively registered (OR=2.02, 95%CI=1.47-2.82). Industry trials were more likely to assess treatment (83%), rather than prevention, education or diagnosis compared to non-industry trials (70%) (OR=3.02, 95%CI=2.17-4.32).

Conclusion: The current study gives insight into differences in trial characteristics by industry involvement at registration stage. The reduced use of active controls in trials with industry involvement may increase effect sizes and thus produce results that are more favourable. Non-industry funders and

sponsors are crucial to ensure research addresses not only treatments, but also prevention, diagnosis and education questions.

Introduction

A large proportion of clinical trials are funded by the commercial sector. For instance, in the United States 70% of money for drug trials is provided by industry.[1] The impact of industry involvement on study outcomes and how best to manage this has been widely debated in the scientific community.[2,3] Some see industry involvement as necessary so that researchers and industry funders can fulfil their joint mission of fighting human disease. [4] Others are concerned that the strong financial incentive of industry-funded trials may threaten the credibility of research and thus poses a risk to evidence-based medicine.[5]

Previous empirical examinations of industry- and non-industry-funded pharmaceutical, tobacco and chemical research found that industry funding was associated with outcomes that favoured the commercial funder, even when controlling for other biases in the methods.[6-14] A Cochrane review examining the association of industry funding and favourable outcomes in primary research studies of drug or medical device studies across different fields of research found that industry-funded studies were more likely to report favourable efficacy results (risk ratio (RR) = 1.27, confidence interval (CI) = 1.21 to 1.44).[15] These differences between industry and non-industry funded research could not be explained by methodological biases. Studies using the Cochrane risk of bias tool found no difference on the domains of allocation sequence concealment, sequence generation, or loss to follow-up, and industry funded trials were of lower risk of bias in the blinding domains.[15]

This effect has previously been named 'funding bias' and is evident not only when comparing industry funded to non-industry funded trials, but also when comparing trials that were funded by different commercial companies.[2] For instance, in head-to-head comparisons of industry funded trials examining statins, results were more likely to favour the funder's drug compared to the competitor drug.[16] Mechanisms beyond the traditional risk of bias tool have been proposed that may explain this funding

bias, including systematic differences in study design, conduct, and the reporting of results.[17] These mechanisms include the choice of an inappropriate control, conducting many small trials to then selectively publish the ones that yield impressive results, and putting a spin on conclusions.[5,17,18]

Clinical trial registries are a valuable resource for exploring the landscape of clinical trials. The International Committee of Medical Journal Editors (ICMJE) requirement of prospective trial registration [19] and the recognition of clinical trial registration as an ethical requirement [20,21] have led to an increase in registration rates over the last decade. A recent study audited registration status of all clinical trials published in 28 general and specialty, high- and low impact journals from January to June 2017. Of the audited trials, 95% of trials were registered on a World Health Organisation recognized clinical trials registry.[22] To date, there has been one study using trial registry data (from the US registry ClinicalTrials.gov) to examine characteristics of drug trials for five drug categories depending on industry funding.[23] This study was however restricted to five drug categories; and it included only trials registered up to 2006, a time at which trial registration was not yet generally required and thus registration rates were low.

The Australian New Zealand Clinical Trials Registry (ANZCTR) routinely collects detailed information on the involvement of the commercial sector in trials, as well as the following trial characteristics relevant to funding bias: *(1) Type of control and sample size* are mechanisms that have previously been proposed to explain funding bias.[5,17] ANZCTR data allow to systematically assess whether type of control and sample size differ depending on industry involvement. (2) *Randomised allocation and registration timing* are two characteristics assessed on the Cochrane risk of bias tool[,23] (in the domains allocation concealment and selective reporting). For published trials, funding bias is not evident in the traditional risk of bias assessment domains of the Cochrane risk of bias tool,[15,24] but to date it is unclear whether there are differences at registration stage. (3) *Study phase and purpose* can indicate whether the general

aim and type of trial differ for trials conducted by industry as opposed to trials conducted by non-industry stakeholders such as universities or governments.

The aim of the current study was to determine whether industry involvement (industry sponsorship, funding, or collaboration) is associated with trial characteristics relevant to funding bias (type of control, sample size, study phase, randomised allocation, registration timing and study purpose) at the time of trial registration.

Methods

Study design, eligibility criteria and data source

This was a cross-sectional analysis, including all interventional studies that were registered on the ANZCTR in 2017. Observational studies were excluded, since many of the examined study characteristics (e.g. type of control, randomisation) do not apply to observational studies. All measures were extracted directly from the ANZCTR database (which contains raw, row-by-row data for all ANZCTR registry records) into a comma-separated values (csv) data file.

The ANZCTR is a Primary Registry in the World Health Organisation Registry Network. It accepts trial registrations from all over the world, but over 80% of all trials registered on the ANZCTR are Australian or New Zealand trials.[25]

Measures

Classification of industry involvement

The ANZCTR collects information on funding, sponsorship and collaborators:

- *Funding* is defined as financial/ material or infrastructure support, and each study can list multiple funding sources.

- *Primary sponsor* is the individual or organisation initiating and managing the study, usually the principal investigator. Only one primary sponsor can be selected on the ANZCTR. Whilst this term has been used differently across the literature, on the ANZCTR the primary sponsor carries the main responsibility but does not necessarily fund the study.
- *Secondary sponsor* is defined as additional individuals or organisations that have agreed with the primary sponsor to jointly take on responsibilities of sponsorship. Studies can list one, none, or multiple secondary sponsors.
- *Collaborators* are individuals or organisations that have also agreed to take on responsibilities of sponsorship. Multiple entries are possible for this field.

For each of these fields, registrants select one of the following options: Commercial sector/industry, University, Government body, Hospital, Individual (which may for instance be an academic lead acting as sponsor for a trial involving multiple stakeholders), Charities/societies/foundations, Other collaborative groups, Other. For the purposes of this study, 'Other collaborative groups' and 'Other' have been merged to a single field 'Other'.

Registrants also give further detailed information (name and contact information) for each involved stakeholder in a free-text field. Information is quality-checked and if necessary queried by ANZCTR staff before being approved for registration.

For this study, a new measure *any industry involvement* was computed, indicating whether 'Commercial sector/ industry' was listed in any of the above fields (i.e. whether there was any industry funding, sponsorship, or collaboration).

Study characteristics

The following study characteristics measures were included in the analysis:

Type of control is the type of treatment against which the intervention is being compared, categorised as: *Placebo* (inactive or sham treatment), *Active* (such as standard care, alternate form of treatment, dose comparison), *Uncontrolled* (same intervention applied to all subjects), *No treatment* (the control group received no treatment), and *Other* (such as historical control groups).

Target sample size was defined as the anticipated number of participants per trial. This was included rather than actual sample size given many of the trials had not completed recruitment at time of analysis since they were registered in 2017. An additional variable was created indicating whether target sample size was above or below the median of all studies.

Study phase was defined as the step at which research is conducted in treatment development. Phase 1 trials evaluate metabolism and pharmacological action of drugs, and monitor side effects. Phase 2 trials evaluate the effectiveness of new drugs in patients with the disease or condition being studied and to determine common short-term side effects and risks. Phase 3 involves the acquisition of additional information on benefits and risk, including possible adverse reactions. In Phase 4 trials, additional information is acquired after a drug has been marketed, monitoring aspects such as toxicity, risks, utility, benefits and optimal use. On the ANZCTR, 'Phase' is an optional field, and registrants can also choose combined phases (e.g. Phase 2/3). For this study, combined phases were re-grouped into the lower phase (e.g. all Phase 2/3 trials were categorised as Phase 2 trials).

Randomised allocation was defined as whether subjects were allocated randomly to their treatment group. In a *randomised-controlled trial*, subjects are allocated randomly to either the intervention or control group. In a *non-randomised trial* subjects are allocated deliberately, or not at random. This includes single-arm trials with no control group.

Registration timing was defined as whether the trial was registered *prospectively* (before enrolment of the first participant) or *retrospectively* (after enrolment of the first participant).

Study purpose includes the categories *treatment (*studies designed to evaluate interventions for treating a health condition)*, prevention (*studies designed to assess interventions aimed at preventing the development of a disease or health condition)*, diagnosis (*studies designed to evaluate interventions aimed at identifying a disease or health condition), or *education/counselling/training (*studies designed to assess interventions in an educational, counselling or training environment).

Analysis

The frequency and proportion of study characteristics was compared by industry involvement and also by primary sponsor type. For binary characteristics, we calculated odds ratios (OR) and 95% confidence intervals (CI) using a logistic regression model to measure the association between industry involvement or primary sponsor and trial characteristics. For analyses by primary sponsor, the largest group (university sponsor) was used as a reference group for logistic regression. For categorical outcomes, chi-square tests were performed to measure the association. For continuous measures, mean differences and 95% CI were calculated using linear regression models. A sensitivity analysis was conducted calculating the associations between trial characteristics and any industry funding (i.e. any financial/material/infrastructure support for the study from the commercial sector/ industry) instead of any industry involvement (as a sponsor, collaborator and/or funder). All analyses were conducted using the open-source software R.[26]

Results

We included a total of 1,433 interventional studies in our analyses. Of these, 300 (21%) reported any industry involvement (industry funding, sponsorship and/or collaborator). Of the trials with industry involvement, the majority (n = 285, 95%) reported industry funding, about half (n = 153, 51%) reported a

primary industry sponsor, and fewer reported a secondary industry sponsor (n = 50, 17%) or an industry collaborator (n = 12, 4%). For primary sponsor type, university sponsorship was reported most commonly (n = 541, 38%), followed by individual sponsors (n = 318, 22%), hospitals (n = 253, 18%), commercial sector/industry (n = 153, 11%) government bodies (n=53, 4%), and charities/societies/foundations (n=24, 2%). The remaining 91 trials (6%) listed 'other' as their primary sponsor. Frequencies for trial characteristics by industry involvement are shown in Table 1, and frequencies for trial characteristics by primary sponsor type are shown in Table 2.

Table 1. Study characteristics by industry involvement.

	Any industry involvement (n = 300)	No industry involvement (n = 1,133)
Type of control		
Active (n = 773), *n(%)*	120 (40%)	653 (58%)
Placebo (n = 251), *n(%)*	99 (33%)	152 (13%)
No treatment (n = 127), *n(%)*	10 (3%)	117 (10%)
Uncontrolled (n = 248), *n(%)*	66 (22%)	182 (16%)
Other (n = 34), *n(%)*	4 (1%)	24 (2%)
Missing (n = 6), *n(%)*	*1 (0.3%)*	*5 (0.4%)*
X^2(df), p-value	*X^2(4) = 84.23, p <.001*	
OR, 95% CI: active vs non-active	*OR = 0.49, 95% CI = 0.38 to 0.63*	
Study phase		
Phase 1 (n = 126), *n(%)*	84 (28%)	42 (4%)
Phase 2 (n = 103), *n(%)*	28 (9%)	75 (7%)
Phase 3(n = 38), *n(%)*	11 (4%)	27 (2%)
Phase 4 (n = 96), *n(%)*	15 (5%)	81 (7%)
Non-applicable/ missing (n = 1,069), *n(%)*	162 (54%)	907 (80%)
X^2(df), p-value	*X^2(4) = 71.46, p <.001*	
Sample size		
Median (IQR)	45 (24-100)	70 (35-160)
Mean (SD)	96 (198)	249 (689)
≤60 (n = 721), *n(%)*	182 (61%)	539 (48%)
>60 (n = 712), *n(%)*	118 (39%)	594 (52%)
OR, 95% CI: above or below 60 (Median)	*OR = 0.59, 95% CI = 0.45 to 0.76*	
MD (95% CI)	*MD = -152.99, 95% CI = -231.99 to -74.98*	
Randomisation		
Randomised-controlled (n = 1,037), *n(%)*	211 (70%)	826 (73%)
Non-randomised (n = 396), *n(%)*	89 (30%)	307 (27%)

OR, 95% CI: randomised vs non-randomised	*OR = 0.88, 95% CI = 0.67 to 1.20*	
Registration timing		
Prospective (n = 1,044), *n(%)*	248 (83%)	796 (70%)
Retrospective (n = 389), *n(%)*	52 (17%)	337 (30%)
OR, 95% CI: prospective vs retrospective	*OR = 2.02, 95% CI = 1.47 to 2.82*	
Purpose of study		
Treatment (n = 980), *n(%)*	249 (83%)	731 (65%)
Prevention (n = 246), *n(%)*	34 (11%)	212 (19%)
Education/counselling/training (n = 133), *n(%)*	5 (2%)	128 (11%)
Diagnosis (n = 74), *n(%)*	12 (4%)	62 (5%)
X^2*(df), p-value*	$X^2(3) = 44.07, p < .001$	
OR, 95% CI: treatment vs other purpose	*OR = 2.68, 95% CI = 1.96 to 3.75*	

Note: Odds ratios and chi-square values were calculated omitting missing cases from the dataset. OR = Odds Ratio; CI = Confidence Intervals; df = degrees of freedom. For the mean and mean difference calculations extreme outliers with sample sizes of 10,000 and above (n = 6) were set as missing

Table 2. Study characteristics by primary sponsor type

	University (n = 541)	Commercial sector/ industry (n = 153)	Government (n = 53)	Hospital (n = 253)	Charities/societies/ foundations (n = 24)	Individual (n = 318)	Other (n = 91)
Type of control							
Active (n = 773), *n(%)*	312 (58%)	53 (35%)	28 (53%)	153 (60%)	12 (50%)	167 (53%)	48 (53%)
Placebo *(n = 251), n(%)*	87 (16%)	58 (38%)	6 (11%)	25 (10%)	4 (17%)	52 (16%)	19 (21%)
No treatment (n = 127), *n(%)*	66 (12%)	3 (2%)	3 (6%)	15 (6%)	1 (4%)	36 (11%)	3 (3%)
Uncontrolled (n = 248), *n(%)*	65 (12%)	38 (25%)	16 (30%)	54 (21%)	7 (29%)	49 (15%)	19 (21%)
Other (n = 34), *n(%)*	9 (2%)	0 (0%)	0 (0%)	5 (2%)	0 (0%)	12 (4%)	2 (2%)
Missing (n = 6), *n(%)*	2 (0%)	1 (1%)	0 (0%)	1 (0%)	0 (0%)	2 (1%)	0 (0%)
OR, 95% CI: active vs non-active	*1 (Reference)*	*0.39 (0.27 to 0.56)*	*0.82 (0.47 to 1.45)*	*1.12 (0.83 to 1.52)*	*0.73 (0.32 to 1.68)*	*0.81 (0.61 to 1.07)*	*0.82 (0.52 to 1.28)*
X^2(df), p-value	*$X^2(24) = 120.36, p < .001$*						
Study phase							
Phase 1 (n = 126), *n(%)*	12 (2%)	76 (50%)	1 (2%)	15 (6%)	5 (20%)	14 (4%)	3 (3%)
Phase 2 (n = 103), *n(%)*	26 (5%)	15 (10%)	5 (9%)	25 (10%)	1 (4%)	16 (5%)	15 (16%)
Phase 3(n = 38), *n(%)*	13 (2%)	5 (3%)	0 (0%)	4 (2%)	1 (4%)	7 (2%)	8 (9%)
Phase 4 (n = 96), *n(%)*	22 (4%)	2 (1%)	12 (23%)	25 (10%)	3 (12%)	22 (7%)	10 (11%)
Non-applicable (n = 1,069), *n(%)*	468 (87%)	55 (36%)	35 (66%)	184 (73%)	15 (60%)	259 (81%)	55 (60%)
X^2(df), p-value	*$X^2(18) = 142.04, p < .001$*						
Sample size							
≤60 (n = 721), *n(%)*	240 (44%)	113 (74%)	20 (38%)	143 (57%)	15 (63%)	150 (47%)	40 (44%)
>60 (n = 712), *n(%)*	301 (56%)	40 (26%)	33 (62%)	110 (43%)	9 (38%)	168 (53%)	51 (56%)
OR, 95% CI: above or below 60 (Median)	*1 (Reference)*	*0.28 (0.19 to 0.42)*	*1.32 (0.74 to 2.39)*	*0.61 (0.45 to 0.83)*	*0.48 (0.20 to 1.09)*	*0.89 (0.68 to 1.18)*	*1.02 (0.65 to 1.60)*
Randomisation							
Randomised-controlled (n = 1,037), *n(%)*	421 (78%)	110 (72%)	34 (64%)	158 (62%)	12 (50%)	234 (74%)	68 (75%)
Non-randomised (n = 396), *n(%)*	120 (22%)	43 (28%)	19 (36%)	95 (38%)	12 (50%)	84 (26%)	23 (25%)
OR, 95% CI: randomised vs non-randomised	*1 (Reference)*	*0.73 (0.49 to 1.10)*	*0.51 (0.28 to 0.94)*	*0.47 (0.34 to 0.66)*	*0.29 (0.12 to 0.66)*	*0.79 (0.58 to 1.10)*	*0.84 (0.51 to 1.43)*
Registration timing							
Prospective (n = 1,044), *n(%)*	391 (72%)	128 (84%)	42 (79%)	173 (68%)	15 (63%)	225 (71%)	70 (77%)
Retrospective (n = 389), *n(%)*	150 (28%)	25 (16%)	11 (21%)	80 (32%)	9 (38%)	93 (29%)	21 (23%)
OR, 95% CI: prospective vs retrospective	*1 (Reference)*	*1.96 (1.25 to 3.20)*	*1.47 (0.76 to 3.06)*	*0.83 (0.60 to 1.15)*	*0.64 (0.28 to 1.55)*	*0.93 (0.68 to 1.26)*	*1.28 (0.77 to 2.20)*
Purpose of study							
Treatment (n = 980), *n(%)*	338 (62%)	141 (92%)	32 (60%)	170 (67%)	16 (67%)	213 (67%)	70 (77%)
Prevention (n = 246), *n(%)*	119 (22%)	8 (5%)	13 (25%)	39 (15%)	6 (25%)	52 (16%)	9 (10%)
Education (n = 133), *n(%)*	72 (13%)	0 (0%)	5 (9%)	11 (4%)	1 (4%)	34 (11%)	10 (11%)
Diagnosis (n = 74), *n(%)*	12 (2%)	4 (3%)	3 (6%)	33 (13%)	1 (4%)	19 (6%)	2 (2%)
OR, 95% CI: treatment vs other purpose	*1 (Reference)*	*7.06 (3.97 to 13.72)*	*0.92 (0.52 to 1.65)*	*1.23 (0.90 to 1.69)*	*1.20 (0.52 to 3.01)*	*1.22 (0.91 to 1.63)*	*2.00 (1.21 to 3.43)*
X^2(df), p-value	*$X^2(18) = 118.39, p < .001$*						

Note: Odds ratios and chi-square values were calculated omitting missing cases from the dataset. OR = Odds Ratio; CI = Confidence Intervals; df = degrees of freedom.

Type of control. Trials with industry involvement were less likely to use active controls (40%) compared to trials without industry involvement (58%) (OR = 0.49, 95% CI = 0.38 to 0.63, Fig 1), and trials that reported an industry primary sponsor (35%) were less likely to use an active control than trials that reported non-industry primary sponsors (56%) (OR = 0.39, 95% CI = 0.27 to 0.56, Fig 2).

Fig 1. Trial characteristics by industry involvement

Fig 2. Control group by primary sponsor type

Target sample size. Trials with industry involvement were smaller on average. They had a median sample size of 45 (Interquartile range [IQR] = 24-100) whilst trials without industry involvement had a median sample size of 70 (IQR = 35-160). The mean difference between trials with and without industry involvement was -153 (95% CI = -231 to -74). Trials with an industry primary sponsor were less likely to have a sample size above the median of 60 (OR = 0.28, 95% CI = 0.19 to 0.42).

Study phase. Since trial phase is an optional field on the ANZCTR, and does not apply to non-drug trials, information on trial phase was only available for 364 (25%) of the included trials. For trials with data available, industry involvement was significantly associated with study phase (Fig 3, X^2 (df)=71.46(4), $p < .0001$). Trials with industry involvement were more likely to be early trials (Phase 1) (61% of trials with available phase data), whilst trials without industry involvement were more likely to be post-marketing trials (Phase 4) (36%).

Fig 3. Trial phases by industry involvement

Randomised allocation. There was no significant difference between trials with (70%) and without industry involvement (73%) for randomised allocation (OR = 0.88, 95% CI 0.67 to 1.20). Similarly, there was no difference by primary sponsor type with 72% of trials with an industry primary sponsor and 72% of trials without an industry primary sponsor using randomisation (OR = 0.73, 95% CI = 0.49 to 1.10).

Registration timing. Trials with any industry involvement were more likely to be prospectively registered (83%) when compared to those with no industry involvement (70%) (OR = 2.02, 95% CI 1.47 to 2.82). A similar association was found for trials that reported a primary industry sponsor (84% prospectively registered) compared to trials with university as a primary sponsor (72%) (OR = 1.96, 95% CI = 1.25 to 3.20).

Study purpose. As shown in Fig 4, trials with industry involvement were more likely to be aimed at treatment (83%) and less likely to assess prevention, education/counselling/training or diagnosis as their purpose compared to non-industry trials of which 70% were aimed at treatment (OR = 2.68, 95% CI = 1.95 to 3.75). Similarly, trials with an industry primary sponsor (92%) were more likely to be aimed at treatment with 92% of trials with an industry primary sponsor aimed at treatment compared to 62% of trials with a university as the primary sponsor (62%) (OR = 7.06, 95% CI = 3.97 to 13.72).

Fig 4. Study purpose by primary sponsor type

We performed a sensitivity analysis examining associations between any industry funding (instead of any industry involvement) with trial characteristics. This did not change any of the proportions by more than two percentage points. This was not surprising since 95% of studies with industry involvement also reported industry funding.

Discussion

In 2017, 21% of all interventional studies registered on the ANZCTR reported industry involvement, and for 11% the individual or organisation taking primary responsibility for the study (i.e. the primary sponsor) was from the commercial sector/ industry. Industry trials differed from non-industry trials for a range of trial characteristics. Trials with industry involvement were smaller on average and less likely to use an active comparator, and they were more likely to be early phase trials and to be prospectively registered. Trials with industry involvement were more likely to be aimed at treatment, and less likely to

list prevention, education/counselling/training or diagnosis as their primary purpose. These differences were even more pronounced when comparing trials with an industry primary sponsor to trials with a non-industry primary sponsor.

Strengths and weaknesses

This study used a complete dataset of 1,433 interventional trials registered on the ANZCTR in 2017. All data were quality-checked and if necessary queried by ANZCTR staff prior to being approved for registration. Thus, data quality was high, and there were little to no missing values for most variables, apart from missing values for fields that were non-applicable to some of the studies (e.g. study phase only applied to drug trials). The dataset contained a range of key metrics to assess different types of industry involvement and various trial characteristics of interest. Examining interventional trials at registration allowed a unique insight into associations between industry involvement and trial characteristics at an early stage, often before trial results are known and thus before studies can be selectively reported based on their results (i.e. publication or selective reporting bias).

There were also some limitations to this study. This was a cross-sectional study reporting unadjusted associations between funding source and trial characteristics. The results are useful for descriptive purposes, however, they should not be interpreted causally. For instance, industry funded trials were more likely to be earlier phase trials but also had a smaller sample size. For earlier phase trials smaller sample sizes may be more appropriate, and thus, the smaller sample sizes may be a result of a larger number of earlier phase trials.

The ANZCTR is one of 15 WHO Primary Registries. It is possible, that studies registered on the ANZCTR are different to studies registered on other registries. For instance, a previous study found the proportion of industry-funded trials on the US-registry ClinicalTrials.gov to be 44% [27] which is higher

than the rate of 21% that we observed on the ANZCTR in this study. Future studies may thus examine the association between industry involvement and trial characteristics in other registries.

Interpretation and implications

This study found an association between industry involvement and lower use of active controls. The use of non-active controls has previously been suggested as a potential mechanism that may partly explain funding bias: comparing a new treatment to a placebo as opposed to the current gold standard treatment (an active control) is likely to yield larger effect sizes and has higher chances of reaching statistical significance. [5,17] Another potential mechanism that has previously been suggested is the conduct of multiple small trials and selectively publishing the ones that yield favourable results. Again, we found an association between industry involvement and smaller sample sizes. Yet, it is important to note that we are presenting descriptive associations in this study and thus these results need to be interpreted with caution. For some conditions there is no current gold standard treatment and thus a placebo control is the best available comparator. Similarly and as discussed above, the association between industry involvement and sample sizes may be explained by industry being involved in earlier phase trials, or it may be that later phase industry trials are more likely to be registered on other registries. Nonetheless, it may be appropriate to pay particular attention to the appropriate use of controls and sufficient sample size when assessing the methodological quality of trials with industry involvement on a case-by-case basis.

Previous studies have reported that funding bias was not evident in traditional risk of bias assessment domains such as the Cochrane risk of bias tool.[24] This study examined two variables that would be assessed in the Cochrane risk of bias tool: randomisation (Cochrane risk of bias tool: allocation concealment) and prospective registration (Cochrane risk of bias tool: selective reporting). We found no association between industry involvement and randomised allocation and trials with industry

involvement were more likely to be prospectively registered. This confirms the previous finding that funding bias does not appear to be reflected on 'traditional' risk of bias assessment tools.

There was a strong association between industry involvement and the primary purpose of the study. Only 17% of trials with industry involvement (compared with 35% of trials without industry involvement) reported an aim other than treatment. This was even more pronounced when examining studies that had an industry primary sponsor, of which only 8% reported an aim other than treatment. The commercial sector needs to invest in clinical trials that are promising to be financially lucrative, and these may most often be related to treatment. Yet, prevention and education are crucial for population health and lead to lower demands and costs for public healthcare systems. Non-industry research is therefore important to ensure that research does not only address treatment, but also prevention and education questions.

Conclusion

The current study gives insight to differences in trial characteristics by industry involvement at design stage. The reduced use of active controls in trials with industry involvement may increase effect sizes and thus produce results that are more favourable. Non-industry funders and sponsors are needed to ensure research addresses not only treatment, but also prevention and education questions.

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Fig 1. Trial characteristics by industry involvement

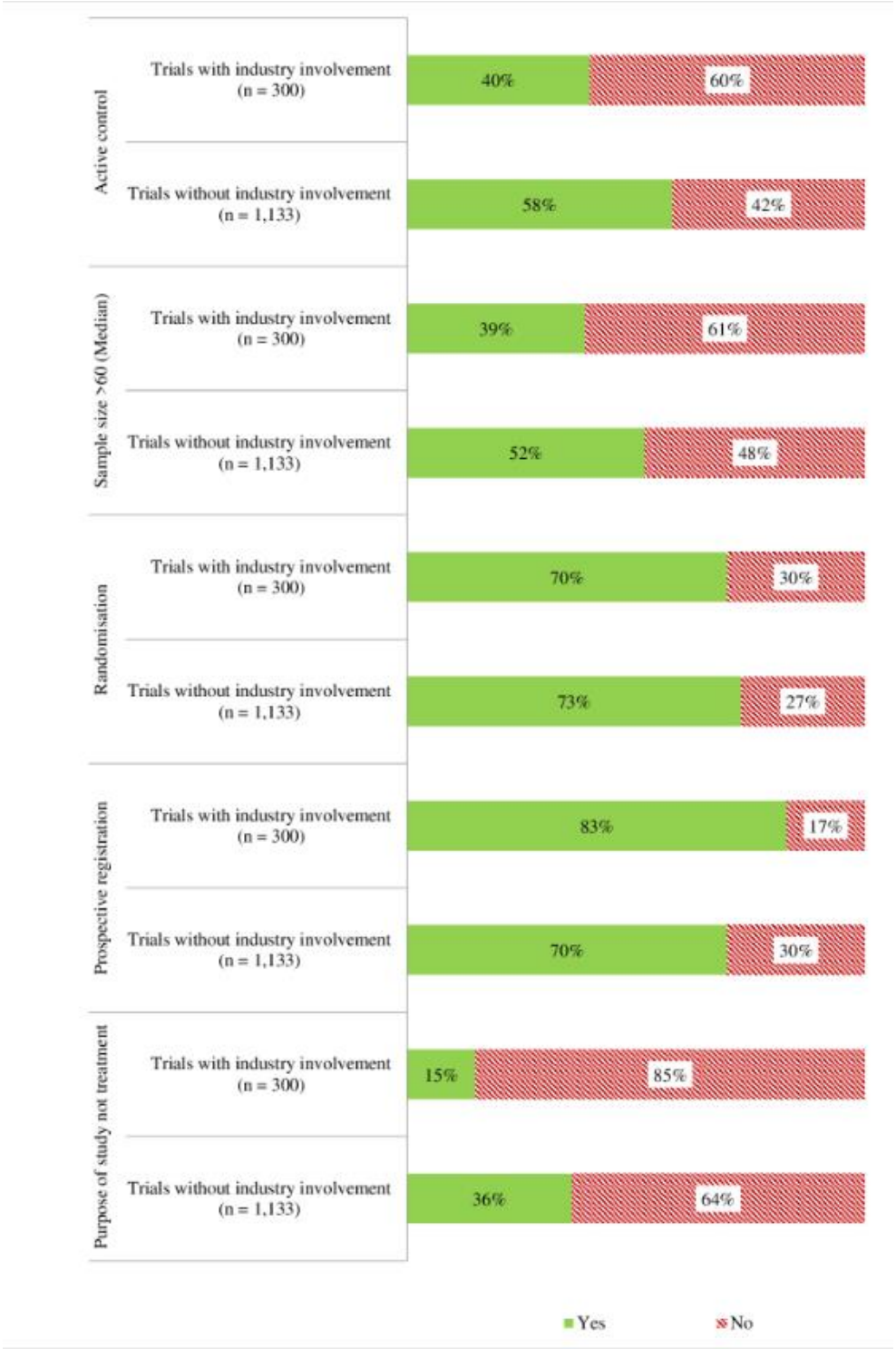


Fig 2. Control group by primary sponsor type

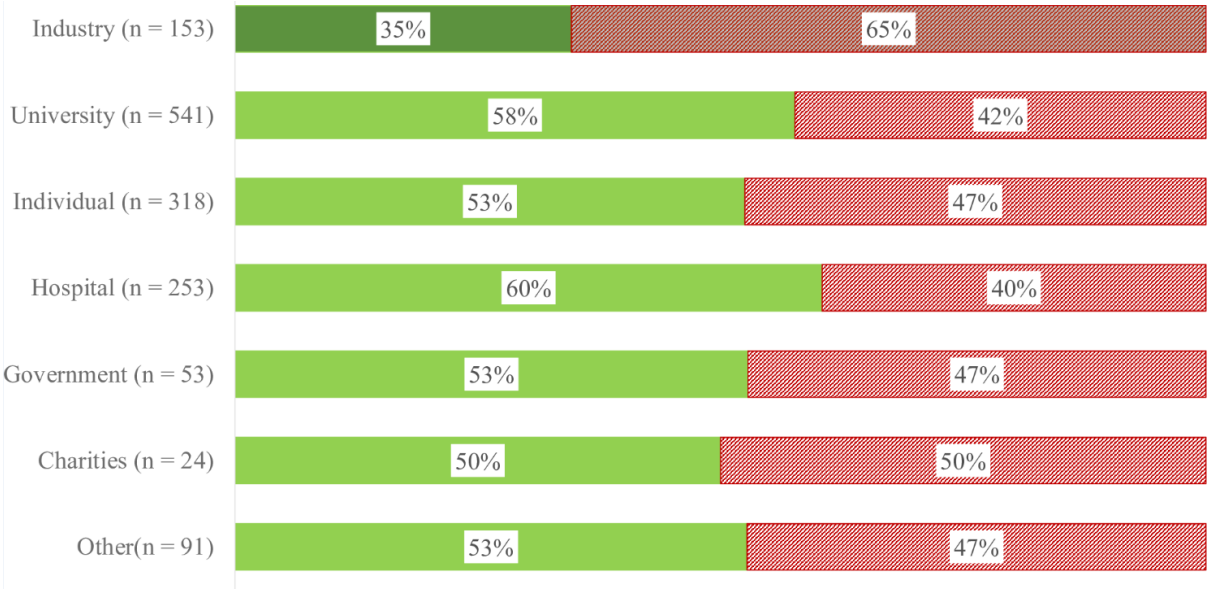
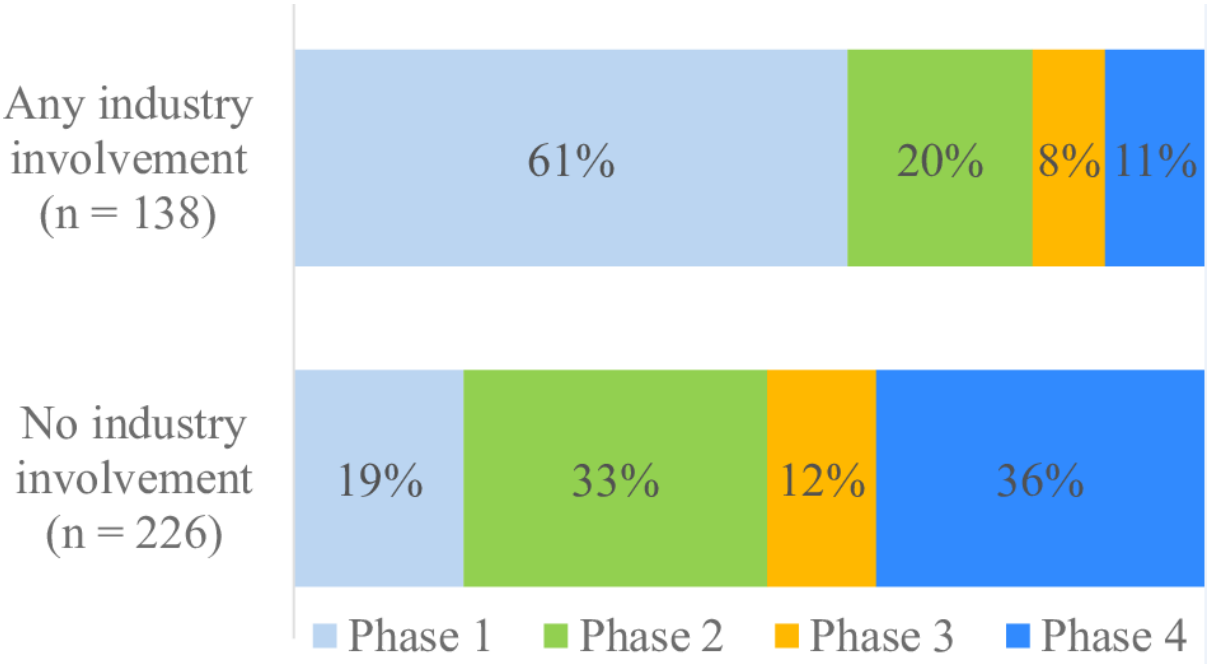


Fig 3. Trial phases by industry involvement



Limitation: phase data only available for **364 (25%)** out of 1,433 trials

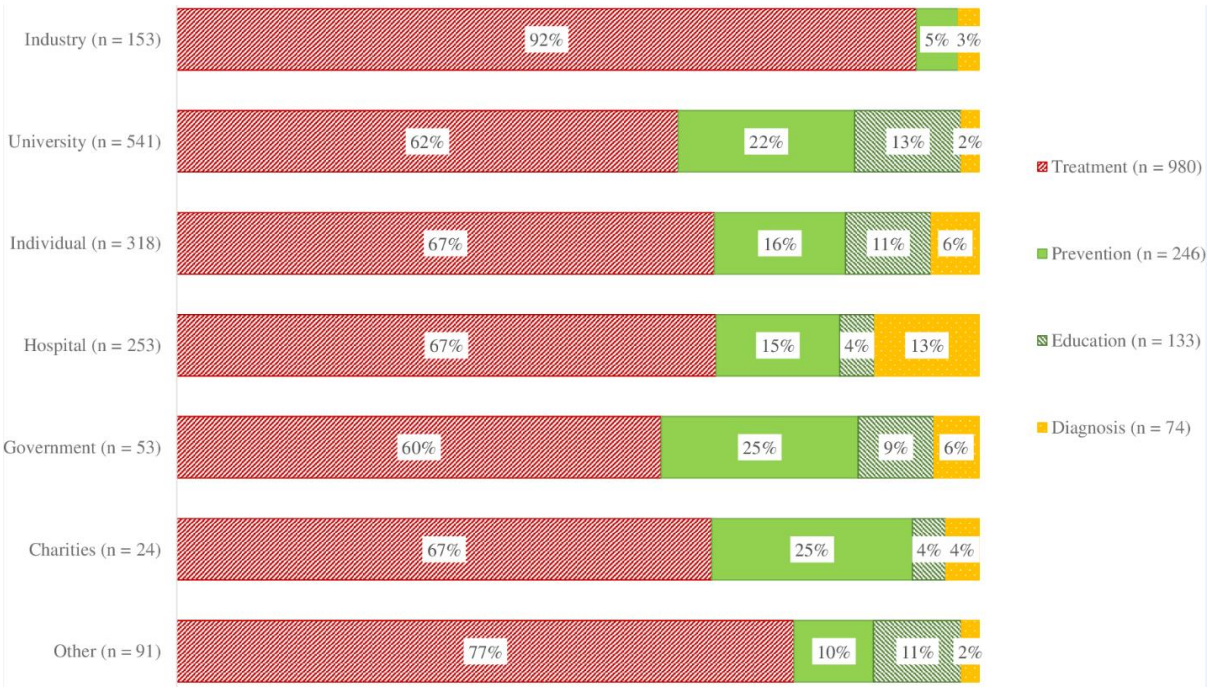



Fig 4. Study purpose by primary sponsor type