Centre for Evidence-Based Medicine Odense (CEBMO)
Odense University Hospital & University of Southern Denmark

Conflicts of interest in clinical research

PhD thesis

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Content

Preface

The sub-studies included in this PhD thesis were conducted at Centre for Evidence-Based Medicine Odense (CEBMO) at Odense University Hospital and University of Southern Denmark. The thesis is based on three sub-studies focusing on conflicts of interest in different types of clinical research publications.

Sub-study I is a Cochrane methodology review. The primary study publication was published in the Cochrane Database of Systematic Reviews:[1]

- Hansen C, Lundh A, Rasmussen K, Hróbjartsson A. Financial conflicts of interest in systematic reviews: associations with results, conclusions, and methodological quality. *Cochrane Database Syst Rev* 2019;Issue 8:MR000047.

The review was based on a Cochrane methodology review protocol also published in the Cochrane Database of Systematic Reviews:

- Hansen C, Lundh A, Rasmussen K, Gøtzsche PC, Hróbjartsson A. Financial conflicts of interest and outcomes and quality of systematic reviews. *Cochrane Database Syst Rev* 2017;Issue 12:MR000047

Sub-study II is another Cochrane methodology review. The study was co-published in Cochrane Database of Systematic Reviews[2] and BMJ:[3]

- Nejstgaard CH, Bero L, Hróbjartsson A, et al. Conflicts of interest in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: associations with recommendations. *Cochrane Database Syst Rev* 2020; Issue 12:MR000040.
- Nejstgaard CH, Bero L, Hróbjartsson A, et al. Association between conflicts of interest and recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: systematic review. *BMJ* 2020;371:m4234.

The review was based on a Cochrane methodology review protocol also published in the Cochrane Database of Systematic Reviews:

- Hansen C, Bero L, Hróbjartsson A, et al. Conflicts of interest and recommendations in clinical guidelines, opinion pieces, and narrative reviews. *Cochrane Database Syst Rev* 2019;Issue 10:MR000040

Sub-study III forms the initial steps in a larger exploration of commercial funding in randomised clinical trials named the COMFIT (COMmercial Funding In Trials) study. The sub-study is reported in two separate publications:[4,5]

- Nejstgaard CH, Laursen DRT, Lundh A, Hróbjartsson A. Commercial funding and estimated intervention effects in randomized clinical trials: a systematic review of meta-epidemiological studies. *Submitted January 2021*
- Nejstgaard CH, Lundh A, Abdi S, et al. Methods and development of a combined database of primary meta-epidemiological studies of commercial funding of randomised clinical trials: the COMFIT study. *Draft manuscript*

The PhD thesis uses the terminology described in Appendix 1.

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I wish to thank all my co-authors for enabling the sub-studies included in this PhD thesis and for their important contributions.

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Warm and heartfelt thanks to Lisa Bero and her lovely team for welcoming me during my research stay at the Charles Perkins Centre at the University of Sydney.

Last but not least, I am very grateful to my family for fantastic support and for reminding me what is really important in life. Special and heartfelt thanks to my husband Rasmus for listening to me going on and on about research, for (almost) tirelessly listening to conference presentations and reading drafts for manuscripts, for always looking out for me, and for providing me with a cool new last name during the course of my PhD studies.

Disclosures

Conflicts of interest

I have no conflicts of interest relevant for any of the sub-studies included in this thesis.

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Thesis abstracts

English abstract

Findings from clinical research have profound impact on patient care. It is therefore essential that clinical research and derived treatment recommendations are valid and trustworthy. Quite often, clinical research is funded by commercial companies or conducted by authors who have ties to such companies. This creates conflicts of interest and it is debated whether this impacts the validity of study results and conclusions, and thus patient care.

The overall aim of this PhD thesis was to describe and analyse the impact of conflicts of interest on results, conclusions, and recommendations expressed in different types of clinical research publications. The thesis includes three sub-studies.

In sub-study I, my co-authors and I investigated to which degree financial conflicts of interest are associated with estimated intervention effects, statistically favourable results, and favourable conclusions in systematic reviews. We conducted a Cochrane methodology review based on ten included studies that investigated 1010 systematic reviews. We found that systematic reviews with financial conflicts of interest more often had favourable conclusions than systematic reviews without financial conflicts of interest. It remains unclear to which degree financial conflicts of interest impact directly on estimated intervention effects and statistically favourable results of systematic reviews.

In sub-study II, my co-authors and I investigated to which degree financial and non-financial conflicts of interest are associated with favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. We conducted another Cochrane methodology review based on 21 included studies that investigated 106 clinical guidelines, 1809 advisory committee reports, 340 opinion pieces, and 497 narrative reviews. We interpreted our findings to indicate that these types of clinical research publications more often had favourable recommendations when they were written by authors with financial conflicts of interest or when advisory committee members had financial conflicts of interest. It remains unclear to which degree non-financial conflicts of interest impact on recommendations.

In sub-study III, my co-authors and I investigated to which degree commercial funding is associated with estimated intervention effects, statistically favourable results, favourable conclusions, and concordance between results and conclusions in randomised clinical trials. To enable this, we developed the COMFIT (COMmercial Funding In Trials) study. The methodological approach is a systematic review based on meta-epidemiological studies with data on funding source and results or conclusions in randomised clinical trials. The third sub-study forms the initial steps of the COMFIT study and consists of two parts. First, we conducted a systematic review based on published summary findings from seven meta-epidemiological studies that investigated 178 meta-analyses including 1627 trials. We found an uncertain impact of commercial funding on estimated intervention effects in randomised clinical trials with an average exaggeration of odds ratios in randomised clinical trials with commercial funding of 8% compared with trials without commercial funding. However, the finding was not statistically significant. Based on the findings, it remains unclear to which degree commercial funding impacts on statistically favourable results, favourable conclusions, and concordance between results and conclusions in randomised clinical trials. Second, to enable further analyses of the impact of commercial funding on randomised clinical trials, my co-authors and I constructed a con-

sortium for data sharing and initiated the development of a database with trial-level data on funding source and results and conclusions from 17 meta-epidemiological studies that investigated 728 meta-analyses and 6841 randomised clinical trials. We will combine these meta-analyses and trials in the COMFIT database, but the numbers will decrease as part of our procedures for constructing the database.

In conclusion, financial conflicts of interest were associated with more favourable conclusions or recommendations in systematic reviews, clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. The analyses showed a consistent direction and provided fairly similar magnitude of effect, but had varying degrees of statistical precision. The findings may be uncertain due to a risk of confounding in the included studies. Commercial funding had an uncertain impact on estimated intervention effects in randomised clinical trials. My co-authors and I established a consortium for data sharing and initiated the development of the COMFIT database. The database will provide an opportunity to perform analyses that are more reliable than those of typical methodological studies, due to a reduced risk of confounding, with a limited risk of reporting bias, due to the inclusion of unpublished data, and with increased statistical power.

Danish abstract

Resultater fra klinisk forskning har stor indflydelse på, hvordan vi behandler patienter. Det er derfor afgørende, at klinisk forskning - og deraf fremsatte anbefalinger - er troværdige. Klinisk forskning er forholdsvis ofte finansieret af kommercielle virksomheder eller udført af forfattere, der har finansielle bånd til sådanne virksomheder. Disse situationer skaber interessekonflikter. Der er en videnskabelig og offentlig debat om, hvorvidt interessekonflikter påvirker validiteten af resultater og konklusioner i klinisk forskning og dermed også patientbehandlingen.

Denne ph.d.-afhandling er baseret på tre delstudier. Det overordnede formål var at beskrive og analysere den potentielle påvirkning, som interessekonflikter måtte have på resultater, konklusioner og anbefalinger i udvalgte typer af klinisk forskning.

I delstudie I undersøgte mine medforfattere og jeg, i hvilken grad finansielle interessekonflikter er associeret med effektestimater, resultatafsnit (baseret på retningen og den statistiske signifikans) og konklusioner, der er positive overfor den eksperimentelle behandling, i systematiske oversigter. Vi udførte en Cochrane-oversigt baseret på ti inkluderede studier, der undersøgte 1010 systematiske oversigter. Vi fandt, at systematiske oversigter med finansielle interessekonflikter oftere har konklusioner, der er positive overfor den eksperimentelle behandling, når man sammenligner med systematiske oversigter uden interessekonflikter. Det er fortsat uklart om finansielle interessekonflikter har en indflydelse direkte på effektmål og resultatafsnit i systematiske oversigter.

I delstudie II undersøgte mine medforfattere og jeg, i hvilken grad finansielle og ikke-finansielle interessekonflikter er associeret med anbefalinger, der er positive overfor den eksperimentelle behandling, i kliniske retningslinjer, rapporter fra rådgivende udvalg, kronikker og ikke-systematiske oversigter. Vi udførte endnu en Cochrane-oversigt baseret på 21 inkluderede studier, der undersøgte 106 kliniske retningslinjer, 1809 rapporter fra rådgivende udvalg, 340 kronikker og 497 ikke-systematiske oversigter. Vores fund indikerer, at disse typer af kliniske forskningspublikationer oftere har anbefalinger, der er positive overfor den eksperimentelle behandling, når de er udarbejdet af forfattere med finansielle interessekonflikter, eller når medlemmer af rådgivende udvalg har finansielle interessekonflikter. Det er fortsat uklart, om ikke-finansielle interessekonflikter påvirker anbefalingerne.

I delstudie III undersøgte mine medforfattere og jeg, i hvilken grad kommerciel finansiering påvirker effektestimater, resultatafsnit, konklusioner og overensstemmelsen mellem resultater og konklusioner i randomiserede forsøg. For at muliggøre en undersøgelse af dette, udviklede vi det såkaldte *COMFIT (COMmercial Funding In Trials)* studie. Den metodiske tilgang er en systematisk oversigt baseret på metaepidemiologiske studier med data på finansieringskilde og resultater eller konklusioner fra randomiserede forsøg. Det tredje delstudie består af to dele, som udgør de indledende trin af *COMFIT* studiet. Først udførte vi en systematisk oversigt baseret på publicerede data fra syv metaepidemiologiske studier, der undersøgte 178 metaanalyser og 1627 randomiserede forsøg. Vi fandt en usikker påvirkning fra kommerciel finansiering på effektestimater i randomiserede forsøg med en gennemsnitlig overdrivelse af odds ratio i randomiserede forsøg med kommerciel finansiering på 8%, når man sammenligner med randomiserede forsøg uden kommerciel finansiering. Denne forskel var dog ikke statistisk signifikant. Baseret på vores fund er det fortsat uklart, om kommerciel finansiering påvirker resultatafsnit, konklusioner og overensstemmelsen mellem resultater og konklusioner i randomiserede forsøg. For at muliggøre yderligere analyser af påvirkningen fra kommerciel finansiering på randomiserede forsøg, konstruerede mine medforfattere og jeg herefter et konsortium for datadeling og påbegyndte arbejdet med at opbygge en database med data på randomiserede forsøgsniveau om finansieringskilde, resultater og konklusioner fra 17 metaepidemiologiske studier, der undersøgte 728 metaanalyser og 6841 randomiserede forsøg. Disse metaanalyser og randomiserede forsøg kommer til at udgøre *COMFIT* databasen, men antallet vil falde som en del af vores procedurer for at konstruere databasen.

Det kan konkluderes, at finansielle interessekonflikter er associeret med konklusioner og anbefalinger, der er positive overfor den eksperimentelle behandling, i systematiske oversigter, kliniske retningslinjer, rapporter fra rådgivende udvalg, kronikker og ikke-systematiske oversigter. Analyserne viste en ensartet påvirkning fra interessekonflikter med samme retning og nogenlunde samme effektstørrelse, dog med varierende grader af statistisk præcision. Resultaterne kan være usikre på grund af en risiko for *confounding* i de inkluderede studier. Kommerciel finansiering havde en indvirkning på effektestimater i randomiserede forsøg. Analysen var dog ikke statistisk signifikant. Mine medforfattere og jeg etablerede et konsortium for datadeling og påbegyndte opbygningen af *COMFIT* databasen. Databasen vil give mulighed for at udføre analyser, der er mere pålidelige end ved typiske metodiske studier, på grund af en reduceret risiko for confounding, der har en begrænset risiko for rapporteringsbias, på grund af inklusion af upublicerede data, og har en øget statistisk styrke.

Introduction

Conflicts of interest – meaning in clinical research

Health researchers aim to improve patient care by conducting clinical research. Findings from such research are often the basis for treatment recommendations, which may have profound impact of patient care. It is therefore essential that clinical research and derived treatment recommendations are valid and trustworthy. However, it is widely debated to which degree conflicts of interest are a potential threat to the validity and trustworthiness of clinical research findings.

The United States (US) Institute of Medicine defines a conflict of interest as "*a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest*".[6] This broad definition includes both financial and non-financial conflicts of interest.

Financial conflicts of interest may be created when commercial companies fund research (e.g. if employees conduct research or if the companies provide research funding), or when researchers have financial ties to commercial companies (e.g. if researchers receive honoraria, own company stocks, or serve on the advisory board). Thus, financial conflicts of interest include both commercial funding and researchers' financial ties to commercial companies. Such conflicts can provide a substantial income for researchers and may therefore impact researchers' perception of company products and thereby also whether these products are recommended as treatment options. In this PhD thesis, I focus solely on financial conflicts of interest related to commercial companies. Non-commercial financial conflicts of interest also exist, for example when research is funded by governmental health departments or foundations, but this has not received much attention.[7]

Authors of clinical research publications may also have non-financial conflicts of interest. For example, researchers sometimes have specialty interests (e.g. belonging to a certain medical subspecialty) or academic interests (e.g. when authors of a clinical guideline are also authors of studies that are part of the evidence base for the guideline) that may influence the recommendation of a particular intervention.[8] It is heavily debated what constitutes non-financial conflicts of interest and whether the term is appropriate.[9]

Historical development of conflicts of interest in clinical research

Collaboration between researchers and commercial companies has a long history. One of the earlier examples is found in the 1920s where Eli Lilly, a pharmaceutical company, collaborated with researchers at the University of Toronto to manufacture insulin in quantities adequate for research and clinical use.[6] In the 1940s, the federal government accounted for only 7% of medical research funding in the US, but after World War II, the proportion of biomedical research with governmental funding started to increase. By 1965, the federal government accounted for 62% of the funding.[10] In the 1970s, the balance began to shift toward a higher proportion of commercial funding.[6] In 1994, 46% of all US medical research was funded by commercial companies. The proportion increased to 58% in 2012.[11]

As the relationships with commercial companies in medical research grew more frequent, responses to these conflicts of interest started evolving. In 1984, *New England Journal of Medicine* announced that authors should disclose their relationships with companies that could be affected by their findings. This ap-

pears to be the first conflicts of interest policy.[6] In 1988, the International Committee of Medical Journal Editors (ICMJE) published its third edition of 'Uniform requirements for manuscripts submitted to biomedical journals'. In this, authors were required to include a statement in the cover letter listing any relationships (financial or other) that could lead to conflicts of interest.[12] From hereon, the conflicts of interest policies have become stricter and stricter by addressing issues beyond reporting of conflicts of interest. In 2001, ICMJE required authors to disclose details of their own and the sponsor's role in the study and abstained from publication of studies in which the sponsor had sole control of the data or the ability to withhold publication.[13] In the most recent update of the requirements from 2019, ICMJE required authors to disclose all relationships and activities, including interactions with any entity that could be considered broadly relevant to the study and all sources of fees paid over the 3 years prior to submission. Authors are also required to disclose any sources of support for the study, including an explanation of the sponsor's role in the study and the nature and extent of authors' access to the study data. Finally, authors are strongly discouraged from entering into agreements with for-profit or non-profit sponsors that interfere with the authors' ability to analyse and interpret the data and to prepare and publish manuscripts.[14]

The public and scientific concern of conflicts of interest

A major concern in relation to conflicts of interest is that implementing untrustworthy research may cause harm or waste resources. For example, the US Food and Drug Administration (FDA) approved the drug rofecoxib in May 1999. The approval was partly based on a randomised trial funded by the pharmaceutical company Merck of 8076 rheumatoid arthritis patients (the VIGOR trial).[15] The problem with the VIGOR trial was that it was not designed to evaluate cardiovascular risk, thereby making the drug appear to be safe.[16] Furthermore, three cases of myocardial infarction in the rofecoxib group was omitted from the trial publication.[17] The drug was withdrawn five years after approval, because it was shown to cause cardiovascular events. At the time of withdrawal, more than 80 million patients had taken the drug, and it is estimated that it has caused tens of thousands cardiovascular events in the US alone.[18] Another example is study 329, a trial funded by SmithKline Beecham (subsequently GlaxoSmithKline), evaluating efficacy and safety of paroxetine and imipramine in adolescents with severe depression. The initial publication reported that paroxetine was beneficial and without major harms.[19] These findings had a major impact on the use of antidepressants in adolescents. However, study 329 was selectively reported with an understatement of adverse event rates and an overemphasis on post-hoc measures that were not consistent with the primary and secondary outcomes stated in the protocol.[20] Furthermore, the study 329 publication was largely ghost written and the sponsor had control over the main messages.[21] Finally in 2015, a reanalysis of the same data reported that paroxetine causes suicidal ideation and imipramine causes cardiovascular problems.[22]

Various organisations are increasingly recognising conflicts of interest as a potential threat to scientific validity. Organisations issuing clinical guidelines have implemented policies in an attempt to ensure that conflicts of interest will not affect the guideline recommendations.[23] Various reporting guidelines, such as The Consolidated Standards of Reporting Trials (CONSORT) statement, recommend that authors disclose any funding sources as well as the role of any funder.[24] Also scientific journals have policies to increase transparency of conflicts of interest. The ICMJE website lists several hundred journals that follow their requirements on disclosure of conflicts of interest, but the organisation does not verify the extent to which a journal does so.[6]

Scientific journals do not only require disclosure of conflicts of interest, some also have policies to prevent any potential impact of such conflicts. For example, *New England Journal of Medicine* prohibits narrative reviews and editorials with significant financial conflicts of interest (defined as >10,000 USD, or any stock or patents). *The Lancet* prohibits commentaries, seminars, reviews, and series by authors with relevant employment or certain financial conflicts of interest. *BMJ* prohibits authors of editorials, clinical reviews, and practice articles to have financial ties related to industries such as drug, device, test, and medical educations, and prohibits all studies partly or wholly funded by the tobacco industry.[25] *Cochrane* has a policy on financial conflicts of interest that is stricter than other scientific journal policies.[26] *Cochrane* requires that two-thirds of review authors, including the first and last author, have no financial conflicts of interest and prohibits review funding by any commercial organisation with a financial interest in the topic.[27]

Conflicts of interest are also an area of ongoing public concern. Newspaper articles focus on conflicts of interest, for example under headlines such as *"Our Conflicted Medical Journals"* in The New York Times,[28] *"Is the staggeringly profitable business of scientific publishing bad for science?"* in The Guardian,[29] and *"Scientists' financial conflicts of interest may skew drug debate"* in The Independent.[30]

Clinical research publications and conflicts of interest

The US Institute of Medicine defines clinical research as *"a component of medical and health research intended to produce knowledge valuable for understanding human disease, preventing and treating illness, and promoting health"*.[31] This covers a continuum of studies including studies on therapeutic interventions, prevention, and health promotion.[31] Findings from clinical research publications have substantial impact on which interventions are offered to patients.

For this PhD thesis, I deploy a broad definition of clinical research, including core clinical research studies, but also studies not normally considered to be original research. I focus solely on six types of clinical research (from here on jointly referred to as 'clinical research publications'): randomised clinical trials, systematic reviews, clinical guidelines, advisory committee reports (transcripts from meetings held in committees that provide recommendations concerning interventions, e.g. FDA advisory committee meetings on oncological drugs), opinion pieces (e.g. editorials and commentaries), and narrative reviews (non-systematic reviews).

Randomised clinical trials are often considered to provide the best available evidence and may be summarised in systematic reviews that then provide an analysis and summary of relevant studies. Clinical guidelines are often based on systematic searches of existing empirical studies and standardised procedures for grading the evidence,[32] and may also be published in scientific journals.[33,34] Reports from advisory committee meetings would typically not be regarded as research publications. However, advisory committees have substantial impact on which treatments are offered to patients, as they often approve new drugs and devices. Moreover, reports from meetings held in such committees are based on findings from clinical research, may be publicly available,[35] and overviews of the meetings may be published in scientific journals.[36,37] Finally, opinion pieces and narrative reviews summarise and interpret existing studies and may be written by key opinion leaders.

The rapid development of clinical research

Since the first randomised trial was published in 1948,[38] the field of clinical research has evolved rapidly with massive growth in scientific and medical information. The science of research synthesis and systematic

reviews as we know it today began to emerge in the 20th century,[39] and the first formal attempt to combine information from multiple sources was published in 1904.[40] Since then, the number of published systematic reviews has increased rapidly. From sporadic cases in the 1980s, through an estimated 3000 indexed in Medline up to year 2000, to more than 200,000 being available nowadays[41] and around 800 planned systematic reviews being registered in The International Prospective Register of Systematic Reviews (PROSPERO) every month.[42] Similar developments has been seen for other types of clinical research publications, for example clinical guidelines.[43] This rapid development makes it, if not impossible, then very difficult for doctors and researchers to keep up to date with their field.[44]

Conflicts of interest in different clinical research publications

It is widely believed that conflicts of interest impact on various types of clinical research publications. However, certain types of clinical research publications may be more susceptible to influence of conflicts of interest than other types. Randomised clinical trials and systematic reviews are developed using strict methods. On a theoretical level, this may allow little room for influence of conflicts of interest. In contrast, other types of clinical research publications, for example opinion pieces and narrative reviews, often provide very specific recommendations concerning patient treatment and authors are typically free to selectively cite studies and interpret evidence. Conflicts of interest may therefore have a stronger impact on these types of clinical research publications.

Common for all types of clinical research publications is that they are often funded by commercial companies or written by authors with financial ties to such companies. In a sample of 195 randomly selected randomised clinical trials on drugs, 69% were funded by commercial companies and 68% had principal (i.e. first or senior) authors with company ties.[45] Compared with randomised clinical trials, systematic reviews are less often funded by commercial companies. In a sample of 300 randomly selected systematic reviews, only eight (3%) reviews were funded by commercial companies.[46] However, there is a large variation between clinical specialties. For example, a quarter of a sample of 185 reviews of trials of antidepressants was funded by commercial companies.[47] Similarly, clinical guidelines, opinion pieces, and narrative reviews are often written by authors with conflicts of interest and members of advisory committees often have conflicts of interest.[48,49] For example, in a sample of 290 randomly selected editorials, commentaries, and narrative reviews, 91 (31%) had at least one author with conflicts of interest.[50]

Empirical studies on the impact of conflicts of interest

The impact of conflicts of interest on clinical research publications has been investigated in numerous studies, typically in methodological observational studies, but also to a lesser extent in systematic reviews and meta-epidemiological studies.

Methodological studies and systematic reviews

Empirical studies on conflicts of interest have mainly focused on the impact on randomised clinical trials. An updated Cochrane review of 75 methodological studies investigated the impact of commercial funding on primary research studies (mainly randomised clinical trials) of drugs and devices. The authors found that commercially funded studies were more likely to have favourable conclusions (relative risk (RR): 1.34, 95% confidence interval (CI): 1.19-1.51) compared to studies without commercial funding.[51]

Methodological studies have also focused on the impact of conflicts of interest on other types of clinical research publications. A study investigated matched pairs of systematic reviews. The authors found that

systematic reviews with commercial funding more often had favourable conclusions than systematic reviews without commercial funding.[52] Methodological studies have also focused on the impact of conflicts of interest on recommendations in clinical guidelines,[53] advisory committee reports,[54] opinion pieces,[55] and narrative reviews.[56]

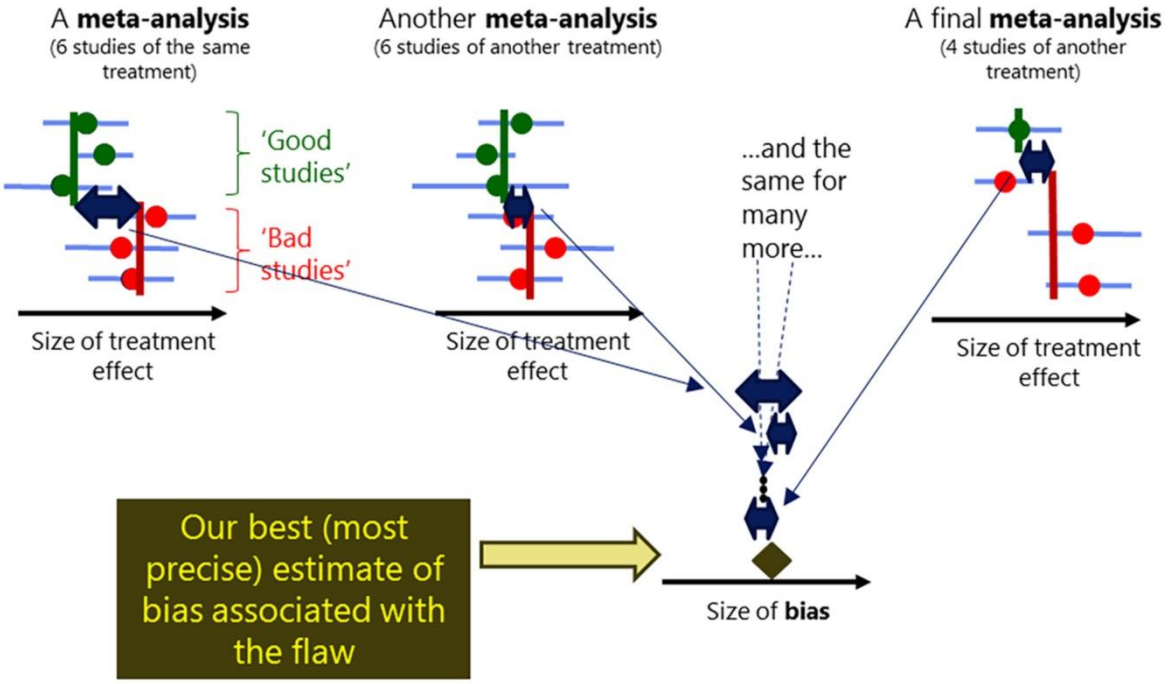
Meta-epidemiological studies

Interpretation of findings from typical methodological studies is hampered by a risk of confounding, because such studies often investigate clinical research publications that may differ for other reasons than conflicts of interest. The risk of confounding is markedly reduced in meta-epidemiological studies, where trials are compared within meta-analyses.

The concept of meta-epidemiology is a relatively new methodological development, and the term is used to describe a variety of different study designs.[57] For the purpose of this thesis, I define meta-epidemiological studies as studies comparing trials with and without a certain characteristic (e.g. conflicts of interest) within meta-analyses. Within each meta-analysis, a trial result (e.g. estimated intervention effect) is summarised separately for the group of trials with and the group of trials without the characteristic. The comparison is then repeated for several meta-analyses, before an average impact of the characteristic on the trial result can be estimated (Figure 1). Analysing trials within meta-analyses ensures that compared trials have broadly similar types of patients, interventions, comparisons, and outcomes.[58]

In meta-epidemiological studies, the impact of the trial characteristic of interest is often expressed as a ratio of odds ratios (ROR) in meta-analyses with binary outcomes and as a difference in standardised mean differences (dSMD) in meta-analyses with continuous outcomes. For binary outcomes, the ROR is based on the ratio between the summary odds ratio (OR) for trials with the characteristic (e.g. conflicts of interest) and the summary OR for trials without the characteristic (e.g. $ROR=OR_{\text{conflicts of interest}}/OR_{\text{no conflicts of interest}}$).[59]

Figure 1. Principles of meta-epidemiological studies. Trials with and without a characteristic of interest (e.g. conflicts of interest) are compared within a meta-analysis and an estimate (e.g. ROR) explaining the difference in a trial result (e.g. estimated intervention effect) between the two groups of trials is estimated. The comparison is repeated for a number of meta-analyses, before an average impact of the characteristic on the trial result is estimated.



From: Moustgaard et al.[58] Reprinted with permission from John Wiley and Sons.

A few studies have used this approach to investigate the impact of commercial funding on estimated intervention effects in randomised clinical trials. For example, the authors of a meta-epidemiological study of randomised clinical trials on testosterone therapy in men found that trials with commercial funding reported estimated intervention effects that were 21% larger than in trials without commercial funding, but the association was not statistically significant (ROR: 0.79, 95% CI: 0.54-1.16).[60] However, another meta-epidemiological study found no evidence for such an impact in critical care randomised clinical trials (ROR: 1.10, 95% CI: 0.96-1.26).[61]

Uncertainties in existing empirical studies

There is a notable uncertainty about core aspects of conflicts of interest in clinical research. First, existing studies have mainly focused on primary research studies and only to a lesser extent on systematic reviews, clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. Individual methodological studies on the matter do exist, but these differ in their methods and findings, and they have not been summarised in a systematic review. It is therefore not well established how conflicts of interest impact on estimated intervention effects, statistically favourable results, conclusions, and recommendations made in such publications.

Second, the majority of the existing studies are methodological studies. Such studies often investigate clinical research publications that differ for many other reasons than conflicts of interest. Thus, the interpretation of findings from typical methodological studies is hampered by a risk of confounding. This means that the association between commercial funding and conclusions in randomised clinical trials may be caused by underlying differences in, for example, the investigated drug and not necessarily by differences in commercial funding.

Third, existing studies on randomised trials have mainly focused on the impact of conflicts of interest on conclusions and only to a lesser extent on the impact on estimated intervention effects. The aforementioned Cochrane review on commercial funding in primary research studies identified 24 studies comparing estimated intervention effects between trials with and without commercial funding. However, the studies reported their findings differently, precluding them from being combined in a meta-analysis. The studies had mixed findings and the impact of commercial funding on estimated intervention effects is unclear.[51]

Fourth, some meta-epidemiological studies have investigated the impact of conflicts of interest on randomised clinical trials. However, these have published different findings. Furthermore, individual meta-epidemiological studies may have limited statistical power due to relatively small sample sizes. This problem may be solved by combining meta-epidemiological studies in a systematic review. However, to my knowledge, such a review has not been conducted.

Aims

The overall aim of this PhD thesis is to describe and analyse the impact of conflicts of interest on results, conclusions, and recommendations expressed in different types of clinical research publications.

The thesis includes the following three sub-aims:

I. To investigate to which degree financial conflicts of interest related to drug and device companies are associated with estimated intervention effects, statistically favourable results, and favourable conclusions in systematic reviews.[1]

II. To investigate to which degree financial and non-financial conflicts of interest are associated with favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews.[2,3]

III. To investigate to which degree commercial funding is associated with estimated intervention effects, statistically favourable results, favourable conclusions, and concordance between results and conclusions in randomised clinical trials.

The first sub-aim is addressed in sub-study I reported in one publication.[1] The second sub-aim is investigated in sub-study II reported in two co-publications.[2,3] The third sub-aim is investigated in sub-study III reported in two separate publications.[4,5]

Description of sub-studies and summary of findings

Financial conflicts of interest in systematic reviews (sub-study I)

Sub-study I is reported in (available in Appendix 3):
Hansen C, Lundh A, Rasmussen K, Hróbjartsson A. Financial conflicts of interest in systematic reviews: associations with results, conclusions, and methodological quality. *Cochrane Database Syst Rev* 2019;Issue 8:MR000047.

Aim

In sub-study I, my co-authors and I focused solely on financial conflicts of interest related to drug and device companies and the impact on systematic reviews. We primarily investigated the impact on estimated intervention effects (outcome data, e.g. RR or OR), statistically favourable results (results that are favourable towards the experimental intervention based on direction and statistically significance), and favourable conclusions (conclusions favourable towards the experimental intervention) in systematic reviews. As a secondary aim, we also investigated the influence on the quality of the systematic review methods (the quality of the systematic reviews as investigated by the authors of the included studies).

Methods

We conducted a Cochrane methodology review following the methods outlined in the protocol.[62] We included studies that compared systematic reviews with and without financial conflicts of interest and investigated estimated intervention effects, frequency of statistically favourable results, frequency of favourable conclusions, or quality of the systematic review methods.

We searched PubMed, Embase, and the Cochrane Methodology Register for studies published up to November 2016, searched reference lists of included studies, Web of Science for studies citing the included studies, and grey literature sources. Two authors independently included studies, extracted data, and assessed methodological quality of included studies. We assessed methodological quality in included studies in relation to the systematic review inclusion process, the coding of financial conflicts of interest and systematic review outcomes, and the methods for dealing with confounding.

We estimated RRs with 95% CIs (RR>1 indicated that systematic reviews with financial conflicts of interest more often had statistically favourable results, favourable conclusions, or lower quality in the systematic review methods). We synthesized findings from studies on estimated intervention effects qualitatively. For the primary analyses on statistically favourable results and favourable conclusions, we used the same definitions of financial conflicts of interest as used by the authors of the included studies and analysed commercial funding and authors' financial conflicts of interest together. For our secondary analysis of quality of the systematic review methods, we pooled similar items across the different tools used in the included studies. We did not include items related to reporting quality (e.g. whether the inclusion criteria were reported) or statistical methods (e.g. whether a Bayesian framework was used).

From the studies included in our pooled analysis on favourable conclusions, we calculated number needed to read based on the methods for calculating number needed to treat (not included in the study publication).[63] The number needed to read indicated the number of systematic reviews with financial conflicts of interest that needed to be read rather than systematic reviews without financial conflicts of interest for one additional review having a favourable conclusion. We also calculated 95% CI with number needed to

read favourable (NNRF) representing the expected number of systematic reviews with financial conflicts of interest needed to be read for one additional review having a favourable conclusion, and number needed to read unfavourable (NNRU) representing the expected number of systematic reviews with financial conflicts of interest needed to be read for one additional review having an unfavourable conclusion.[64]

We assessed the certainty of the evidence for our primary outcomes using the GRADE approach for intervention studies.[32]

Summary of main findings

We included ten studies with a total of 1010 systematic reviews (median number of included systematic reviews: 48, range: 11-318).[47,52,65-72] We received unpublished data from five studies. In addition, three studies published individual data from each included systematic review separately. We received published or unpublished protocols from five studies and found no discrepancies in reporting between the protocols and study publications.

We assessed two included studies as having overall adequate methodological quality, and the remaining studies as inadequate methodological quality. The majority of the studies were assessed as adequate in relation to the study inclusion process and coding methods, whereas they were assessed as inadequate in relation to dealing with confounding.

Based on one study of seven pairs of systematic reviews, estimated intervention effects were not statistically significantly different between systematic reviews with and without financial conflicts of interest (z-score: 0.46, p-value: 0.64). Also, one study of 124 systematic reviews found no clear difference in frequency of a statistically favourable results between reviews with and without financial conflicts of interest (RR: 0.84, 95% CI: 0.62-1.14).

Based on seven studies including 411 systematic reviews, the association between financial conflicts of interest and favourable conclusions was RR: 1.98, 95% CI: 1.26-3.11, I^2: 69%. The number needed to read was 2.2. The corresponding 95% CI was NNRF 8.3 to NNRF 1.8.

Based on four studies including 302 systematic reviews, we analysed 11 different dimensions of quality of the systematic review methods (e.g. search methods and assessing risk of bias). The RRs for the 11 dimensions spanned from 1.00 to 1.83 and were statistically significant for three dimensions.

Interpretation and conclusion

We found that financial conflicts of interest are associated with more favourable conclusions in systematic reviews. Our findings should be interpreted cautiously, because the included studies had a risk of confounding as the compared systematic reviews may differ in other aspects than financial conflicts of interest (e.g. investigating different interventions used for different diseases). Furthermore, we assessed the certainty of the evidence as very low for estimated intervention effects and statistically favourable results, and low for favourable conclusions. However, two studies investigating pairs of systematic reviews (thereby having a matched study design) and additionally one study performing analyses adjusted for possible confounding due to methodological quality (i.e. score on Oxman Guyatt index[73]) provided similar findings on estimated intervention effects, statistically favourable results, favourable conclusions, and quality of the systematic review methods as our pooled analyses.[52,70,72]

In conclusion, we found that systematic reviews with financial conflicts of interest more often have favourable conclusions. It remains, however, uncertain to which degree financial conflicts of interest impact directly on estimated intervention effects and statistically favourable results of systematic reviews. In a secondary aim, we addressed quality of the systematic review methods and found that systematic reviews with financial conflicts of interest tend to have lower quality of the systematic review methods.[1]

Conflicts of interest in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews (sub-study II)

Sub-study II is reported in two co-publications (available in Appendix 4 and 5):
Nejstgaard CH, Bero L, Hróbjartsson A, et al. Conflicts of interest in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: associations with recommendations. Cochrane Database Syst Rev 2020;Issue 12: MR000040.

Nejstgaard CH, Bero L, Hróbjartsson A, et al. Association between conflicts of interest and recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: systematic review. *BMJ* 2020;371:m4234.

Aim

In sub-study II, my co-authors and I focused on both financial and non-financial conflicts of interest and the impact on clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. We investigated the impact of conflicts of interest on favourable recommendations (e.g. recommendation of a specific drug).

Methods

We conducted a Cochrane methodology review following the methods outlined in the review protocol.[74] We included studies that compared clinical guidelines, advisory committee reports, opinion pieces, or narrative reviews with and without conflicts of interest and investigated differences in frequency of favourable recommendations. We included studies on financial conflicts of interest (regardless of the type) and non-financial conflicts of interest (limited to intellectual, academic, professional, or specialty interests, and personal or professional relationships).[8]

We searched PubMed, Embase, and the Cochrane Methodology Register for studies published up to February 2020, searched reference lists of included studies, Web of Science for studies citing the included studies, PubMed for publications by the first and last authors of the included studies, and grey literature sources. Two authors independently included studies, extracted data, and assessed methodological quality. Methodological quality in included studies was assessed in relation to the process used to include publications (i.e. clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews), the coding of conflicts of interest and recommendations, and the methods for dealing with confounding.

We estimated RRs with 95% CIs (RR>1 indicating that e.g. clinical guidelines with conflicts of interest more often had favourable recommendations than clinical guidelines without conflicts). We analysed financial and non-financial conflicts of interest separately, and analysed clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews both separately (pre-planned) and combined (post-hoc). For

our analysis on advisory committee reports, we used meeting level (advisory committee reports and the overall voting outcome) in the primary analysis.

Based on the methods described for sub-study I, we calculated number needed to read for each publication type separately and combined.

We interpreted our findings in the context of statistical precision (i.e. width of 95% CIs) and risk of confounding. We also assessed the evidence using both the GRADE approach for intervention studies[32] and for prognostic studies.[75]

Summary of main findings

We included 21 studies with a total of 106 clinical guidelines (median number of included guidelines: 9, range: 2-50), 1809 advisory committee reports (median number of included reports: 376, range: 79-416), 340 opinion pieces (median number of included opinion pieces: 44, range: 8-131), and 497 narrative reviews (median number of included narrative reviews: 84, range: 7-213).[49,53,55,56,68,71,76-90] We received unpublished data from 11 studies; eight full data sets and three summary data sets. We received unpublished protocols for two studies and found no discrepancies in reporting between the protocols and study publications.

We assessed one study as having overall adequate methodological quality, and the remaining studies as inadequate methodological quality. Around half of the studies were assessed as adequate in relation to the publication inclusion process and the majority were assessed as adequate in relation to the coding of conflicts of interest and recommendations, whereas only six studies were assessed as adequate in relation to dealing with confounding.

Based on four studies of 86 clinical guidelines, the association between financial conflicts of interest and recommendations was RR: 1.26, 95% CI: 0.93-1.69, I^2: 0%. The number needed to read was 9.1. The corresponding 95% CI was NNRU 33.3 to ∞ to NNRF 3.4.

Based on four studies of 629 advisory committee reports, the association between having at least one committee member with financial conflicts of interest and the committee voting in favour of the drug or device was RR: 1.20, 95% CI: 0.99-1.45, I^2: 24%. The number needed to red was 7.7. The corresponding 95% CI was NNRU 100.0 to ∞ to NNRF 3.4.

Based on four studies of 284 opinion pieces, the association between financial conflicts of interest and recommendations was RR: 2.62, 95% CI: 0.91-7.55, I^2: 78%. The number needed to read was 2.3. The corresponding 95% CI was NNRU 50.0 to ∞ to NNRF 1.4.

Based on four studies of 457 narrative reviews, the association between financial conflicts of interest and favourable recommendations was RR: 1.20, 95% CI: 0.97-1.49, I^2: 39%. The number needed to read was 8.3. The corresponding 95% CI was NNRU 50.0 to ∞ to NNRF 3.4.

In a post-hoc analysis, we combined all types of publications and the association between financial conflicts of interest and favourable recommendations was RR: 1.26, 95% CI: 1.09-1.44, I^2: 38%. The number needed to read was 7.1. The corresponding 95% CI was NNRF 20.0 to NNRF 4.2.

For our analysis on non-financial conflicts of interest, we only identified one study including 12 clinical guidelines on mammography screening. The association between having radiologists in the guideline panel and recommending routine screening for breast cancer was RR: 2.10, 95% CI: 0.92-4.77. The number needed to read was 2.1. The corresponding 95% CI was NNRU 25.0 to ∞ to NNRF 1.8.

Interpretation and conclusion

We found a suggested association between financial conflicts of interest and favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews.[2,3] Our findings should be interpreted cautiously, because the included studies had a risk of confounding as they compared for example clinical guidelines that may differ in other aspects than conflicts of interest (e.g. guidelines on different interventions used for different diseases). Only six of the included studies were assessed a having adequate methodological quality in relation to dealing with confounding as they included quite comparable publications, and only two of these were included in our pooled analyses. However, three studies performed analyses adjusted for possible confounders and two of these provided similar findings as our pooled analyses on advisory committee reports and opinion pieces.[53-55]

Our primary analyses had varying degrees of statistical precision. Using the GRADE approach for intervention studies, we assessed the certainty of the evidence as very low for all types of publications. Using the GRADE approach for prognostic studies, we assessed the certainty of the evidence as low for clinical guidelines, advisory committee reports, and narrative reviews and very low for opinion pieces.

In conclusion, we interpreted our findings to indicate that financial conflicts of interest are associated with more favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. However, we also emphasise that the included studies had a risk of confounding and our individual analyses were statistically imprecise. It remains uncertain to which degree non-financial conflicts of interest impact on recommendations.[2,3]

Commercial funding in randomised clinical trials (sub-study III)

Introduction

In order to investigate the impact of commercial funding on randomised clinical trials, we developed the COMFIT (COMmercial Funding In Trials) study. The methodological approach is a systematic review based on meta-epidemiological studies with data on funding source and results or conclusions from randomised clinical trials. The third sub-study forms the initial steps of the COMFIT study and consists of two parts. In the first part, my co-authors and I conducted a systematic review based on meta-epidemiological studies with published findings on the impact of commercial funding on randomised clinical trials. While doing so, we identified a surprisingly large number of meta-epidemiological studies, though the majority of them only had unpublished data on commercial funding. In response, we planned to reach out to the authors of the meta-epidemiological studies in an attempt to establish the COMFIT consortium (i.e. a collaborative network comprised of authors of meta-epidemiological studies and methodologists with expertise in meta-epidemiology) and obtain trial-level data. We then planned to combine this trial-level data in the COMFIT database. In the second part of sub-study III, we described the methods for establishing the COMFIT consortium and database.

In principle, The COMFIT study involves information from four levels: 1) the included meta-epidemiological studies, 2) the systematic reviews included in the meta-epidemiological studies, 3) the meta-analyses included from the systematic reviews, and 4) the randomised trials included from the meta-analyses.

Analysing published findings from meta-epidemiological studies

The first part of sub-study III is reported in (available in Appendix 6):
Nejstgaard CH, Laursen DRT, Lundh A, Hróbjartsson A. Commercial funding and estimated intervention effects in randomized clinical trials: a systematic review of meta-epidemiological studies. *Submitted January 2021.*

Aim

In the first part of sub-study III, my co-authors and I focused on two types of commercial funding: 1) commercial funding per se (related solely to type of trial funding source) and 2) commercial funding with increased risk of funder influence (combining information on trial funding source with an assessment, done by the meta-epidemiological study authors, of whether a commercial funder had an influence on the trial design, conduct, analysis, or reporting). Based on published summary findings, we investigated the impact on estimated intervention effects, statistically favourable results, favourable conclusions, and concordance between results and conclusions (whether favourable conclusions are supported by statistically favourable results) in randomised clinical trials.

Methods

We included meta-epidemiological studies with published ROR or measures convertible to ROR (e.g. dSMD) for the impact of commercial funding on estimated intervention effects; or any published measure for the impact of commercial funding on statistically favourable results, favourable conclusions, or concordance between results and conclusions in randomised clinical trials. We included studies aimed to investigate: 1) commercial funding per se and 2) commercial funding with increased risk of funder influence.

We searched PubMed, Embase, and the Cochrane Methodology Register for meta-epidemiological studies published up to June 2020, Web of Science, and Google Scholar. We searched reference lists of included studies, studies included in a systematic review of meta-epidemiological studies,[91] studies included and excluded from two versions of a Cochrane review on industry funding on primary research studies,[51,92] and grey literature sources. Two authors independently included studies.

Two authors independently extracted data from the included meta-epidemiological studies. We selected one meta-epidemiological result for the impact of commercial funding on estimated intervention effects per study using the following procedure: we preferred unadjusted ROR or converted other measures (e.g. dSMD) to ROR. If several unadjusted RORs were published, we used the ROR from the main analysis, as defined by the meta-epidemiological study authors.

We pooled findings from meta-epidemiological studies using random-effects meta-analysis sub-grouped by study aim. We used meta-epidemiological study authors' definition of commercial funding. For our analysis on estimated intervention effects, we estimated ROR with 95% CI (ROR<1 indicated larger effect estimates in trials with commercial funding). For our analysis on statistically favourable results, favourable conclusions, and concordance between results and conclusions, we synthesized findings from meta-epidemiological studies qualitatively.

Summary of main findings

We included seven meta-epidemiological studies with a total of 178 meta-analyses including 1627 trials.[60,61,93-97] One of the included studies were reported in two separate publications[97,98] and the ROR for the same analysis differed between the publications. We contacted the authors, but they were unable to explain the reason for this inconsistency. Therefore, we excluded the study from our main analysis.

Based on six meta-epidemiological studies of 166 meta-analyses including 1545 trials, ROR spanned from 0.76 to 1.10, with a pooled average of 0.92, 95% CI: 0.80-1.03, I^2: 51%. For two meta-epidemiological studies aimed to investigate commercial funding per se, the pooled average ROR was 0.98, 95% CI: 0.68-1.27, I^2: 68%. For four meta-epidemiological studies aimed to investigate commercial funding with increased risk of funder influence, the pooled average ROR was 0.86, 95% CI: 0.77-0.96, I^2: 0%. None of the included meta-epidemiological studies investigated statistically favourable results.

One meta-epidemiological study investigated favourable conclusions by calculating an arcsine difference based on a within meta-analysis approach (arcsine difference>0 indicated that conclusions were more favourable in commercially funded trials). The authors found no clear difference in frequency of favourable conclusions between trials with and without commercial funding (summary arcsine estimate: 0.04, 95% CI: -0.09-0.17).[61]

None of the included meta-epidemiological studies investigated concordance between results and conclusions.

Interpretation and conclusion

We found an average exaggeration in ORs in randomised clinical trials with commercial funding of 8% compared with trials without commercial funding. The findings was, however, not statistically significant with the 95% CI ranging from a 20% exaggeration to a 3% underestimation. Our findings suggest that the impact of commercial funding with increased risk of funder influence may be stronger than the impact of commercial funding per se, though with overlapping 95% CIs.

Our findings are based on studies with a reduced risk of confounding, but they should be interpreted cautiously. First, they are based on published summary data only, implying that they may be influenced by reporting bias. Second, we had to rely on the meta-epidemiological study authors' definition and operationalisation of commercial funding. As a consequence, the comparisons included in our pooled analysis were not consistent between the meta-epidemiological studies. For example, one meta-epidemiological study excluded trials with unreported funding source altogether,[61] and another meta-epidemiological study grouped these trials with non-commercially funded trials,[60] whereas five meta-epidemiological studies grouped these trials with commercially funded trials.[93-97]

In conclusion, based on a systematic review of seven meta-epidemiological studies, we found an uncertain impact of commercial funding on estimated intervention effects in randomised clinical trials. Based on our findings, it was unclear to which degree commercial funding impacts on statistically favourable results, favourable conclusions, and concordance between results and conclusions.[4]

Establishing the COMFIT consortium and database

The second part of sub-study III is reported in (available in Appendix 7):
Nejstgaard CH, Lundh A, Abdi S, et al. Methods and development of a combined database of primary meta-epidemiological studies of commercial funding of randomised clinical trials: the COMFIT study. *Draft manuscript.*

Aims

In the second part of sub-study III, my co-authors and I described the methods for establishing of the COMFIT consortium, detailed the procedures for constructing the COMFIT database, and provided core baseline data of the included meta-epidemiological studies.[5]

Methods

From the pool of studies located through the search strategy described above, we included meta-epidemiological studies with published or unpublished data on 1) commercial funding per se, 2) commercial funding with increased risk of funder influence, or 3) trial authors' financial conflicts of interest. We included meta-epidemiological studies investigating the following: estimated intervention effects, statistically favourable results, favourable conclusions, or concordance between results and conclusions.

We established the COMFIT consortium consisting of methodologists and authors of included meta-epidemiological studies. We invited lead authors from each meta-epidemiological study to join the consortium and share trial-level data. We then plan to combine the trial-level data into the COMFIT database. Before combining data, we will check the data quality for each meta-epidemiological dataset by comparing with the study publication (e.g. we will compare the number of trials with commercial funding per se between the dataset and study publication). We will also identify references for the included trials as well as obtain PubMed identifier numbers (PMID numbers) when these are not available from the dataset. We will convert the categories used for variables in the individual meta-epidemiological studies into common categorisations for the COMFIT database. Finally, we will remove non-informative meta-analyses (i.e. meta-analyses with no contrast between the trials, e.g. if all trials have the same type of funding source), and remove correlated or duplicate meta-analyses and trials (i.e. several meta-analyses included from the same systematic review and several trial comparisons included from the same trial).

Summary of main findings

We identified 18 eligible meta-epidemiological studies and included trial-level data for 17 of them in the COMFIT database.[60,61,93-97,99-108] Ten studies investigated commercial funding in randomised trials; seven had published findings based on a within-meta-analysis approach and three studies published other measures of the impact. The remaining seven studies did not analyse the impact of commercial funding, but collected data on commercial funding as a descriptive or analytical adjustment factor. The last study was from 1998 and data had been lost.[109]

The 17 meta-epidemiological studies included 728 (median: 33, range: 6-156) meta-analyses and 6841 (median: 326, range: 32-1236) trials. We will combine these meta-analyses and trials in the COMFIT database, but the numbers will decrease as part of our procedures for constructing the database. Ten meta-epidemiological studies investigated trials within specific clinical specialties (e.g. critical care), and the remaining seven studies investigated trials from a range of multiple specialties. Fourteen studies investigated

a mixture of outcomes, two studies investigated patient-reported pain outcomes, and one study investigated mortality outcomes.

Interpretation and conclusion
We established a consortium for data sharing and initiated the development of a database combining trial-level data from 17 meta-epidemiological studies. The database will provide an opportunity to perform analyses that are more reliable than those of typical methodological studies, due to a reduced risk of confounding, with a limited risk of reporting bias, due to the inclusion of unpublished data, with minimised multiplicity issues by removal of correlated or duplicate meta-analyses and trials between the meta-epidemiological studies, and with increased statistical power.

The COMFIT database will enable us to investigate the impact of commercial funding per se, commercial funding with increased risk of funder influence, and authors' financial conflicts of interest on results and conclusions in randomised clinical trials. Moreover, the database enables analysis of the potential dose-response relation between degree of commercial funding per se and estimated intervention effects, as well as the potential association between risk of bias and sources of funding.

Discussion

Summary of main findings

My co-authors and I found associations between financial conflicts of interest and favourable conclusions or recommendations of drugs and devices in systematic reviews, clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. Our analyses showed a consistent direction and provided fairly similar magnitude of effect, but had varying degrees of statistical precision. Our findings on the association between commercial funding and favourable conclusions in randomised clinical trials were unclear.

We found an uncertain impact of commercial funding on estimated intervention effects in randomised clinical trials. Our findings on the impact of financial conflicts of interest on estimated intervention effects and statistically favourable results in systematic reviews and from commercial funding on statistically favourable results in randomised clinical trials were unclear. It is therefore uncertain to which degree conflicts of interest impact directly on estimated intervention effects and statistically favourable results in these types of clinical research publications. To enable future analyses on the impact on randomised clinical trials, we established a consortium for data sharing and initiated the development of a database with trial-level data from 17 meta-epidemiological studies including 728 meta-analyses and 6841 trials.[5]

Strengths and challenges of the PhD thesis

The findings of this PhD thesis are based on summarising and analysing studies investigating a large number of clinical research publications. In all sub-studies, I used rigorous methods. For example, all sub-studies were based on protocols and two of these were peer reviewed.[62,74] Moreover, in sub-study I and II, I attempted to address publication bias and selective outcome reporting bias by searching for unpublished studies and grey literature and comparing published studies with corresponding protocols.

A major strength is the inclusion of unpublished data from five included studies in sub-study I, 11 included studies in sub-study II, and 17 included studies in the COMFIT database in sub-study III. This enabled my co-authors and me to perform comprehensive analyses, including several subgroup and sensitivity analyses. Sub-study III provided findings with a markedly reduced risk of confounding. The COMFIT database will provide an opportunity to perform analyses with a reduced risk of confounding, minimised risk of reporting bias due to inclusion of unpublished data, minimised multiplicity issues by removal of correlated and duplicate meta-analyses and trials between the meta-epidemiological studies, and increased statistical power.

Challenges related to synthesising findings from various included methodological studies

Nevertheless, there are some challenges that arose because the sub-studies are based on synthesising existing methodological studies. In sub-study I and II, the majority of the included studies had a risk of confounding because they compared clinical research publications that differed in other aspects than conflicts of interest. Consequently, the apparent impact of financial conflicts of interest on conclusions and recommendations in systematic reviews, clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews may be influenced by underlying differences in, for example, type of intervention. However, in both sub-studies the findings were supported by a few included studies that had a reduced risk of confounding.

Furthermore, the same clinical research publication may have been investigated in one or more of the included studies. For example, in sub-study II three included studies investigated advisory committee reports from overlapping time periods. As I only had access to unpublished data from one of these studies, I was not able to remove duplicate advisory committee reports. Furthermore, in the systematic review in sub-study III, I relied solely on published summary data. Consequently, the same trial or meta-analysis may have been included in several meta-epidemiological studies. This may have impacted the effect estimates. For example, if a commercially funded trial with a weak effect of the experimental intervention is included twice, this may lead to an underestimation of the average impact of commercial funding. Moreover, this creates dependency in data that can lead to an overestimation in precision (i.e. standard errors that are too small and thus CIs that are too narrow).

My findings have some degree of statistical imprecision. In sub-study II and the systematic review of meta-epidemiological studies in sub-study III, the primary analyses indicated an impact of financial conflicts of interest and commercial funding, but none of them were statistically significant at the conventional 5% level with wide 95% CIs. This could possibly be due to insufficient statistical power to detect an important impact.

Challenges related to how conflicts of interest are defined and disclosed

A general challenge in the methodological studies included in my three sub-studies seemed to be a lack of a uniform definition of conflicts of interest. For example, in sub-study I one included study compared systematic reviews with financial conflicts of interest related to one drug company, with both systematic reviews with financial conflicts of interest related to multiple drug companies and systematic reviews without any financial conflicts of interest. Moreover, in sub-study III, some meta-epidemiological studies coded public funded trials with free provision of trial materials from commercial companies as commercially funded trials, whereas other meta-epidemiological studies coded them as non-commercially funded trials. As a consequence, the comparisons made were not always identical. Assuming that there is an impact of having ties to multiple drug companies or receiving study material from commercial companies, this may have led to an underestimation (i.e. bias towards the null) of my findings in all three sub-studies. Furthermore, it may have been a source of heterogeneity between in the included studies.

Another general challenge is related to how conflicts of interest are disclosed. The majority of the included studies relied only on disclosed information when coding conflicts of interest in each investigated clinical research publication. For example, 11 of the 21 included studies in sub-study II relied solely on disclosed information. The remaining ten included studies relied on a mix of disclosed and undisclosed information. For example, one included study checked the conflicts of interest statements in other narrative reviews on the same topic by the same authors.[56] At the same time, conflicts of interest are often underreported in various publication types, including randomised clinical trials[110] and clinical guidelines.[48] Clinical research publications with unreported or unclear conflicts of interest were often merged with publications without conflicts of interest, resulting in a comparison group that may in fact contain publications with conflicts of interest. Therefore, this may have led to an underestimation of my findings.

Challenges related to interpreting the findings

Finally, the interpretation of my findings is challenging, especially in relation to assessing how certain the evidence is. Assessing certainty in the evidence from methodological studies is difficult because there are

no published guidelines specifically tailored for this. One approach could be to use the GRADE system. However, the study funding sources and authors' financial ties cannot be randomised and using the GRADE approach for intervention studies may provide too conservative interpretations.[32] In sub-study I, I used this approach, which resulted in low to very low certainty of the evidence. In sub-study II, I focused on interpreting the findings in the context of statistical precision and risk of confounding. I also provided assessments using both the GRADE approach for intervention studies[32] and for prognostic studies,[75] which resulted in low to very low certainty depending of type of publication and the system used.[2,3] The combined procedure from sub-study II may provide the most accurate assessment, though the main interpretation is based on a process that is not formalised and systematic.

Comparison with other studies

My findings on the association between conflicts of interest and favourable conclusions or recommendations in systematic reviews, clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews are in line with the findings of a Cochrane review on commercial funding in primary research studies that also found an association with favourable conclusions.[51]

The authors of the Cochrane review also found that studies with commercial funding more often had statistically favourable results compared with studies without commercial funding (RR: 1.27, 95% CI: 1.17-1.37).[51] In contrast, I found no statistically significant association between conflicts of interest and statistically favourable results in systematic reviews, though this was based on only one included study. This discrepancy may be explained by systematic reviews on the same topic often including the same randomised clinical trials. Two systematic reviews with and without conflicts of interest investigating the same topic, may thereby obtain similar results because they are based on the same trials. However, a randomised clinical trial may report multiple findings for the same outcome, for example when the same outcome is measured at different time points. There are, therefore, ample possibilities for selecting different outcome measurements for inclusion in a meta-analysis in a systematic review, even in a situation where the same trials have been included.

My finding of an average exaggeration of estimated intervention effects of 8% in commercially funded randomised clinical trials is of somewhat similar magnitude, but with less statistical precision, as the impact of well-established risk of bias domains. A systematic review of 24 studies (mainly meta-epidemiological) of randomised clinical trials found that inadequate or unclear sequence generation was associated with a 7% exaggeration of estimated intervention effects on average (ROR: 0.93, 95% CI: 0.86-0.99), and that inadequate or unclear allocation concealment was associated with a 10% exaggeration of estimated intervention effects on average (ROR: 0.90, 95% CI: 0.84-0.97).[111]

Furthermore, the impact of conflicts of interest has also been investigated in relation to non-drug and non-device industries. For example, Chartres and colleagues reported that nutrition studies with commercial funding appeared to have more favourable conclusions than studies without commercial funding (RR: 1.31, 95% CI: 0.99-1.72).[112] Likewise, Barnes and colleagues reported that review articles with financial conflicts of interest related to the tobacco industry more often concluded that passive smoking is not harmful compared with review articles without financial conflicts of interest (OR: 88.4, 95% CI: 16.4-476.5).[113]

Finally, the methods for constructing the COMFIT database reported in sub-study III are based on experiences from the construction of a database used in the BRANDO (Bias in Randomised and Observational

Studies) study. BRANDO included data from 7 meta-epidemiological studies and aimed at investigating the influence of various study design characteristics on estimated intervention effects. The BRANDO database contained 234 meta-analyses and 1973 trials with varying numbers included in the individual analyses (from 27 informative meta-analyses on the analysis on attrition to 146 informative meta-analyses on the analysis on allocation concealment).[114] To my knowledge, BRANDO is the only other study combining trial-level data from meta-epidemiological studies. The size of COMFIT will likely surpass quite considerable that of the BRANDO study.

Meaning of the findings

Potential explanations for the findings

My findings on favourable conclusions in systematic reviews may be explained by underlying differences in systematic review results. For example, if systematic reviews with financial conflicts of interest have exaggerated estimated intervention effects compared with systematic reviews without financial conflicts of interest, this would naturally lead to more favourable conclusions. However, I found no statistically significant difference in estimated intervention effects or statistically favourable results. This could suggest that results are interpreted differently in systematic reviews with and without financial conflicts of interest and that the association may be explained by more frequent use of spin in conclusions of systematic reviews with financial conflicts of interest.[115]

My uncertain finding indicating an impact of commercial funding on estimated intervention effects in randomised clinical trials may be explained by type of trial outcomes included in the meta-epidemiological studies. A large study combining data from seven meta-epidemiological studies found that the degree of bias differs between trials with objective and subjective outcomes.[114] The meta-analyses included in the meta-epidemiological studies in sub-study III often analysed trials with mortality outcomes. If the assumption that trials with objective outcomes are less susceptible to influence from bias holds for commercial funding, the ROR of 0.92 from sub-study III may be a conservative measure of the average impact. However, commercial funding may impact estimated intervention effects in randomised clinical trials in a variety of ways, irrespectively of type of outcomes. Furthermore, differences in degree of bias for subjective and objective outcomes have not been demonstrated in subsequent studies,[116] and the terms 'subjective' and 'objective' have been found to be ambiguous when used to describe outcomes in randomised clinical trials.[117]

My findings from sub-study III is in line with uncertain findings from recent meta-epidemiological studies. For example, blinding has long been considered an important method for reducing risk of bias in randomised trials.[118] However, MetaBLIND, a large meta-epidemiological study, recently found no statistically significant difference in estimated intervention effects between trials with and without blinded patients, healthcare providers, or outcome assessors.[107] In relation to sub-study III, the question is whether limitations in the design of meta-epidemiological studies may explain my finding. Meta-epidemiological studies are limited to investigating meta-analyses in which there is a contrast between the included trials. This means that meta-analyses from clinical fields where trials are very often funded by commercial companies (e.g. oncology[45]) may not be included in meta-epidemiological studies, because it is challenging finding meta-analyses where not all trials have the same type of funding. The same would apply for clinical fields with a very low prevalence of commercially funded trials. Furthermore, trials reporting results in a way that does

not enable inclusion in meta-analyses would not be included in meta-epidemiological studies either. Moreover, the decision to pool trials in a meta-analysis may partly rely on the reported estimated intervention effects. For example, if commercially funded trials report larger estimated intervention effects than non-commercially funded trials, reviewers may be less inclined to combine them in a meta-analysis to avoid statistical heterogeneity. In this way, informative meta-analyses may not be available for clinical fields with large differences in estimated intervention effects between commercially and non-commercially funded trials.[58] Therefore, meta-epidemiological studies may investigate a selective sample of randomised trials.

Even though meta-epidemiological studies considerably reduce the risk of confounding compared to typical methodological studies, it is still debated whether confounding may impact the findings. First, meta-epidemiological studies deploy a simple form of matching by comparing trials within meta-analyses. However, this strategy may control imperfectly for patient group, intervention, and control, especially if the meta-analysis inclusion criteria are broad.[119] Second, other trial characteristics (e.g. sample size) may influence estimated intervention effects. For example, a meta-epidemiological study of 93 meta-analyses and 735 randomised trials found that estimated intervention effects were stronger in small randomised trials (less than 50 patients) than in large randomised trials (more than 1000 patients, ROR: 0.52, 95% CI: 0.41-0.66).[120] Controlling for such characteristics may reduce the risk of confounding.[121] In the systematic review in sub-study III, I solely summarised findings from unadjusted analyses and residual confounding may potentially explain my finding.

Differences and similarities between clinical research publications

The methodological rigour behind the results, conclusions, and recommendations differ between the various types of clinical research publications, and I had anticipated finding differences in the impact of conflicts of interest. In contrast to systematic reviews and randomised clinical trials, clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews may follow less strict methods. Clinical guidelines are often developed based on systematic searches of existing evidence and may follow standardised procedures for grading the evidence supporting the recommendations.[32] In contrast, authors of opinion pieces may freely and selectively cite studies and interpret evidence. Advisory committee reports and narrative reviews are developed using more or less systematic procedures, but also involve subjective elements. Thus, systematic reviews and randomised clinical trials may be least susceptible to influence of conflicts of interest. Advisory committee reports and narrative reviews may be more susceptible to influence of conflicts of interest than clinical guidelines, but less than opinion pieces.

However, I found fairly consistent associations between financial conflicts of interest and favourable conclusions or recommendations. The RRs ranged from 1.20 in advisory committee reports and narrative reviews to 2.62 in opinion pieces, though with some degree of statistical imprecision. Even though only one meta-epidemiological study investigated favourable conclusions in randomised clinical trials, the aforementioned Cochrane review had findings of similar magnitude.[51] My findings from the different types of clinical research publications to a large extent had overlapping 95% CIs. Furthermore, in a combined analysis of clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews, I found only moderate statistical heterogeneity (I^2: 38%). Therefore, the impact of financial conflicts of interest does not seem to differ markedly between the investigated clinical research publications (with the possible exception of opinion pieces).

On an absolute scale, the number needed to read for one additional favourable conclusion or recommendation ranged from 2.2 in systematic reviews to 9.1 in clinical guidelines, though with some degree of statistical imprecision and overlapping 95% CIs. Unfortunately, it was not possible to estimate number needed to read for randomised clinical trials. Absolute measures may be less consistent than relative effect measures.[122] Moreover, the numbers needed to read are based on the clinical research publications included in my sub-studies, and may differ had other publications from different clinical situations been included. Nevertheless, the fairly low numbers needed to read raise the question of when an impact of conflicts of interest should be considered relevant. My calculation of number needed to read is based on the methods used for estimating numbers needed to treat. Compared with reported numbers needed to treat, conflicts of interest seem to have a potentially great impact. For example, the FDA-approved treatments for bipolar disorder generally have numbers needed to treat ranging between 3 and 9,[123] and numbers needed to treat of 32, 46, and 72 have been reported for cardiac rehabilitation trials on mortality.[124] However, numbers needed to treat are rarely reported in randomised clinical trials[125] and it is not meaningful to determine one general cut-point for when numbers needed to treat indicate high and low effects. For example, a high number needed to treat may be acceptable for interventions that are cheap or when outcome measures are clinical important (e.g. mortality measures).[126,127]

Potential mechanisms for the impact of conflicts of interest on clinical research publications

The discussion above raises the question of whether conflicts of interest are best regarded as having a similar or differential impact on different types of clinical research publications. Even though the impact seems to be fairly similar from an empirical perspective, conflicts of interest may work through different mechanisms in the different types of clinical research publications. Unfortunately, our knowledge of the mechanisms of the influence in systematic reviews, clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews is incomplete. For systematic reviews, clinical guidelines, and narrative reviews, conflicts of interest may influence the study design (e.g. if authors choose to focus on outcomes where the experimental drug has a large effect and thereby ignore studies of outcomes with a less profound effect), interpretation of study findings (e.g. by an increased use of spin in conclusions), and reporting of study findings (e.g. if only results favourable towards the sponsor are fully reported). For opinion pieces and advisory committee reports, authors and committee members with financial conflicts of interest may be more likely to confirm prior beliefs by selectively citing supporting literature and interpreting literature in a favourable way.[128]

For randomised clinical trials, a more frequent use of inferior comparator interventions,[129,130] selective reporting of favourable findings,[131-133] as well as funders' constrains on publication rights[134] have been highlighted as potential mechanisms explaining the impact of conflicts of interest. For example, if a randomised clinical trial is supplying the sponsor's drug in a higher dose than the comparison drug, this may lead to the drug being perceived as more effective. Furthermore, studies have also suggested that commercially funded trials more often use placebo instead of active controls[135,136] and more often use surrogate outcomes.[137] This may also explain differences in results and conclusions between commercially and non-commercially funded trials. However, in meta-epidemiological studies, where trials are compared within meta-analyses, ideally the control intervention and the outcome measure should be the same. Therefore, these potential mechanisms may not explain my findings on estimated intervention effects from sub-study III.

The impact of conflicts of interest may sometimes come from unconscious decisions or out of ignorance (e.g. being unaware of the problems involved in selective reporting of results) or from a conscious choice in an attempt to have results that favour a specific point of view.[7] For example, authors may unconsciously cite literature that supports the authors' preconception, without this being a case of knowingly suppressing literature with other points of views. On the other hand, commercially funded randomised clinical trials often investigate new treatments with the purpose of regulatory approval. Commercial companies may gain financially (e.g. through increasing stock prices) from publication of favourable results.[138] Therefore, commercial companies may make conscious decisions (e.g. regarding which dose to use of which drugs) to ensure favourable results.

Different researchers are likely to have different perceptions of what is considered to be conflicts of interest.[7] This creates problems for conflicts of interest disclosures as they are often based on researchers' individual decision of what to disclose. Unfortunately, the threshold for when conflicts of interest matter has not been investigated. From a theoretical point of view, it would make sense if the impact of financial conflicts of interest differs according to the amount of money received. For example, getting a one-time speaker fee may have less influence than earning a substantial part of one's income from advisory board memberships and consulting fees from commercial companies. This perception is also to some extent supported by an empirical study of 2444 physicians. The authors reported that physicians' prescribing rate increases with amount of money they receive from commercial companies.[139]

Unanswered questions and future research

Limitations in the study design of existing studies

In an ideal situation, we would prefer having evidence from randomised trials in order to estimate the causal relationship between conflicts of interest and estimated intervention effects, statistically favourable results, and favourable conclusions and recommendations in clinical research publications. When well-conducted, randomised trials utilise the study design with the lowest risk of bias.[140] However, in the case of studying conflicts of interest, randomised trials are not feasible. While being theoretically thinkable (e.g. randomising guideline topics to panels of conflicted and non-conflicted authors), true randomisation of conflicts of interest is not practically doable, especially not in a world with limited resources and a constant development in research priorities. Furthermore, even well-conducted randomised trials have limitations, for example insufficient statistical power. This also explains the necessity of conducting systematic reviews of randomised trials. Moreover, the preference of randomised trials rests on an assumption that randomisation protects against bias equally well in intervention studies as in methodological studies. In the theoretical example of randomising guideline topics to different author panels, randomisation will likely minimise bias to some degree, but it will not ensure that panels are similar in regards to other aspects than financial conflicts of interest (e.g. medical specialties or non-financial conflicts of interest). Therefore, we have to rely on evidence from methodological studies with other designs.

In the absence of randomised trials, the best available evidence would come from empirical studies with a minimised risk of confounding. This can be achieved by using a matched study design, for example by identifying a systematic review with conflicts of interest and then searching for a second systematic review investigating the same drug used for the same disease and with similar publication years, but without conflicts of interest. This approach is very challenging and may not be feasible for all types of clinical research

publications. For example, it may be difficult to find two clinical guidelines of the same topic that are conducted in similar contexts using similar methods. Another option would be to address confounding on the analysis level, and perform adjusted analyses. However, this requires a sufficient sample size and multiple confounders may be correlated with each other. Alternatively, minimising confounding may also be done by sampling clinical research publications using quite narrow inclusion criteria. For example, by sampling editorials and commentaries that all comment on the same randomised clinical trial. Finally, for investigations of randomised clinical trials, an ideal approach to minimise confounding may be to conduct meta-epidemiological studies. To my knowledge, a few studies have used these approaches, but they lack statistical power and have imprecise findings. Therefore, we need more empirical studies with a minimised risk of confounding to determine the magnitude of the impact of conflicts of interest with certainty.

A potential solution is presented in the COMFIT study (sub-study III). Instead of spending resources on conducting additional individual methodological studies with limited statistical power, my co-authors and I combine multiple sources of data. Such an approach will also enable targeting other methodological issues, for example by ensuring uniform definitions of commercial funding. In this way, findings from analyses made on the basis of the COMFIT database will importantly influence our perception of commercial funding in randomised clinical trials and bring us a lot closer to having a certain estimate of the potential impact.

Definitions of conflicts of interest

It remains unclear whether certain types of financial conflicts of interest have greater impact on clinical research publications. As hinted in the systematic review in sub-study III, commercial funding with increased risk of funder influence may affect trial estimated intervention effects more than commercial funding per se. Additional studies may clarify this. Another important aspect is the role of the author with conflicts of interest. For example, the lead and senior authors of a systematic review may have a greater influence on the conclusions than authors with less prominent roles. Similarly, the chair of a guideline committee may have more influence on the final recommendations than other guideline committee members. Moreover, it also remains unclear whether non-commercial financial conflicts of interest (e.g. related to foundations or governmental agencies) impacts on clinical research publications, and whether there are any differences in the impact between clinical fields.

It is unclear whether there is a dose-response relationship between conflicts of interest and estimated intervention effects, statistically favourable results, conclusions, and recommendations of clinical research publications. This will be important to investigate, as journal policies may prohibit conflicts of interest above certain thresholds (e.g. based on number of conflicted authors or monetary amount).[25,27] Moreover, establishing whether a potential dose-response relationship exists will have important implications for our confidence in the findings from observational studies, as it is recognised as an important criterion for believing in a causal relationship[141] and is one of the factors for grading up the certainty of the evidence in the GRADE system.[142]

Investigating the impact of non-financial conflicts of interest may be especially challenging as no uniform definition exists. On one side, no researcher is completely free from interests and intellectual preconceptions.[9] Therefore, placing emphasis on non-financial conflicts of interest may risk detracting attention from financial conflicts of interest. On the other side, conditions such as personal beliefs and personal relationships may impact on judgements made when conducting clinical research.[8] Furthermore, the distinction

between financial and non-financial conflicts of interest is not always clear, and sometimes conflicts of interest may be financial in their nature, but still differ from what we conventionally consider financial conflicts of interest. For example, when radiologists are conducting clinical guidelines on mammography screening (i.e. specialty interest),[84] they often also have a direct financial income from breast cancer screening. It remains unclear to which degree non-financial conflicts of interest impact on clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. Future studies could focus on investigating various types of non-financial conflicts of interest. Findings from such studies could inform the discussion on whether the term 'non-financial conflicts of interest' is appropriate and which types of interests should be considered important and therefore also should be disclosed.

Results of clinical research publications

It remains unclear to which degree conflicts of interest impact directly on estimated intervention effects of systematic reviews and randomised clinical trials, and future research could focus on establishing this. The impact on estimated intervention effects will be addressed for randomised clinical trials in the COMFIT study described in sub-study III.

Implications for research and practice

The findings from the three sub-studies support conflicts of interest disclosure policies from scientific journals, guideline issuing organisations, and regulatory agencies. Such policies may enforce transparent reporting of conflicts of interest, which will enable users to interpret the study findings in light on conflicts of interest, but does not eliminate the problem. Unfortunately, conflicts of interest are not always disclosed accurately and there is a need for developing methods to ensure completeness in the declaration of financial conflicts of interest.[138] Inaccurate disclosure of conflicts of interest may arise for several reasons. For example, if researchers have different perceptions of what constitutes conflicts of interest and when they matter,[7] this may lead to diverse disclosures. Therefore, requirements for disclosure should be clear, consistent and ideally list examples of financial conflicts of interest, following the example of the ICMJE disclosure form.[9,14] An alternative approach could be to ask authors to disclose everything and let the editors decide which conflicts to report. Whether and what types of non-financial conflicts of interest authors should disclose has been debated. However, at the moment the empirical basis for requiring disclosure of non-financial conflicts of interest related to drug and device studies is very limited and more studies are needed to confirm the necessity.

Deciding what to disclose will always contain subjective elements. Furthermore, researchers will have different preferences for reporting conflicts of interest transparently. Therefore, tools to verify the accurateness and completeness of declared financial conflicts of interest will be helpful.[138] However, existing appraisal tools only superficially address conflicts of interest.[25] Therefore, I support the development of the 'Tool for Addressing Conflicts of Interest in Trials' (TACIT).[143] The TACIT tool will enable assessment of the completeness of conflicts of interest declarations as well as the potential concern about such conflicts of interest.

Another strategy to manage conflicts of interest may be to restrict publication with the aim of minimising the number and role of authors with conflicts of interest and funding by commercial companies. However, publication of commercially-funded trials may increase journal impact factor and provide substantial financial income for the journal through reprint sales.[144] Therefore, editors may be faced with a dilemma when

considering implementing strict conflicts of interest policies. Journal editors may consider implementing safeguards against the impact of conflicts of interest. For example, by ensuring that the sponsor of a trial does not constrain publication rights or controls the analyses.

The COMFIT database described in sub-study III was enabled because of a willingness to share trial-level data by the authors of the included meta-epidemiological studies. The principles of data sharing have long been discussed and are recognised as an important part of conducting research.[145] Many scientific journals have data sharing policies, but with wide variation in the requirements,[146] and authors of randomised clinical trials often support sharing trial data.[147] However, a study based on requests for unpublished data reported that authors often do not deliver such data.[148] Based on my experiences, obtaining unpublished data creates opportunities to perform analyses that are not possible to do in single studies. The approach my co-authors and I used to obtain trial-level data in the COMFIT study may be useful for future investigations based on combining primary data from multiple studies.

The Cochrane tool to assess risk of bias in randomised trials (RoB 2) has recently been revised. Currently, the tool does not include conflicts of interest as a separate domain leading to bias.[149] It has been debated whether conflicts of interest should be an integrated part of the tool.[143] The main argument in favour is that conflicts of interest are a bias that is not captured by the other risk of bias domains (e.g. allocation concealment).[150] The main argument against is that the impact of conflicts of interest on randomised trials is already captured by the tool (e.g. through selective outcome reporting).[151] The Cochrane Handbook for Systematic Reviews of Interventions discourage authors to include information on conflicts of interest directly in the risk of bias assessments of systematic reviews, as RoB 2 is based on independent bias mechanisms.[152] Based on the COMFIT database (sub-study III), my co-authors and I plan to analyse the potential interaction from the traditional risk of bias domains (e.g. sequence generation and blinding), thereby examining if the association between commercial funding and estimated intervention effects in randomised trials differ according to risk of bias. These findings will inform the debate.

Conclusion

There is a strong scientific and public concern regarding conflicts of interest in clinical research publications. This is of crucial importance to ensure that patient care is based on trustworthy research and not unduly influenced by secondary interests.

The general aim of this PhD thesis was to describe and analyse the impact of conflicts of interest on results, conclusions, and recommendations expressed in different types of clinical research publications: systematic reviews, clinical guidelines, advisory committee reports, opinion pieces, narrative reviews, and randomised clinical trials.

I found an impact of financial conflicts of interest on conclusions in systematic reviews. My results indicate that it is expected that one additional systematic review will have a favourable conclusion for every 2.2 systematic reviews with, rather than without, financial conflicts of interest that are read. The impact on estimated intervention effects and statistically favourable results was investigated in only one included study each and it remains unclear to which degree financial conflicts of interest impact directly on results of systematic reviews.

I found an impact of financial conflicts of interest on recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. However, this conclusion was based on disregarding the statistical imprecision in each individual publication type. My results indicate that it is expected that one additional favourable recommendation will occur for every 9.1 clinical guidelines, 7.7 advisory committee reports, 2.3 opinion pieces, and 8.3 narrative reviews with, rather than without, financial conflicts of interest that are read. The impact of non-financial conflicts of interest was only investigated in one included study and it remains unclear to which degree non-financial conflicts of interest have an impact.

My findings for systematic reviews, clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews may be uncertain due to a risk of confounding in the included studies. Thus, I cannot exclude that differences in conclusions and recommendations are influenced by underlying differences in, for example, included patients, interventions, or outcomes.

I found an uncertain impact of commercial funding on estimated intervention effects in randomised clinical trials. On average, ORs in randomised clinical trials with commercial funding was exaggerated by 8% compared with trials without commercial funding. However, the finding was not statistically significant and may be influenced by reporting bias, as it was based on published summary data only. Based on my findings, it remains unclear to which degree commercial funding impacts on statistically favourable results, favourable conclusions, and concordance between results and conclusions in randomised clinical trials.

To enable further analyses on the impact of commercial funding on randomised clinical trials, my co-authors and I initiated the development of a database with trial-level data on funding source and results and conclusions from 17 meta-epidemiological studies including 728 meta-analyses and 6841 randomised clinical trials. The database will provide an opportunity to perform analyses with a reduced risk of confounding, minimised risk of reporting bias, and increased statistical power.

The impact of conflicts of interest on conclusions or recommendations in the investigated types of clinical research publications was of somewhat similar magnitude, but the mechanisms through which conflicts of interest work may differ quite substantially.

Based on the findings and my knowledge of the scientific field and its literature, I suggest that journals should supply authors with clear and consistent requirements to enable transparent disclosure of conflicts of interest. Transparency in disclosure will enable users of clinical research publications to interpret findings in light of conflicts of interest, but it will not eliminate the potential influence. To minimise this, I suggest that patients, clinicians, health care decision makers, and researchers search for clinical research publications that are free from financial conflicts of interest and use rigorous methods. Such research may not always be available. If this is the case, I suggest that users read conclusions and recommendations in publications with financial conflicts of interest with extra scepticism, critically appraise the used methods, and interpret the results with caution.

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Appendices

List of appendices

Appendix 1. Terminology

For the purpose of this PhD thesis, I use the following terminology that is based on the terminology used in the three sub-studies.

Terminology related to conflicts of interest

I use the term '*conflicts of interest*' to refer to both financial and non-financial conflicts of interest as specified below.[2]

I use the term '*financial conflicts of interest*' to refer to both commercial funding and authors' financial conflicts of interest as specified below.[1,2]

I use the term '*commercial funding*' to refer to any funding by commercial companies, authorship by full-time employees at commercial companies, and assistance by commercial companies.[1] This term covers both commercial funding per se and commercial funding with increased risk of funder influence as specified below.

I use the term '*commercial funding per se*' to refer to the type of funding source of the trial.[4,5]

I use the term '*commercial funding with increased risk of funder influence*' to refer to type of trial funding source combined with an assessment of whether a commercial funder had an influence on the trial design, conduct, analysis, or reporting (e.g. a trial funded by a pharmaceutical company that also conducted the statistical analyses).[4,5]

I use the term '*authors' financial conflicts of interest*' to refer to any financial relationships of authors, apart from full-time employment, with a commercial company (e.g. consultancy work).[1]

I use the term '*non-financial conflicts of interest*' to refer to personal and professional relationships (e.g. research collaboration), professional and specialty interests (e.g. belonging to a certain medial subspecialty), or intellectual and academic conflicts of interest (e.g. authorship of studies that are part of the evidence base for reaching a particular recommendation).[8] In some cases an interest may be considered both a financial and non-financial, e.g. a surgeon who uses a particular surgical intervention which he/she then investigates in a clinical guideline. This can be viewed as financial, because the surgeon may financially benefit from a favourable recommendation. It can also be viewed as non-financial, because the surgeon uses the surgical procedure as part of clinical practice. For this PhD thesis, I regard such relationships as non-financial because they differ from what is typically regarded as financial conflicts of interest.[2]

Terminology related to clinical research publications

I use the term '*randomised clinical trial*' to refer to clinical trials that randomly allocate participants to different treatments, e.g. an experimental intervention group and a placebo group.

I use the term '*systematic review*' to refer to literature reviews with a systematic search of the literature with clear eligibility criteria.

I use the term '*clinical guidelines*' to refer to guidelines defined as systematically developed statements with the purpose of assisting practitioner and patient decisions about appropriate health care for specific clinical circumstances.[2]

I use the term '*advisory committee reports*' to refer to transcripts from meetings held in committees, boards, councils, or similar to advise an organisation and provide recommendations concerning interventions (e.g. the FDA advisory committee on oncological drugs).[2]

I use the term '*opinion pieces*' to refer to documents that are not primary research studies in which an author expresses a personal opinion about a specific intervention, for example editorials, commentaries, and letters-to-the-editor.[2]

I use the term '*narrative reviews*' to refer to literature reviews without a systematic search of the literature with clear eligibility criteria.[2]

I use the term '*meta-epidemiological study*' to refer to a study comparing randomised clinical trials within meta-analyses as defined in the introduction section of this PhD thesis.

I use the term '*statistically favourable results*' to refer to results that are favourable towards the experimental intervention based on direction and statistical significance.

I use the term '*estimated intervention effects*' to refer to outcome data, e.g. OR or RR.

I use the term '*favourable conclusions*' to refer to conclusions that are favourable towards the experimental intervention.

I use the term '*favourable recommendations*' to refer to recommendations that are favourable towards the experimental intervention.

I use the term *'concordance between results and conclusions'* to refer to whether favourable conclusions are supported by statistically favourable results.

I use the term '*the quality of the systematic review methods*' to refer to the quality (e.g. assessed by the Oxman and Guyatt index) of the systematic reviews investigated by the studies included in sub-study I.

Terminology related to the methods in this PhD thesis

I use the term '*sub-study*' to refer to the three studies that constitutes this PhD thesis.

I use the term '*clinical research publications*' to refer jointly to randomised clinical trials, systematic reviews, clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews.

I use the term *'included studies'* to refer to studies included in any of the sub-studies.

I use the term '*methodological quality*' to refer to the quality assessment my co-authors and I performed on the studies included in the three sub-studies.

Appendix 2. List of abbreviations

BRANDO – Bias in Randomised and Observational studies (study acronym)
CI – confidence interval
COMFIT – COMmercial Funding In Trials (study acronym)
CONSORT – Consolidated Standards of Reporting Trials
dSMD – difference in standardised mean differences
FDA – Food and Drug Administration
ICMJE – International Committee of Medical Journal Editors
NNRF – number needed to read favourable
NNRU – number needed to read unfavourable
OR – odds ratio
PROSPERO – The International Prospective Register of Systematic Reviews
RoB 2 – The revised Cochrane Tool to assess risk of bias in randomised trials
ROR – ratio of odds ratios
RR – relative risk
TACIT – Tool for Addressing Conflicts of Interest In Trials (study acronym)
US – United States

Appendix 3. Publication for sub-study I

Sub-study I is reported in:

Hansen C, Lundh A, Rasmussen K, Hróbjartsson A. Financial conflicts of interest in systematic reviews: associations with results, conclusions, and methodological quality. *Cochrane Database Syst Rev* 2019;Issue 8:MR000047.

Cochrane Library

Cochrane Database of Systematic Reviews

Financial conflicts of interest in systematic reviews: associations with results, conclusions, and methodological quality (Review)

Hansen C, Lundh A, Rasmussen K, Hróbjartsson A

Hansen C, Lundh A, Rasmussen K, Hróbjartsson A.
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TABLE OF CONTENTS

[Methodology Review]

Financial conflicts of interest in systematic reviews: associations with results, conclusions, and methodological quality

Camilla Hansen[1,2,3,4], Andreas Lundh[1,2,3,5], Kristine Rasmussen[4], Asbjørn Hróbjartsson[1,2,3]

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ABSTRACT

Background

Financial conflicts of interest in systematic reviews (e.g. funding by drug or device companies or authors' collaboration with such companies) may impact on how the reviews are conducted and reported.

Objectives

To investigate the degree to which financial conflicts of interest related to drug and device companies are associated with results, conclusions, and methodological quality of systematic reviews.

Search methods

We searched PubMed, Embase, and the Cochrane Methodology Register for studies published up to November 2016. We also read reference lists of included studies, searched grey literature sources, and Web of Science for studies citing the included studies.

Selection criteria

Eligible studies were studies that compared systematic reviews with and without financial conflicts of interest in order to investigate differences in results (estimated treatment effect and frequency of statistically favourable results), frequency of favourable conclusions, or measures of methodological quality of the review (e.g. as evaluated on the Oxman and Guyatt index).

Data collection and analysis

Two review authors independently determined the eligibility of studies, extracted data, and assessed risk of bias. We synthesised the results of each study relevant to each of our outcomes. For meta-analyses, we used Mantel-Haenszel random-effects models to estimate risk ratios (RR) with 95% confidence intervals (CIs), with RR > 1 indicating that systematic reviews with financial conflicts of interest more frequently had statistically favourable results or favourable conclusions, and had lower methodological quality. When a quantitative synthesis was considered not meaningful, results from individual studies were summarised qualitatively.

Main results

Ten studies with a total of 995 systematic reviews of drug studies and 15 systematic reviews of device studies were included. We assessed two studies as low risk of bias and eight as high risk, primarily because of risk of confounding. The estimated treatment effect was not

statistically significantly different for systematic reviews with and without financial conflicts of interest (Z-score: 0.46, P value: 0.64; based on one study of 14 systematic reviews which had a matched design, comparing otherwise similar systematic reviews). We found no statistically significant difference in frequency of statistically favourable results for systematic reviews with and without financial conflicts of interest (RR: 0.84, 95% CI: 0.62 to 1.14; based on one study of 124 systematic reviews). An analysis adjusting for confounding due to methodological quality (i.e. score on the Oxman and Guyatt index) provided a similar result. Systematic reviews with financial conflicts of interest more often had favourable conclusions compared with systematic reviews without (RR: 1.98, 95% CI: 1.26 to 3.11; based on seven studies of 411 systematic reviews). Similar results were found in two studies with a matched design, which therefore had a reduced risk of confounding. Systematic reviews with financial conflicts of interest tended to have lower methodological quality compared with systematic reviews without financial conflicts of interest (RR for 11 dimensions of methodological quality spanned from 1.00 to 1.83). Similar results were found in analyses based on two studies with matched designs.

Authors' conclusions

Systematic reviews with financial conflicts of interest more often have favourable conclusions and tend to have lower methodological quality than systematic reviews without financial conflicts of interest. However, it is uncertain whether financial conflicts of interest are associated with the results of systematic reviews. We suggest that patients, clinicians, developers of clinical guidelines, and planners of further research could primarily use systematic reviews without financial conflicts of interest. If only systematic reviews with financial conflicts of interest are available, we suggest that users read the review conclusions with skepticism, critically appraise the methods applied, and interpret the review results with caution.

PLAIN LANGUAGE SUMMARY

Financial conflicts of interests and results, conclusions, and quality of systematic reviews

Patient treatment practices are often based on clinical research. Systematic reviews are a core type of such clinical research. When several similar studies (i.e. studies investigating the same research questions using similar methods) have been conducted, these can be identified and analysed in a systematic review. Systematic reviews thereby summarise existing studies and provide an overview of a specific research field. Thus, systematic reviews may have a major influence on decisions about patient care and it is essential that such reviews are trustworthy.

Sometimes, systematic reviews are funded by companies with a financial interest in the review's results and conclusions, for example because they produce a drug or device investigated in the review. At other times, systematic reviews are carried out by researchers with a personal financial interest in a specific result, for example when the researcher acts as a consultant for the company producing an intervention that is assessed in the review. These financial conflicts of interest may impact on how systematic reviews are conducted and reported. Our Cochrane Methodology Review focuses on financial conflicts of interest related to drug or device companies in systematic reviews. Our primary aim was to investigate the degree to which systematic reviews with financial conflicts of interest present review results and make conclusions that are more favourable than systematic reviews without such financial conflicts of interest. Our secondary aim was to investigate the degree to which systematic reviews with financial conflicts of interest differ in methodological quality from systematic reviews without such financial conflicts of interest.

We found 10 studies comparing systematic reviews with and without financial conflicts of interest. Based on two of these studies, we found no evidence of a difference in review results between systematic reviews with and without financial conflicts of interest. Based on seven studies, we found that systematic reviews with financial conflicts of interest more often had conclusions favourable towards the experimental intervention (risk ratio (RR): 1.98, 95% confidence interval (CI): 1.26 to 3.11). Also, based on four studies, systematic reviews with financial conflicts of interest tended to have lower methodological quality (RR for 11 dimensions of methodological quality spanned from 1.00 to 1.83).

Our analyses suggest that when systematic reviews have financial conflicts of interest related to drug or device companies, they are of lower methodological quality, and have more favourable conclusions. However, it is not clear whether this derives from actual differences in the review's results or the over-interpretation of those results. Based on our findings, we suggest that people who use systematic reviews, including patients, clinicians, developers of clinical guidelines, and planners of future research, could primarily use systematic reviews without financial conflicts of interest. If such reviews are not available, we suggest that users are especially cautious when they read and interpret systematic reviews with financial conflicts of interest.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Systematic reviews with financial conflicts of interest compared with systematic reviews without

Sample: systematic reviews

Intervention: systematic reviews with financial conflicts of interest

Comparison: systematic reviews without financial conflicts of interest

Outcomes	Absolute effect* (95% CI)		Relative effect	Number of studies	Certainty of the evidence (GRADE)	Comments**
	Assumed risk	Corresponding risk				
	Number of industry reviews with the outcome	Number of non-industry reviews with the outcome				
Estimated treatment effect measured as Z-scores*** after adjustment for the number of patients			**Pooled Z-score: 0.46** (P value: 0.64)	1 study including 7 pairs of industry and non-industry systematic reviews	⊕⊖⊖⊖ **very low**	Downgraded due to imprecision (only one study of 14 systematic reviews)
Frequency of statistically favourable results	549 (405 to 745) reviews with statistically favourable results per 1000 industry reviews	653 reviews with statistically favourable results per 1000 non-industry reviews	**RR: 0.84** (0.62 to 1.14)	1 study including 124 systematic reviews	⊕⊖⊖⊖ **very low**	Downgraded due to limitations in design (only one study with high risk of bias) and imprecision (wide confidence intervals)
Frequency of favourable conclusions	895 (569 to 1000****) reviews with favourable conclusions per 1000 industry reviews	452 reviews with favourable conclusions per 1000 non-industry reviews	**RR: 1.98** (1.26 to 3.11)	7 studies including 411 systematic reviews	⊕⊕⊖⊖ **low**	Fairly large effect estimate, which was substantially higher in the one study with low risk of bias.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

CI: confidence interval; **RR:** risk ratio

*The **assumed risk** of the control group (i.e. non-industry systematic review group) was calculated as the mean risk (i.e. number of systematic reviews with favourable conclusions divided by total number of systematic reviews). The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the control group and the relative effect of the intervention (and its 95% CI).
**See 'Assessment of certainty of the evidence' for a detailed description.
***A Z-score expresses the number of standard deviations by which a value differs from the mean. If a Z-score is interpreted as a standardised mean difference, a Z-score of 0.46 would indicate a moderate effect (Kirkwood 2003). A Z-score of 0.46 indicates that effect estimates are larger in industry reviews compared with non-industry reviews (Jorgensen 2006).
****Upper limit of event rate truncated at 1000.

BACKGROUND

Description of the problem or issue

Systematic reviews provide a rational basis for developing clinical guidelines, for therapeutic decision making, and for planning clinical trials. They have a major impact on which interventions are offered to patients (Guyatt 2008). It is therefore essential that such reviews are trustworthy and unbiased.

One area of concern is the degree to which financial conflicts of interest impact on the conduct and reporting of systematic reviews (Institute of Medicine 2011). The pharmaceutical and clinical device industries frequently fund clinical trials (Atal 2015; Chan 2005), and to a lesser extent also systematic reviews. For example, in a random sample of 300 systematic reviews, Page and colleagues found that eight (3%) were industry-funded (Page 2016). On the other hand, another review found that a quarter of 185 meta-analyses of trials of antidepressants were industry-funded (Ebrahim 2016). Furthermore, systematic reviews are often produced by authors with financial conflicts of interest; a random sample of 194 systematic reviews found that 60 (31%) had at least one author with financial conflicts of interest (Hakoum 2016).

Numerous studies have investigated the relation between financial conflicts of interest and outcomes of individual research studies, mainly clinical trials. A recent update of a Cochrane Review reported clear associations between funding source and statistically significant trial efficacy results (based on 25 empirical studies) and trial conclusions (based on 29 empirical studies) (Lundh 2017). In contrast, fewer studies have investigated how financial conflicts of interest at the level of the systematic review impact on their results and conclusions.

Why it is important to do this review

The retrospective nature of a systematic review and the subjective element in selecting inclusion criteria and outcomes is likely to make such research more susceptible to influence from financial conflicts of interest than prospective clinical trials.

This concern is supported by a review of pairs of Cochrane Reviews and paper-based reviews of the same drugs used for the same disease that reported that industry-funded reviews had more favourable conclusions (Jorgensen 2006). However, other studies have reported a less clear association with wide confidence intervals (Yank 2007). To our knowledge, this Cochrane Methodology Review is the first systematic review of methodology to identify, analyse, and summarise such studies.

OBJECTIVES

Our primary objectives were to investigate the degree to which financial conflicts of interest related to drug or device companies in systematic reviews are associated with the following.

1. Results
   a. Estimated treatment effect
   b. Results statistically favourable to the experimental intervention
2. Conclusions favourable to the experimental intervention

Our secondary objective was to investigate the degree to which financial conflicts of interest related to drug or device companies in systematic reviews are associated with the following.

1. Methodological quality of the reviews

Terminology

We use the following definitions.

1. Financial conflicts of interest: any funding of the systematic reviews by drug or device companies or any review author with financial conflicts of interest in relation to such companies.
2. Industry funding: any funding of the systematic review by industry, authorship by full-time industry employees, assistance by industry (e.g. statistical analysis by company statistician, or writing assistance by a medical writer funded by the company).
3. Author financial conflicts of interest: any financial relationship of authors, apart from full-time employment, with a drug or device company (e.g. receiving grants, owning stocks, being on an advisory board, or consultancy work).
4. Industry reviews: reviews that are consistent with one or more of the above definitions.
5. Non-industry reviews: reviews that fulfil none of the above definitions.
6. Drugs: medications that require approval from regulatory agencies.
7. Devices: instruments used in diagnosis, treatment, or prevention of a disease. This definition follows the definition of the Food and Drug Administration (FDA) (FDA 2017) and includes imaging technologies.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies that investigated samples of systematic reviews with and without financial conflicts of interest. We defined systematic reviews according to the definitions used by the authors of the included studies.

Eligible studies had to investigate at least one of our primary or secondary outcomes. If a study contained a mixture of systematic reviews and research of other designs (e.g. randomised trials), we included the study, but only included separate data for the systematic reviews. If this distinction was not reported in a study with a variety of research designs, we requested the data for the systematic reviews from the authors unless it contained fewer than five reviews and, therefore, was too small to be informative.

We excluded studies that investigated financial conflicts of interest related to non-pharmaceutical or non-device industries (e.g. tobacco and food industries). Studies of mixed domains (e.g. pharmaceuticals and nutritional supplements) were included in the review and in our analyses if separate data for the systematic reviews with drug or device industry financial conflicts of interest were obtainable. If this distinction was not reported in the study, we requested the data from the authors unless the number of systematic reviews was too small to be informative (i.e. less than five reviews).

Studies were eligible regardless of the language in which they had been reported.

Types of data

We included data on estimated treatment effect (e.g. Z-scores and P values), frequency of statistically favourable results, and frequency of favourable conclusions (e.g. number of events and odds ratios). For methodological quality, we included both continuous and binary data for industry and non-industry reviews (e.g. overall methodological quality score and number of events in each item of a tool such as the Oxman and Guyatt index) (Oxman 1991).

Types of methods

We included studies that investigated financial conflicts of interest related to drug and device companies. We included studies regardless of type of investigated financial conflicts of interest.

Types of outcome measures

Primary outcomes

We included the following primary outcomes.

1. Results
   a. Estimated treatment effect (e.g. relative risks)
   b. Frequency of statistically favourable results (e.g. occurrence of results statistically in favour of the experimental intervention)
2. Frequency of favourable conclusions (e.g. recommendation of the experimental intervention without reservations)

Secondary outcomes

We included one secondary outcome.

1. Methodological quality of the systematic reviews. This included, for example, assessment using the Oxman and Guyatt index (Oxman 1991) (i.e. how many industry and non-industry reviews fulfilled each item that was assessed for quality)

Search methods for identification of studies

Electronic searches

We searched PubMed, Embase, and the Cochrane Methodology Register (searches performed 30 November 2016) for studies. We searched Web of Science (search performed 17 January 2017) for studies citing any of the included studies. We used the strategy shown in Appendix 1 for PubMed and adapted it for the other databases. These searches were done in advance of our protocol (Hansen 2017) being published in the Cochrane Library.

Searching other resources

Grey literature

We searched proceedings from Peer Review Congresses (American Medical Association 2017) and Cochrane Colloquia (Cochrane Community 2017) for conference abstracts published up to November 2016, bearing in mind the evidence on the high proportion of research studies that are presented at conferences but not published in full (Chapman 2012; Scherer 2018). We also searched PROSPERO (search performed 01 March 2017) for registered systematic reviews and the ProQuest database (search performed 01 March 2017) for dissertations and theses. Finally, we searched Google Scholar (search performed 16 March 2017) for unpublished studies. For all searches, we adapted the search strategy shown in Appendix 1.

Reference lists

We checked the reference lists of the included studies for additional potentially eligible studies (Horsley 2011).

Data collection and analysis

Selection of studies

One review author (CH) screened titles and abstracts of all retrieved records for obvious exclusions. Two review authors (CH and KR) independently assessed potentially eligible studies based on full text. Disagreements were resolved by discussion, and arbitration by another review author was not needed.

Data extraction and management

Two review authors (CH and AL) independently extracted data from the included studies. Any difference in data extraction was resolved by discussion or with arbitration by another review author (AH). We extracted data on basic characteristics and financial conflicts of interest of the included studies. For continuous outcome data, we extracted information on difference in estimated treatment effect between industry and non-industry reviews (reported as pooled Z-scores and P values). For binary outcome data, we extracted the number of industry and non-industry reviews with statistically favourable results and favourable conclusions. When reported, we also extracted risk ratios (RR) or odds ratios (OR). We extracted data for industry and non-industry reviews based on the definitions used by the authors of the included studies, but also for reviews with industry funding only and with author financial conflicts of interest only, based on our definitions. We ensured that all numbers and effect sizes had the same directionality, e.g. a RR >1 indicated that industry reviews more often had favourable conclusions than non-industry reviews. The full plan for data extraction is shown in Appendix 2.

Assessment of risk of bias in included studies

There are no validated criteria for assessing risk of bias in these types of studies, so we developed a set of criteria similar to criteria developed for a previous Cochrane Review by one of the authors of this review (Lundh 2017), which were influenced by items from the AMSTAR tool (Shea 2007). Two review authors (CH and AL) independently assessed risk of bias. Any disagreements were resolved by discussion, with arbitration provided by a third review author (AH) when needed. We categorised each component as high risk of bias, low risk of bias, or unclear. We used the following criteria.

1. Whether there was a risk of bias in the study inclusion process (low risk of bias could, for example, include two or more assessors independently selecting studies)
2. Whether there was a risk of bias in the coding of financial conflicts of interest and outcomes (low risk of bias could, for example, include an extraction done independently by two or more assessors)
3. Whether there was a risk of bias in the comparability of systematic reviews (low risk of bias could, for example, imply industry and non-industry reviews of the same intervention used for the same disease)

Our aim was primarily to differentiate between studies with higher and lower risk of bias. We coded a study as low risk of bias if all three criteria were assessed as low risk of bias. Otherwise, we coded it as high risk of bias.

Dealing with missing data

We contacted authors of the included studies in an attempt to obtain unpublished data, to clarify issues on our 'Risk of bias' assessments, or to receive unpublished protocols (Appendix 3) (Young 2011).

Assessment of heterogeneity

We assessed statistical heterogeneity using the I^2 statistic. We defined substantial heterogeneity as $I^2 > 50\%$.

Data synthesis

Due to heterogeneity between the included studies, we used Mantel-Haenszel random-effects models to estimate RR with 95% confidence intervals (CIs) (RR > 1 indicated that industry reviews more often had statistically favourable results or favourable conclusions). We used a qualitative synthesis for our analysis of estimated treatment effect, and a quantitative synthesis for our analyses of frequency of statistically favourable results, frequency of favourable conclusions, and methodological quality. We also calculated prediction intervals (IntHout 2016; Riley 2011) (Appendix 4).

For our primary analyses, we complied with the definitions of financial conflicts of interest used by the authors of the included studies and analysed industry funding and author financial conflicts of interest together.

For our analysis of methodological quality, we pooled similar items across the different quality assessment tools used in the included studies. For example, we pooled items on appropriateness of search methods in the systematic reviews (Appendix 5). We did not pool items related to reporting quality (e.g. whether the inclusion criteria were reported) or statistical methods (e.g. whether a Bayesian framework was used). We used Mantel-Haenszel random-effects models to estimate RR with 95% CI (RR > 1 indicated that industry reviews had lower methodological quality, i.e. more often did not fulfil the item or did not provide information on the item).

Subgroup analysis and investigation of heterogeneity

We planned to conduct the following pre-specified subgroup analyses for our primary outcomes.

1. High risk of bias studies versus low risk of bias studies
2. Cochrane Reviews versus non-Cochrane systematic reviews
3. Systematic reviews of drug studies versus systematic reviews of device studies
4. Systematic reviews with major financial conflicts of interest versus systematic reviews with moderate financial conflicts of interest versus systematic reviews with minor financial conflicts of interest (where "major", "moderate" and "minor" were as defined by the authors of the included studies)

We planned to conduct the following post-hoc subgroup analyses for our primary outcomes (see Differences between protocol and review).

1. Studies defining favourable conclusions as conclusions in favour of the intervention versus studies defining favourable conclusions as conclusions recommending the intervention without reservations

Sensitivity analysis

We planned to conduct the following pre-specified sensitivity analyses for our primary outcomes.

1. Re-categorising industry reviews into systematic reviews with industry funding only (i.e. excluding systematic reviews with author financial conflicts of interest from the industry group) and comparing with non-industry reviews (i.e. systematic reviews without industry funding or author financial conflicts of interest)
2. Re-categorising industry reviews into systematic reviews with author financial conflicts of interest only (i.e. excluding systematic reviews with industry funding from the industry group) and comparing with non-industry reviews (i.e. systematic reviews without author financial conflicts of interest or industry funding)
3. Excluding included studies with conflicts of interest
4. Re-analysing our data using fixed-effect models

We planned to conduct the following post-hoc sensitivity analyses for our primary outcomes (see Differences between protocol and review).

1. Excluding systematic reviews with unclear or undeclared financial conflicts of interest from the non-industry group
2. Excluding one atypical study (Yank 2007) from our pooled analyses because it compared industry reviews (financial conflicts of interest with a single drug company) with a group of both industry and non-industry reviews (multiple drug companies, no statement, both drug and non-profit companies, and non-profit companies)
3. Restricting our analyses to studies assessed as low risk of bias in the comparability criteria or studies performing adjusted regression analyses
4. Re-categorising industry reviews into reviews with financial conflicts of interest related to any for-profit organisation or to the manufacturer of the investigated intervention in two separate analyses

In addition, we planned to conduct sensitivity analyses for our secondary outcomes (i.e. methodological quality) to address the issue of confounding.

1. Restricting our analyses to studies assessed as low risk of bias in the comparability criteria

Assessment of certainty of the evidence

We graded the certainty of the evidence for each of our primary outcomes as high, moderate, low, or very low. In the standard GRADE approach for studies of treatment effect (Goldet 2013), observational studies are initially graded as low certainty and randomised trials as high certainty (Guyatt 2011; Schünemann 2017). We followed these principles, and initially graded the included observational studies as providing low certainty.

We assessed the following criteria for downgrading: limitations in the study design, indirectness of evidence, inconsistency of results, imprecision of results, and publication bias. We assessed the following criteria for upgrading the certainty: large magnitude of effect, dose-response gradient, and all plausible confounding would decrease the effect (Guyatt 2011).

RESULTS

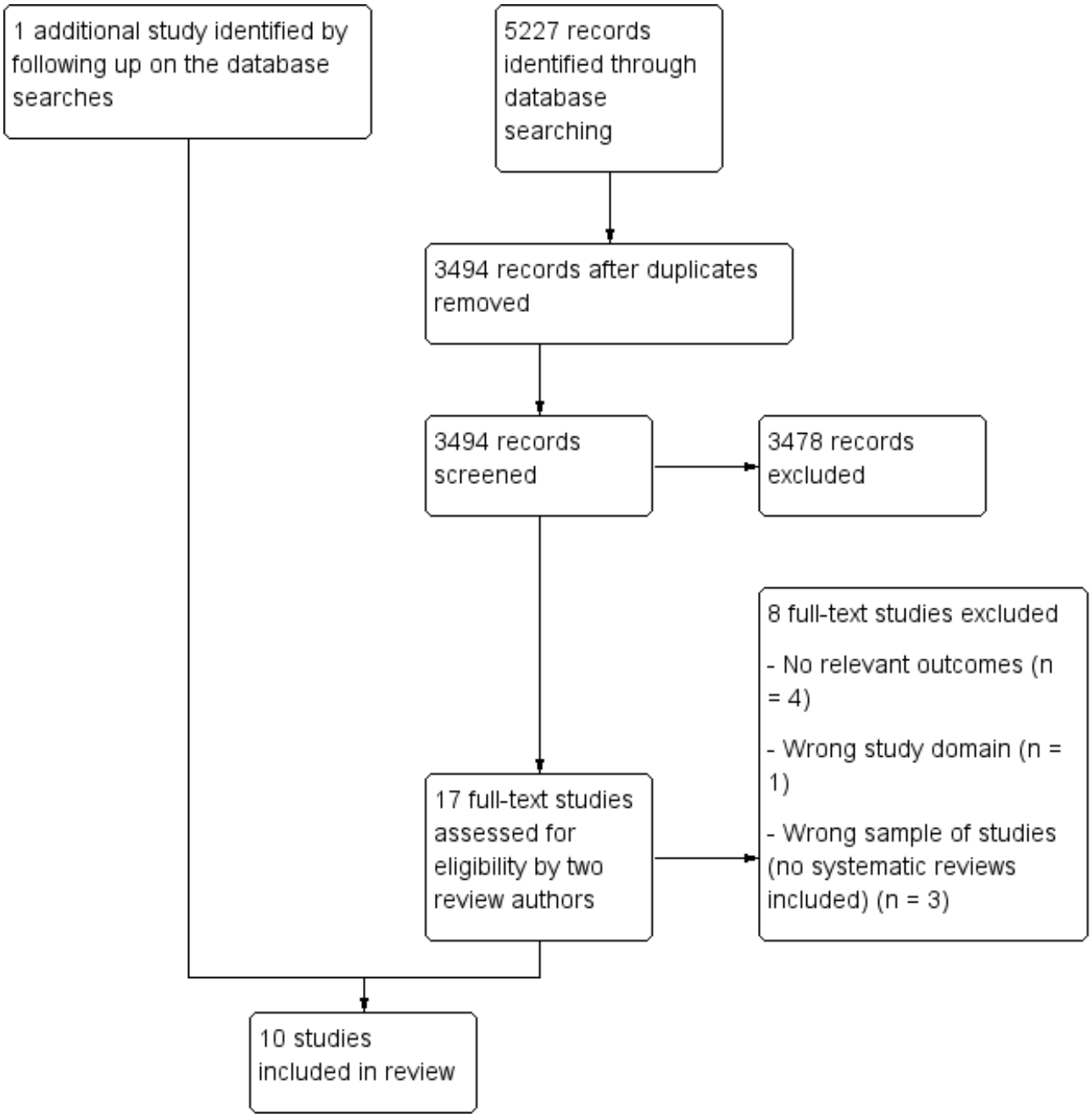
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

See: Figure 1.

Figure 1. Study flow diagram.



We identified a total of 5227 records through our electronic database searches. After removing duplicates, we screened 3494 records. After assessing 17 full-text article, we included 10 studies. Nine of these were identified through the database search and one study was identified through other sources (Figure 1). We did not identify any unpublished studies or protocols for planned studies.

Included studies

See: Characteristics of included studies.

The 10 included studies were published between 2006 and 2017 and investigated a total of 1010 systematic reviews. The median number of included systematic reviews per study was 48 (range 11 to 318). Three studies investigated systematic reviews of randomised trials, six investigated systematic reviews of both randomised trials and non-randomised studies, and one investigated network meta-analyses. One study included systematic reviews of both drug and device interventions, whereas nine studies included solely systematic reviews of drug interventions. Five studies included systematic reviews related to specific drug classes (e.g. antidepressants), one related to a specific disease (skin psoriasis), and four included various drug comparisons. One study investigated estimated treatment effects, one investigated frequency of statistically favourable results, seven investigated frequency of favourable conclusions, and six investigated methodological quality. According to the declarations in their reports, three studies had conflicts of interest in the form of using industry facilities during the study and author employment at pharmaceutical companies (Lane 2013), or receiving honoraria for research, lecturing, and consultancy from pharmaceutical companies (Gomez-Garcia 2017; Hartog 2012).

We received unpublished data from five studies (Gomez-Garcia 2017; Hartog 2012; Jorgensen 2008; Wang 2010; Yank 2007) and obtained published individual review data from three studies (Dunn 2014; Ebrahim 2016; Jorgensen 2006).

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

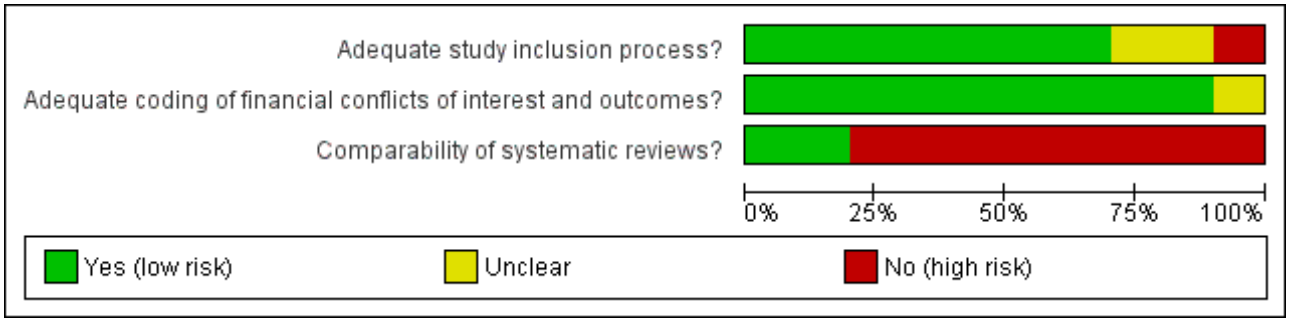
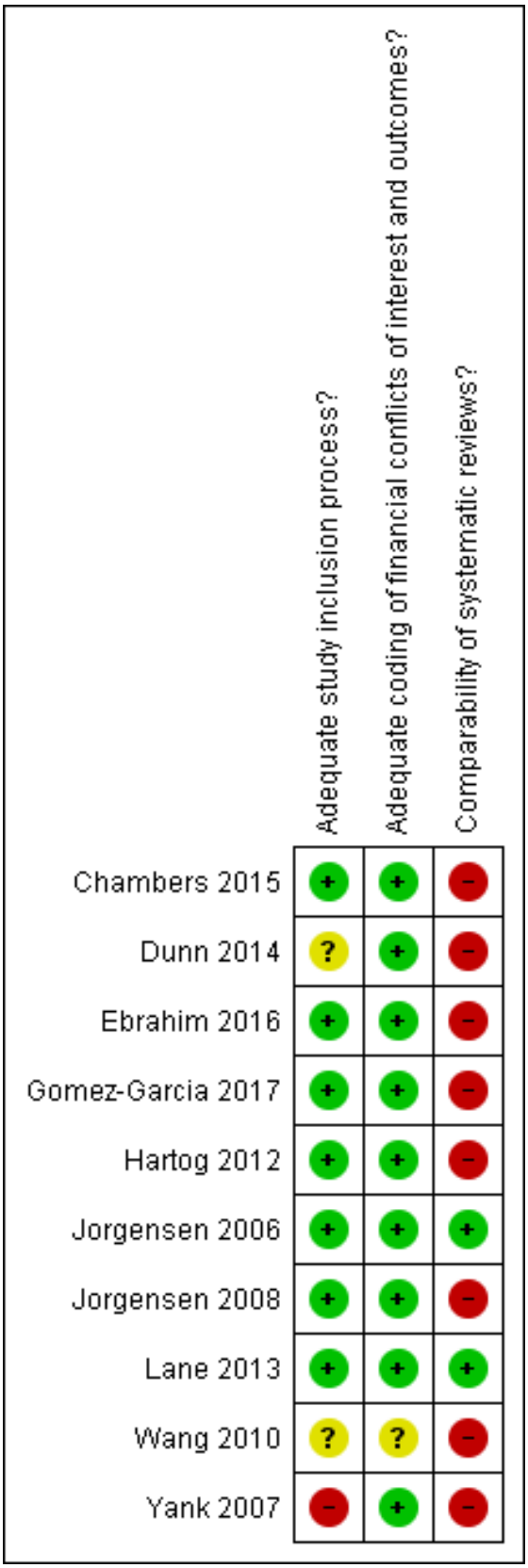


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Overall, we assessed two studies as low risk of bias (Jorgensen 2006; Lane 2013), and the other eight included studies as high risk of bias. The majority of the studies were assessed as low risk of bias in the study inclusion process and extraction methods, whereas they were assessed as high risk of bias in the comparability of investigated systematic reviews.

We were able to obtain one publicly available protocol (through PROSPERO) (Gomez-Garcia 2017) and four unpublished protocols (Ebrahim 2016; Jorgensen 2006; Jorgensen 2008; Lane 2013) for the included studies. We compared outcomes between these protocols and the corresponding publications of the included studies and found that the reported outcomes were prespecified in the protocols in all cases.

Effect of methods

See: **Summary of findings for the main comparison**

Differences in results

Estimated treatment effect

One study comparing seven pairs of Cochrane Reviews and industry-funded reviews of the same drug used for the same disease, investigated the estimated treatment effect. The authors calculated Z-scores for the difference in effect estimates between each pair and found that the estimated treatment effect was not statistically significantly different between systematic reviews with and without financial conflicts of interest (pooled Z-score: 0.46, P value: 0.64) (Jorgensen 2006).

Frequency of statistically favourable results

One study, including 124 meta-analyses, investigated frequency of statistically favourable results (Yank 2007). Based on this study, we found no statistically significant difference in frequency of statistically favourable results (risk ratio (RR): 0.84, 95% confidence interval (CI): 0.62 to 1.14, Analysis 1.1).

Differences in frequency of favourable conclusions

Seven studies, including a total of 411 systematic reviews, investigated the frequency of favourable conclusions. Industry reviews more frequently had favourable conclusions compared with non-industry reviews (RR: 1.98, 95% CI: 1.26 to 3.11, I^2: 69%, Analysis 2.1). The analysis was mainly driven by two studies that contributed 33.2% (Yank 2007) and 30.2% (Ebrahim 2016) of the weight of the analysis.

The prediction interval for the RR including all studies was 0.62 to 6.31 (Appendix 4). Thus, one can expect industry reviews to more often have favourable conclusions compared with non-industry reviews, although this relationship is reversed in some cases.

Differences in methodological quality

Five studies investigated methodological quality using either the Oxman and Guyatt index (Jorgensen 2006; Jorgensen 2008; Yank 2007), the AMSTAR tool (Gomez-Garcia 2017), or a tool the authors developed for their study (Lane 2013). Similar items across these tools could be pooled from four studies only because the fifth (Yank 2007) reported an overall summary score without results of individual items. Additionally, a sixth study measured methodological quality of network meta-analyses using the ISPOR guidance (Chambers 2015), but we analysed this study separately because these criteria for methodological quality differed from the quality criteria related to conventional systematic reviews.

In total, we analysed 11 different dimensions of methodological quality. The overall trend showed that all point estimates were above 1, and the methodological quality tended to be lowest among industry reviews (i.e. they tended to fulfil the dimensions of the quality less often) (Analysis 3.1 to Analysis 3.11). For three dimensions, the difference in methodological quality was statistically significant (Analysis 3.1; Analysis 3.3; Analysis 3.8).

In two of these 11 analyses (Analysis 3.2; Analysis 3.3), we found substantial statistical heterogeneity ($I^2$of 60% and 57%, respectively). One study was somewhat different from the other studies in these analyses, because the authors had used the AMSTAR tool to assess methodological quality and included both drug and device systematic reviews (Gomez-Garcia 2017).

The study on methodological quality in the network meta-analyses had similar results (Chambers 2015, Appendix 5).

Subgroup analyses

Due to lack of data, it was only meaningful to carry out three of five planned subgroup analyses (Appendix 6).

For frequency of favourable conclusions, we found no statistically significant difference between studies with high risk of bias compared with those with low risk of bias (RR: 1.81, 95% CI: 1.21 to 2.69, based on six studies of 397 systematic reviews; versus RR: 15.00, 95% CI: 1.02 to 220.92, based on one study of 14 systematic reviews, test for interaction P value: 0.13; Analysis 4.1).

Our subgroup analysis comparing frequency of favourable conclusions between Cochrane Reviews and non-Cochrane systematic reviews found no statistically significant difference between non-Cochrane systematic reviews (RR: 1.32, 95% CI: 1.15 to 1.52, based on six studies of 351 non-Cochrane systematic reviews) and Cochrane Reviews (RR: 2.17, 95% CI: 0.63 to 7.44, based on three studies of 38 Cochrane Reviews, test for interaction P value: 0.43, Analysis 4.2). Seven of the observational studies we included in this methodology review provided data from 411 systematic reviews (for our primary analysis of frequency of favourable conclusions). Out of these 411 systematic reviews, 53 were Cochrane Reviews (of which 38 were included in our subgroup analysis comparing Cochrane Reviews and non-Cochrane Reviews). The authors of the included observational studies classified 15 of the 53 Cochrane Reviews as having authors with financial conflicts of interest or as having received industry funding. One of the 15 Cochrane Reviews was partly funded by the industry (published in 2004), and two had lead authors with financial conflicts of interest (published in 2009 and 2011). In ten of the Cochrane Reviews, less than half of the non-lead authors had financial conflicts of interest (published between 2009 and 2013), and in the remaining two Cochrane Reviews, the reason for the classification was unclear.

For differences in the definition of favourable conclusions, we found no statistically significant difference between conclusions in favour of the interventions (RR: 1.94, 95% CI: 0.93 to 4.07, based on four studies of 173 systematic reviews) and conclusions recommending the intervention without reservations (RR: 2.11,

95% CI: 1.18 to 3.79, based on three studies of 238 systematic reviews) (test for interaction P value: 0.86; Analysis 4.3).

Sensitivity analyses

We were able to carry out all of the four pre-planned sensitivity analyses and the four post hoc sensitivity analyses for at least one of our primary outcomes (Appendix 7). In general, all sensitivity analyses showed similar findings for frequency of statistically favourable results and frequency of favourable conclusion as our primary analyses.

The statistical heterogeneity in our primary analysis of frequency of favourable conclusions was substantial (Analysis 2.1), and the RR spanned from 1.25 to 15.00. One of the studies (Yank 2007) compared systematic reviews with financial conflicts of interest to a single drug company with a group of industry and non-industry systematic reviews. Excluding this atypical study, the statistical heterogeneity decreased substantially (I^2 reduced from 69% to 0%), but the effect estimate remained approximately the same (RR: 2.03, 95% CI: 1.56 to 2.64, Analysis 5.9).

We also carried out sensitivity analyses for 10 dimensions of methodological quality. These analyses showed similar findings as our primary analyses.

Assessment of certainty of the evidence

See Summary of findings for the main comparison.

The certainty of the evidence on estimated treatment effect was assessed as low. Only one study (Jorgensen 2006) investigated estimated treatment effect based on 14 systematic reviews (certainty downgraded for imprecision). The study may therefore be underpowered, and we find it likely that further research will have an impact on the estimate and our confidence in the estimate.

The certainty of the evidence on frequency of statistically favourable results was assessed as very low. Only one study (Yank 2007) investigated frequency of statistically favourable results, and this study was assessed as high risk of bias (certainty downgraded for limitation in design) and the confidence interval was quite wide (95% CI: 0.62 to 1.14, Analysis 1.1) (certainty downgraded for imprecision).

The certainty of the evidence on frequency of favourable conclusions was assessed as moderate. In our assessment, we did not up- or downgrade the certainty. The effect estimate was fairly large and based on seven studies (RR: 1.98, Analysis 2.1). Among the one study assessed as low risk of bias, the effect estimate was substantially higher, though with a wide confidence interval (RR: 15.00, 95% CI: 1.02 to 220.92, Analysis 4.1).

DISCUSSION

Summary of main results

We included 10 studies that investigated a total of 1010 systematic reviews. All studies included systematic reviews of drug interventions (995 systematic reviews), and only one study also included systematic reviews of device interventions (15 systematic reviews). We found no statistically significant difference in results (estimated treatment effect and frequency of statistically favourable results) between systematic reviews with and without financial conflicts of interest. Systematic reviews with financial conflicts of interest more frequently had favourable conclusions compared with systematic reviews without. Systematic reviews with financial conflicts of interest tended to have lower methodological quality compared with systematic reviews without these financial conflicts of interest. Our findings were robust in a number of sensitivity analyses, and analyses based on matched studies or adjusted regression analyses (which had thereby reduced the risk of confounding) had similar results. Only two of the 10 included studies were assessed as low risk of bias.

Quality of the evidence

The majority of the included studies were assessed as having high risk of bias, because the investigated systematic reviews differed in aspects other than financial conflicts of interest (e.g. investigated different interventions used for different diseases). Thus, the included studies had a risk of confounding. Two of the included studies used a matched design and thereby reduced the risk of confounding markedly, but did not eliminate it (Jorgensen 2006; Lane 2013). We also noted a less pronounced reduction of risk of confounding in a third study adjusting for confounders (Yank 2007). Our analyses of results (estimated treatment effect and statistically favourable results) had some risk of confounding and were imprecise, and our analysis of conclusions and methodological quality had some risk of confounding.

We assessed the certainty of the evidence using the GRADE approach. All included studies were of observational design, and certainties of evidence ranged from very low to low. Despite being possible in theory, randomisation is not feasible in these types of studies, and the assessment may be too conservative and should be considered tentative.

Potential biases in the review process

Our review has several strengths. We obtained unpublished data from five studies, which enabled us to conduct subgroup and sensitivity analyses. We found no unpublished studies despite doing a comprehensive search for conference abstracts and unpublished literature. We addressed selective outcome reporting by comparing the published studies with their corresponding protocols for five studies (Ebrahim 2016; Gomez-Garcia 2017; Jorgensen 2006; Jorgensen 2008; Lane 2013) and found no signs of selective outcome reporting.

We only found one study investigating estimated treatment effect. Investigating effect sizes involves complicated statistics in measuring differences between effect estimates expressed in varying units. Surprisingly, we only found one study investigating statistically favourable results, which seems contradictory to the fact that multiple studies investigated favourable conclusions. However, based on the five protocols we had access to, we have no reason to believe that this is due to selective reporting.

Nevertheless, our review has some limitations. First, our ability to conduct subgroup and sensitivity analyses was limited by inclusion of only 10 studies. Second, we only identified one study investigating estimated treatment effect and only one study investigating frequency of statistically favourable results. Third, for the association between financial conflicts of interest and frequency of favourable conclusions we found substantial statistical heterogeneity (I^2: 69%). One possible reason for this was

the inclusion of one study that compared systematic reviews with financial conflicts of interest to one drug company to a comparison group comprised of both industry and non-industry reviews (Yank 2007). When we excluded this study from the analysis, the statistical heterogeneity decreased to an I^2 of 0%.

Agreements and disagreements with other studies or reviews

A Cochrane Methodology Review by Lundh and colleagues investigated the impact of industry sponsorship on outcomes in individual research studies, mainly clinical trials. It found that industry sponsored studies more often had statistically favourable results (RR: 1.27, 95% CI: 1.17 to 1.37) and favourable conclusions (RR: 1.34, 95% CI: 1.19 to 1.51) compared with non-industry sponsored studies (Lundh 2017). Contrary to that study, we did not find an association between financial conflicts of interest and statistically favourable results in systematic reviews. This may be due, at least in part, to systematic reviews on the same topic often including the same randomised trials and thereby obtaining similar results in their meta-analyses. However, our findings on estimated treatment effect and statistically favourable results are based on only one study each and are fairly imprecise with wide confidence intervals. Furthermore, the authors of the other Cochrane Methodology Review found no overall difference in risk of bias between industry and non-industry funded trials (Lundh 2017). This is in contrast to the tendency that industry reviews had lower methodological quality than non-industry reviews that we found. One potential explanation for the higher quality of non-industry reviews could be that such reviews may more often be authored by methodologists (Gotzsche 2012).

The association between financial conflicts of interest and conclusions has also been investigated in relation to narrative reviews, editorials, and letters to the editor for drug interventions in a number of studies. Authors with financial conflicts of interest seem to recommend a drug more often compared with authors without such conflicts of interest (Stelfox 1998; Wang 2010), but we are not aware of any systematic review of this topic.

Finally, financial conflicts of interest have also been investigated in relation to non-drug and non-device industries. Chartres and colleagues undertook a systematic review of the association between financial conflicts of interest in relation to the food industry and study outcomes. They found a tendency that primary research studies and reviews with financial conflicts of interest more often had favourable conclusions compared with studies without (RR: 1.31, 95% CI: 0.99 to 1.72) (Chartres 2016). Similarly, Barnes and colleagues found that authors of review articles with financial conflicts of interest related to the tobacco industry more often concluded that passive smoking is not harmful compared with reviews without such conflicts of interest (odds ratio (OR): 88.4; 95% CI: 16.4 to 476.5) (Barnes 1998).

Meaning of our review

The association between financial conflicts of interest and conclusions of systematic reviews may be explained by underlying differences in results (i.e. estimated treatment effect and frequency of statistically significant results). However, we found no statistically significant difference in review results between industry and non-industry reviews. Even though our analyses of results had some risk of confounding and were imprecise, this could suggest that results are interpreted differently in industry and non-industry reviews, which might be associated with the lower methodological quality of industry reviews. For example, industry reviews less often interpret results in the light of risk of bias of included studies. Another reason could be a more frequent use of spin in industry review conclusions (Yavchitz 2016). Nonetheless, our finding on the association between financial conflicts of interest and review results remains uncertain, because it is based on only one study. Second, any association may be affected by confounding (e.g. if industry and non-industry reviews investigate different types of interventions used for different diseases). However, it is unlikely that the differences in frequency of favourable conclusions is an issue of confounding, because the association was also found in one study that used a matched design (Jorgensen 2006).

AUTHORS' CONCLUSIONS

Implication for methodological research

We found only single studies on the association between financial conflicts of interest and estimated treatment effect and frequency of statistically favourable results, respectively, and our findings for these outcomes are imprecise. Future research could focus on establishing the degree to which financial conflicts of interest are associated with the results of systematic reviews. Furthermore, none of the included studies investigated the association between financial conflicts of interest and results about the potential harms of interventions, and future studies could investigate this.

According to our 'Risk of bias' assessment, only two studies investigated comparable samples of systematic reviews. Future research should focus on comparing industry and non-industry systematic reviews that are similar in important aspects other than financial conflicts of interest. Furthermore, the included studies defined financial conflict of interest differently and it remains unclear whether some types of financial conflicts of interest have a greater impact. Future studies should investigate various types of financial conflicts of interest, including non-financial conflicts of interest.

None of the included studies provided an explanatory mechanism for the association between financial conflicts of interest and conclusions of systematic reviews. Future empirical studies should try to address such explanatory mechanisms, for example by addressing the use of spin in systematic review conclusions.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Chambers 2015

Methods	To assess the methodological quality of published network meta-analyses. All published network meta-analyses in the Ovid-MEDLINE database up to 30 July 2014.
Data	318 network-meta-analyses of pharmaceuticals.
Comparisons	Network meta-analyses with financial conflicts of interest (defined as support of the study) and network meta-analyses without financial conflicts of interest.
Outcomes	Methodological quality (assessed by criteria from the quote: “checklist of good research practices” in the ISPOR guidance for interpreting and conducting indirect-treatment-comparison and network-meta-analysis studies).
Funding source	No funding was received for the study.
Declaration of conflicts of interest	The authors declared no conflicts of interest related to any for-profit organisation.
Notes	
Risk of bias	

Chambers 2015 *(Continued)*

Item	Authors' judgement	Description
Adequate study inclusion process?	Yes	Two review authors assessed included studies
Adequate coding of financial conflicts of interest and outcomes?	Yes	Two review authors extracted data
Comparability of systematic reviews?	No	Compared systematic reviews of different interventions and different diseases

Dunn 2014

Methods	To determine whether there is an association between financial conflicts of interest and the favourable presentation of evidence in systematic reviews. Systematic reviews identified through PubMed, PubMed In Process, Embase and the Cochrane Database of Systematic Reviews published between 1 January 2005 and 26 May 2014.
Data	26 systematic reviews on the use of neuraminidase inhibitors in the prophylaxis or treatment of influenza.
Comparisons	Systematic reviews with financial conflicts of interest (defined as employment, funding of grants, and the funding of medical writers) and systematic reviews without financial conflicts of interest.
Outcomes	Conclusions (defined as whether the systematic review was favourable or unfavourable towards the use of neuraminidase inhibitors).
Funding source	This study was funded by the Australian National Health and Medical Research Council and no additional funding related to any for-profit organisation was declared.
Declaration of conflicts of interest	The authors declared no conflicts of interest related to any for-profit organisation.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate study inclusion process?	Unclear	Not described
Adequate coding of financial conflicts of interest and outcomes?	Yes	One review author extracted data on financial conflicts of interest and coded each systematic review. A second review author checked all of the identified financial conflicts of interest. Two review authors assessed conclusions
Comparability of systematic reviews?	No	Compared systematic reviews of the same drug class used for the same disease. However, large overlap in individual authors (e.g. single person is author of seven included systematic reviews), which may confound the association.

Ebrahim 2016

Methods	To identify the impact of industry involvement in the publication and interpretation of meta-analyses of antidepressant trials in depression. Meta-analyses published from 1 January 2007 to 5 March 2014.
Data	185 meta-analyses on antidepressants for depression.
Comparisons	Meta-analyses with industry funding (defined as industry funding for a meta-analysis that involves one or more of the drugs that it manufactures) and meta-analyses without industry funding. Meta-analyses with author financial conflicts of interest (defined as all the situations where one or more authors are either company employees of the industry or received any support from the industry for any of their work) and meta-analyses without author financial conflicts of interest.
Outcomes	Conclusions (defined as whether the meta-analysis included any negative statements expressing caveats about the effectiveness or safety/toxicity of the assessed antidepressant).
Funding source	No funding was received for the study.
Declaration of conflicts of interest	The authors declared no conflicts of interest related to any for-profit organisation.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate study inclusion process?	Yes	Four review authors assessed included studies
Adequate coding of financial conflicts of interest and outcomes?	Yes	Two review authors extracted data
Comparability of systematic reviews?	No	Compared meta-analyses of the same class of drugs used for the same disease. However, compared meta-analyses including both placebo and active control and meta-analyses based on a systematic literature review and meta-analyses without a systematic literature review

Gomez-Garcia 2017

Methods	To assess the methodological quality of systematic reviews published on psoriasis. Systematic reviews and meta-analyses published up to 4 July 2016.
Data	121 systematic reviews on drugs or devices used for skin psoriasis.
Comparisons	Systematic reviews with industry funding (defined as pharmaceutical company funding) and systematic reviews without industry funding. Systematic reviews with author conflicts of interest and systematic reviews without author financial conflicts of interest.
Outcomes	Methodological quality (assessed by the 11-item AMSTAR criteria).
Funding source	The study was partly funded by grants from the ISCIII-Subdireccion General de Evaluacion and European Regional Development Fund (ERDF) and Plan Propio de movilidad para investigadores Del Insti-

Gomez-Garcia 2017 *(Continued)*

	tuto Maimonides de Investigacion Biomedica De Cordoba (IMIBIC) and no additional funding related to any for-profit organisation was declared.
Declaration of conflicts of interest	FG-G (lead author) has received honoraria from Pfizer, AbbVie, Janssen-Cilag, and Novartis. JR (second author) and AVG-N (ninth author) have received honoraria and financial benefits from Pfizer, Janssen-Cilag, Novartis, and AbbVie.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate study inclusion process?	Yes	Two review authors assessed included studies
Adequate coding of financial conflicts of interest and outcomes?	Yes	Two review authors extracted data and assessed methodological quality
Comparability of systematic reviews?	No	Compared systematic reviews of different interventions

Hartog 2012

Methods	To examine recommendations and methodological quality of meta-analyses published on hydroxyethyl starch fluid. Meta-analyses identified in MEDLINE via Ovid and PubMed, Web of Science, Embase, and the Cochrane Library published up to June 2010.
Data	12 meta-analyses on widespread clinical use of hydroxyethyl starch fluid.
Comparisons	Meta-analyses with financial conflicts of interest (defined as financial relationships with or support from a manufacturer of commercially available intravenous fluids) and meta-analyses without financial conflicts of interest.
Outcomes	Conclusions (defined as whether the meta-analyses recommend hydroxyethyl starch over other fluids).
Funding source	The study was funded by the Intramural Research Program of the U.S. National Institutes of Health and no additional funding related to any for-profit organisation was declared.
Declaration of conflicts of interest	KR (last author) has received research grants, speaker's fees, and consultancy fees from B. Braun, Melsungen, Germany.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate study inclusion process?	Yes	Two review authors assessed included studies
Adequate coding of financial conflicts of interest and outcomes?	Yes	Two review authors coded the conclusions of each meta-analysis

Hartog 2012 *(Continued)*

Comparability of systematic reviews?	No	Compared meta-analyses of hydroxyethyl starch for different indications and different publication periods

Jorgensen 2006

Methods	To compare the methodological quality and conclusions in Cochrane Reviews with those in industry-supported meta-analyses and other meta-analyses of the same drugs. Pairs of a Cochrane Review and a similar review published in another journal comparing the same drug used for the same disease published within two years of each other.
Data	24 pairs of a Cochrane Review and another review of drug comparisons published between 1998 and 2003.
Comparisons	Systematic reviews with industry funding (defined as support by the pharmaceutical industry as provision of grants, authorship, or other major assistance such as help with the statistical analysis) and Cochrane Reviews without industry funding.
Outcomes	Estimated treatment effect (assessed by pooled comparative Z-scores). Conclusions (defined as whether the experimental intervention was recommended without reservations, not recommended, or recommended only with reservations). Methodological quality (assessed by the 9-item Oxman & Guyatt index).
Funding source	No funding was received for the study.
Declaration of conflicts of interest	The authors declared no conflicts of interest related to any for-profit organisation.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate study inclusion process?	Yes	Two review authors assessed included studies
Adequate coding of financial conflicts of interest and outcomes?	Yes	Two review authors extracted data
Comparability of systematic reviews?	Yes	Compared pairs of Cochrane Reviews and other reviews of the same drug, used for the same disease, and published within two years of each other

Jorgensen 2008

Methods	To investigate whether meta-analyses supported by the pharmaceutical industry are of poorer methodological quality and have conclusions favouring the experimental drug, compared to meta-analyses with non-profit or no support. Meta-analyses published in 2004.
Data	39 meta-analyses comparing different drugs or classes of drugs.

Jorgensen 2008 *(Continued)*

Comparisons	Systematic reviews with industry funding (defined as authorship, provision of grants to authors of the meta-analysis, or other major assistance such as help with the statistical analysis) and systematic reviews without industry funding.
Outcomes	Conclusions (defined as whether the experimental intervention was recommended without reservations, not recommended, or recommended with reservations). Methodological quality (assessed by the 9-item Oxman and Guyatt index).
Funding source	No funding was received for the study.
Declaration of conflicts of interest	The authors declared no conflicts of interest related to any for-profit organisation.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate study inclusion process?	Yes	One review author assessed eligibility of all potentially eligible meta-analyses. A second review author assessed all included meta-analyses and 10% of excluded meta-analyses for eligibility
Adequate coding of financial conflicts of interest and outcomes?	Yes	Two review authors extracted data
Comparability of systematic reviews?	No	Compared meta-analyses of different interventions and diseases

Lane 2013

Methods	To compare the quality of pharmaceutical industry-supported meta-analyses with academic meta-analyses. Pairs of industry-supported meta-analyses and non-industry-supported meta-analyses matched on the basis of medical subject heading and publication dates. Meta-analyses published in 2002 to 2004 and 2008 to 2009.
Data	63 pairs of industry-supported meta-analyses and non-industry-supported meta-analyses of randomised trials assessing the efficacy or safety of any pharmaceutical intervention in humans.
Comparisons	Meta-analyses with industry funding (defined as first or corresponding author having primary affiliation to a pharmaceutical company, two or more non-lead authors having primary affiliation to the same pharmaceutical company, or any author having primary affiliation to the pharmaceutical company who manufactures the product under investigation) and meta-analyses without industry funding.
Outcomes	Methodological quality (assessed by a 43-item assessment tool that provides a qualitative assessment of statistical appropriateness and adequacy of interpretation developed and piloted by the authors).
Funding source	No funding was received for the study, but teleconference facilities of a pharmaceutical company were used for meetings regarding the study.
Declaration of conflicts of interest	PWL (first author) is an employee at GlaxoSmithKline. NFB (fifth author) is an employee at Amgen Ltd. JCC (sixth author) and SHa (seventh author) are employees at Pfizer. SHo (eighth author) is an employee at AstraZeneca. PM (tenth author) is an employee at Vifor Pharma.

Lane 2013 *(Continued)*

Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate study inclusion process?	Yes	Two review authors assessed included studies
Adequate coding of financial conflicts of interest and outcomes?	Yes	Multiple review authors extracted data
Comparability of systematic reviews?	Yes	Compared pairs of systematic reviews with similar publication date and medical subject heading

Wang 2010

Methods	To explore a possible link between authors' financial conflicts of interest and their position on the association of rosiglitazone with increased risk of myocardial infarction in patients with diabetes. Systematic reviews published between 2007 and 2009.
Data	11 systematic reviews commenting on rosiglitazone and the risk of myocardial infarction.
Comparisons	Systematic reviews with financial conflicts of interest (defined as pharmaceutical company funding of the article in question, author employment by a pharmaceutical company, pharmaceutical company funding of research other than that covered in the article in question, or the author acting as consultant, advisory board member, speaker, lecturer, or receives travel or honoraria from a pharmaceutical company, or owns stock) and systematic reviews without financial conflicts of interest.
Outcomes	Conclusions (defined as whether the authors present a favourable view of the safety of rosiglitazone (rosiglitazone does not increase the risk of myocardial infarction), a neutral view, or an unfavourable view).
Funding source	No funding was received for the study.
Declaration of conflicts of interest	The authors declared no conflicts of interest related to any for-profit organisation.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate study inclusion process?	Unclear	Not described
Adequate coding of financial conflicts of interest and outcomes?	Unclear	Not described
Comparability of systematic reviews?	No	Compared systematic reviews of different outcomes, study designs, and inclusion criteria (based on assessment of abstracts of included systematic reviews)

Yank 2007

Methods	To determine whether financial ties to one drug company are associated with favourable results or conclusions in meta-analyses on antihypertensive drugs. Meta-analyses published up to December 2004.
Data	124 meta-analyses evaluating the effects of antihypertensive drugs on clinical outcomes in adults.
Comparisons	Meta-analyses with financial conflicts of interest (defined as financial ties to one drug company) and meta-analyses without financial conflicts of interest (defined as financial ties to multiple drug companies, no statement, financial ties to both drug and non-profit companies, and financial ties to non-profit companies).
Outcomes	Statistically significant results (defined as whether the results were statistically favourable towards the study drug or statistically unfavourable towards the study drug). Conclusions (defined as whether the conclusions were favourable towards the study drug or unfavourable towards the study drug). Methodological quality (assessed by the 9-item Oxman and Guyatt index).
Funding source	The study was funded partly by the Eugene Garfield Foundation and no additional funding related to any for-profit organisation was declared.
Declaration of conflicts of interest	The authors declared no conflicts of interest related to any for-profit organisation.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate study inclusion process?	No	One review author assessed included studies
Adequate coding of financial conflicts of interest and outcomes?	Yes	One review author extracted data and coded all 124 meta-analyses. A second review author coded 24 meta-analyses. The degree of agreement between the two review authors was high
Comparability of systematic reviews?	No	Compared meta-analyses of the same intervention used for the same disease. However, compared meta-analyses including both placebo and active control. Performed adjusted analyses, but did not adjust for intervention type

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahmer 2006	No relevant outcomes
Kopelman 2013	No relevant outcomes
Lesser 2007	Wrong study domain (not related to drug or device companies)
Radecki 2011	Wrong sample of studies (no systematic reviews included)

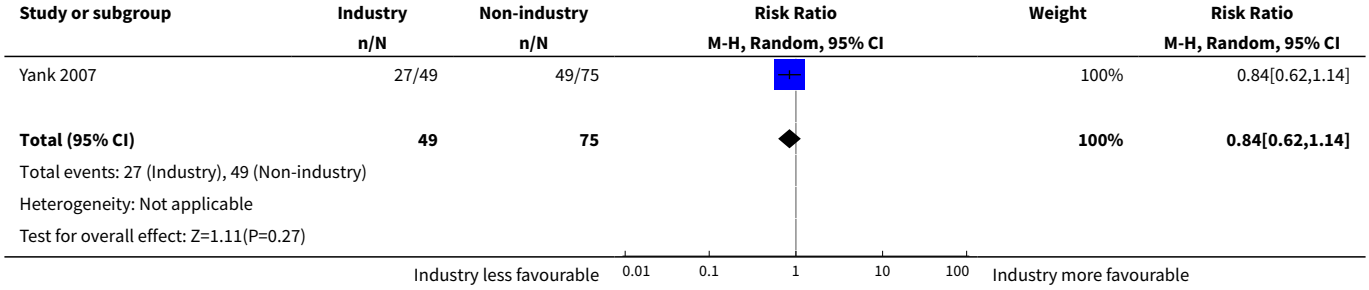
Study	Reason for exclusion
Schuit 2016	No relevant outcomes
Sismondo 2008	Wrong sample of studies (no systematic reviews included)
Sismondo 2008a	Wrong sample of studies (no systematic reviews included)
Warner 2003	No relevant outcomes

DATA AND ANALYSES

Comparison 1. Frequency of statistically favourable results: systematic reviews with financial conflicts of interest versus systematic reviews without

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of statistically favourable results	1	124	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.62, 1.14]

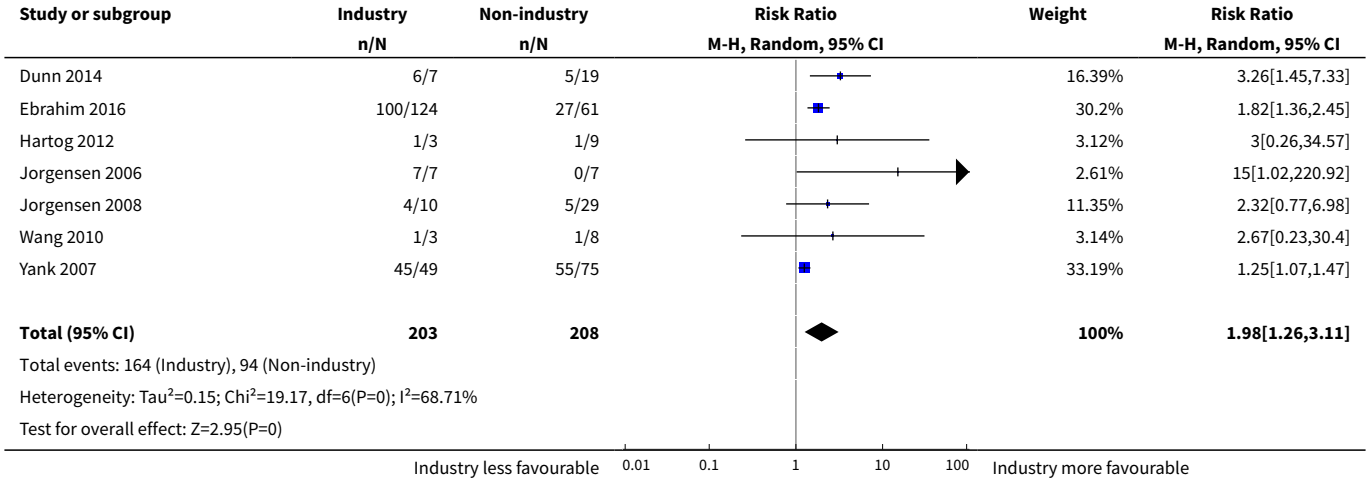
Analysis 1.1. Comparison 1 Frequency of statistically favourable results: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 1 Frequency of statistically favourable results.



Comparison 2. Frequency of favourable conclusions: systematic reviews with financial conflicts of interest versus systematic reviews without

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of favourable conclusions	7	411	Risk Ratio (M-H, Random, 95% CI)	1.98 [1.26, 3.11]

Analysis 2.1. Comparison 2 Frequency of favourable conclusions: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 1 Frequency of favourable conclusions.

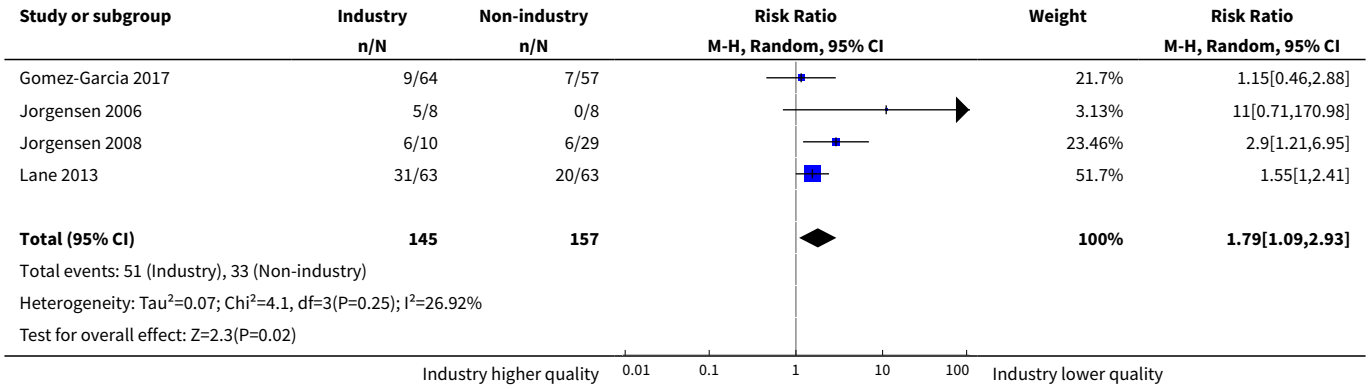


Comparison 3. Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without

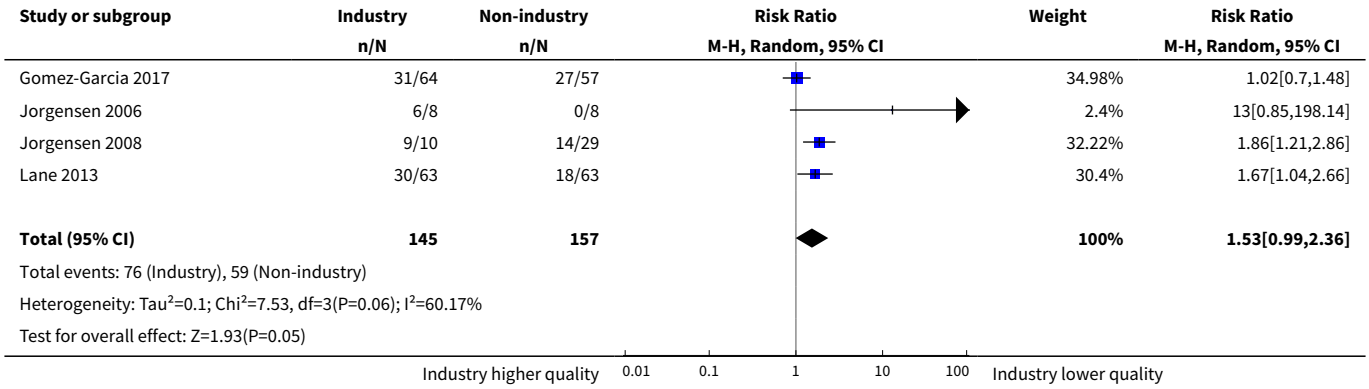
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Low methodological quality related to search methods	4	302	Risk Ratio (M-H, Random, 95% CI)	1.79 [1.09, 2.93]
2 Low methodological quality related to selecting studies	4	302	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.99, 2.36]
3 Low methodological quality related to assessing risk of bias	4	302	Risk Ratio (M-H, Random, 95% CI)	1.83 [1.22, 2.74]
4 Low methodological quality related to addressing missing outcome data	1	126	Risk Ratio (M-H, Random, 95% CI)	1.1 [0.94, 1.29]
5 Low methodological quality related to addressing publication bias	1	121	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.85, 1.18]
6 Low methodological quality related to analysing individual studies appropriately and without avoidable bias	1	126	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.97, 1.77]
7 Low methodological quality related to combining findings of relevant studies using appropriate meta-analysis methods	4	302	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.78, 1.45]
8 Low methodological quality related to interpretation of results in light of risk of bias	2	247	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.13, 1.79]
9 Low methodological quality related to interpretation of results in light of reporting bias	1	126	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.82, 1.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Low methodological quality related to interpretation of results in light of multiplicity	1	126	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.82, 1.97]
11 Low methodological quality related to having conclusions supported by the data	3	181	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.87, 1.77]

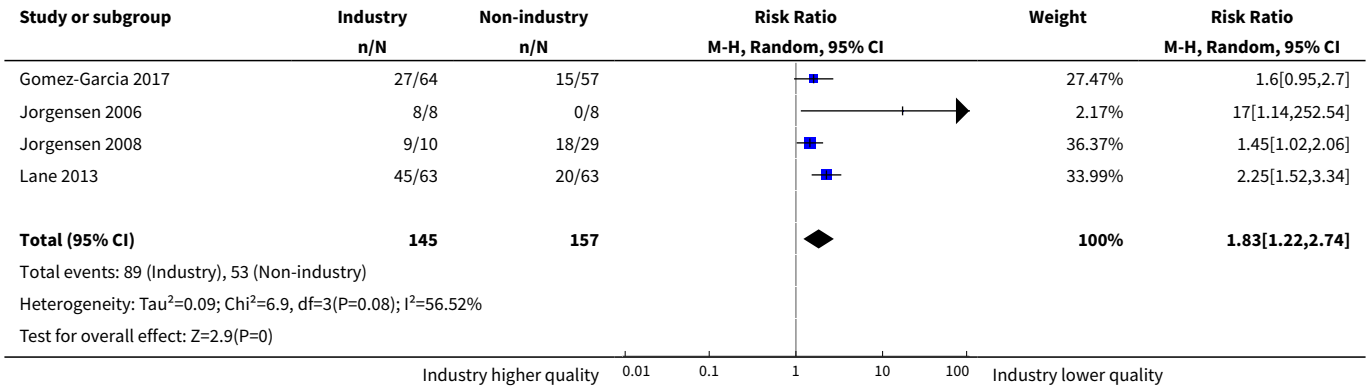
Analysis 3.1. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 1 Low methodological quality related to search methods.



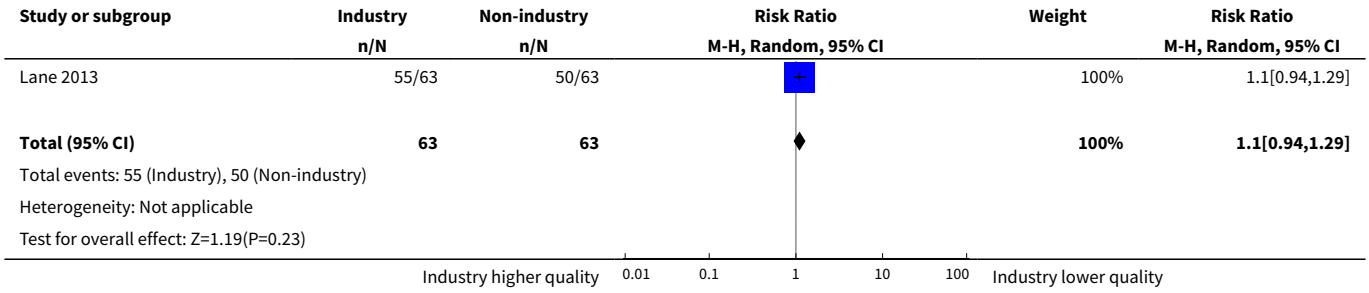
Analysis 3.2. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 2 Low methodological quality related to selecting studies.



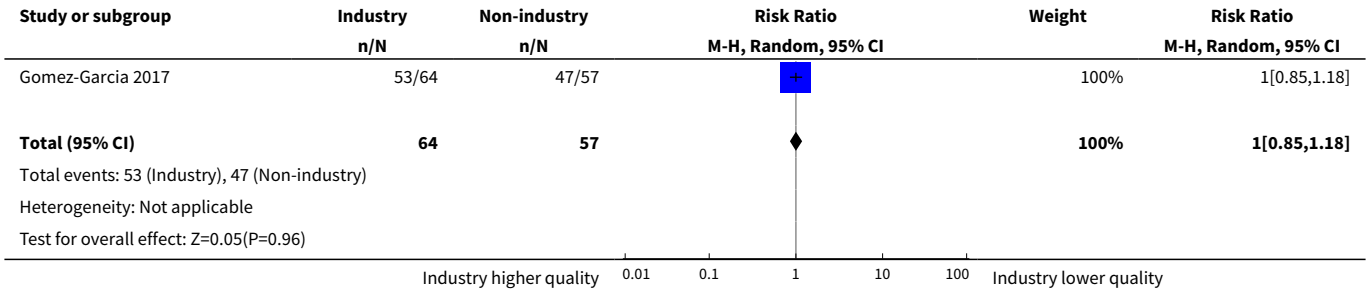
Analysis 3.3. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 3 Low methodological quality related to assessing risk of bias.



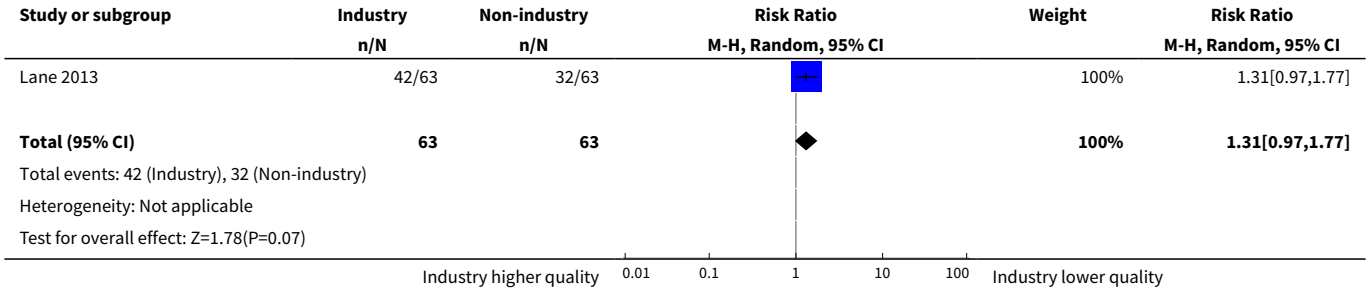
Analysis 3.4. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 4 Low methodological quality related to addressing missing outcome data.



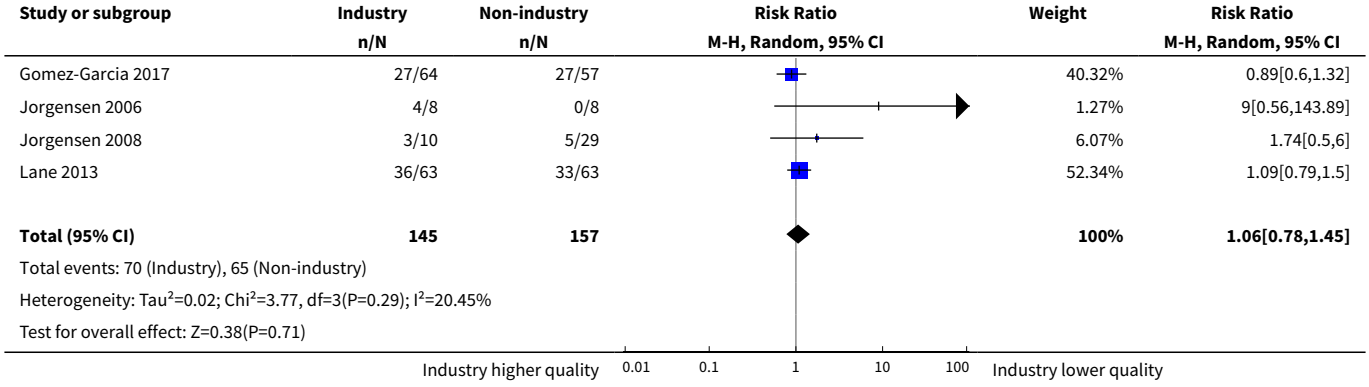
Analysis 3.5. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 5 Low methodological quality related to addressing publication bias.



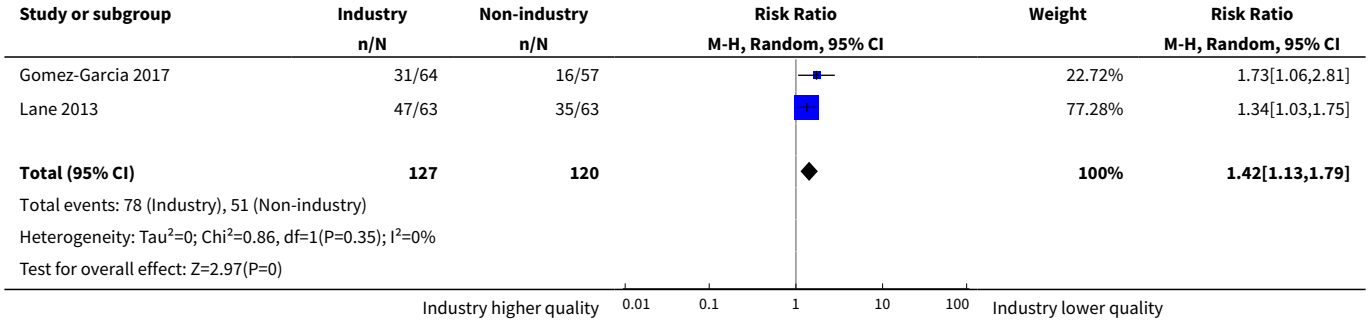
Analysis 3.6. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 6 Low methodological quality related to analysing individual studies appropriately and without avoidable bias.



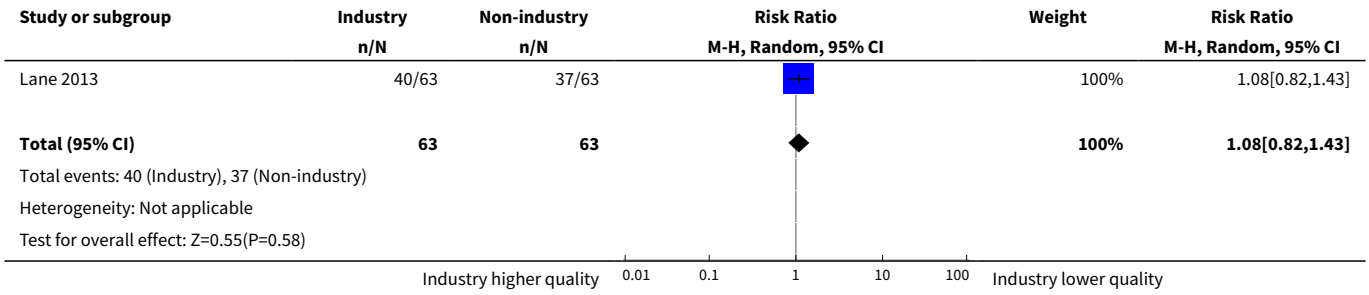
Analysis 3.7. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 7 Low methodological quality related to combining findings of relevant studies using appropriate meta-analysis methods.



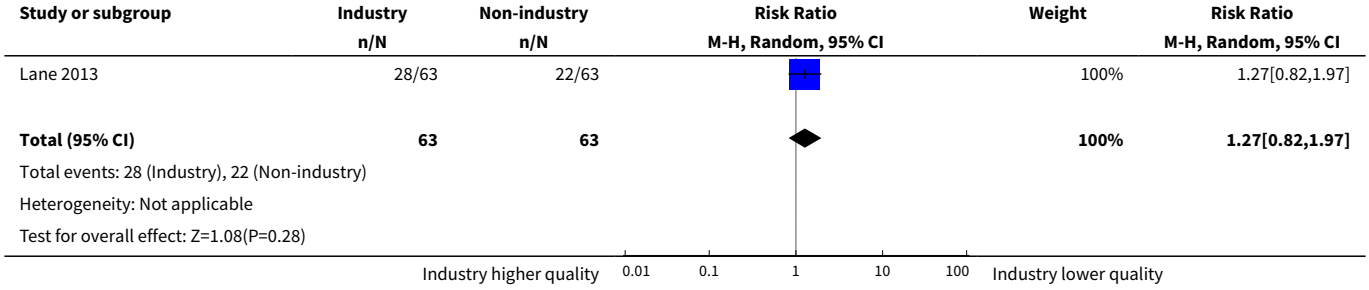
Analysis 3.8. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 8 Low methodological quality related to interpretation of results in light of risk of bias.



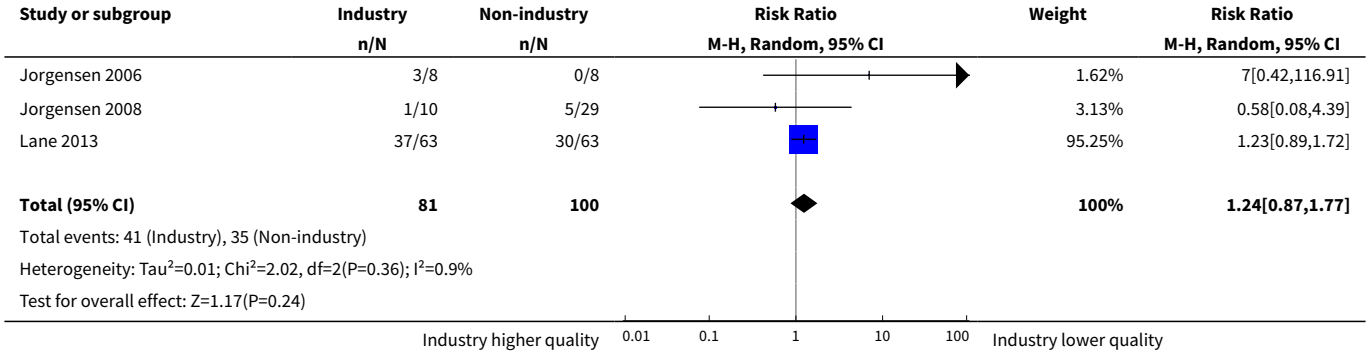
Analysis 3.9. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 9 Low methodological quality related to interpretation of results in light of reporting bias.



Analysis 3.10. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 10 Low methodological quality related to interpretation of results in light of multiplicity.



Analysis 3.11. Comparison 3 Methodological quality: systematic reviews with financial conflicts of interest versus systematic reviews without, Outcome 11 Low methodological quality related to having conclusions supported by the data.

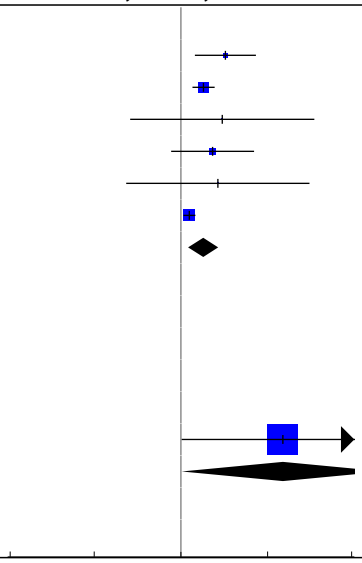


Comparison 4. Subgroup analyses for primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequency of favourable conclusions: studies with high risk of bias versus studies with low risk of bias	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 High risk of bias	6	397	Risk Ratio (M-H, Random, 95% CI)	1.81 [1.21, 2.69]
1.2 Low risk of bias	1	14	Risk Ratio (M-H, Random, 95% CI)	15.0 [1.02, 220.92]
2 Frequency of favourable conclusions: Cochrane Reviews versus non-Cochrane systematic reviews	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Non-Cochrane systematic reviews	6	351	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.15, 1.52]
2.2 Cochrane Reviews	3	38	Risk Ratio (M-H, Random, 95% CI)	2.17 [0.63, 7.44]
3 Frequency of favourable conclusions: recoding favourable conclusions	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Conclusions in favour of the intervention	4	173	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.93, 4.07]
3.2 Interventions recommended without reservations	3	238	Risk Ratio (M-H, Random, 95% CI)	2.11 [1.18, 3.79]

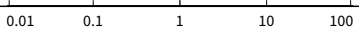
Analysis 4.1. Comparison 4 Subgroup analyses for primary outcomes, Outcome 1 Frequency of favourable conclusions: studies with high risk of bias versus studies with low risk of bias.

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 High risk of bias					
Dunn 2014	6/7	5/19		15%	3.26[1.45,7.33]
Ebrahim 2016	100/124	27/61		32.72%	1.82[1.36,2.45]
Hartog 2012	1/3	1/9		2.48%	3[0.26,34.57]
Jorgensen 2008	4/10	5/29		9.83%	2.32[0.77,6.98]
Wang 2010	1/3	1/8		2.5%	2.67[0.23,30.4]
Yank 2007	45/49	55/75		37.46%	1.25[1.07,1.47]
Subtotal (95% CI)	**196**	**201**		**100%**	**1.81[1.21,2.69]**
Total events: 157 (Industry), 94 (Non-industry)					
Heterogeneity: Tau^2=0.1; Chi^2=13.76, df=5(P=0.02); I^2=63.66%					
Test for overall effect: Z=2.92(P=0)					
4.1.2 Low risk of bias					
Jorgensen 2006	7/7	0/7		100%	15[1.02,220.92]
Subtotal (95% CI)	**7**	**7**		**100%**	**15[1.02,220.92]**
Total events: 7 (Industry), 0 (Non-industry)					
Heterogeneity: Not applicable					



Industry less favourable — Industry more favourable

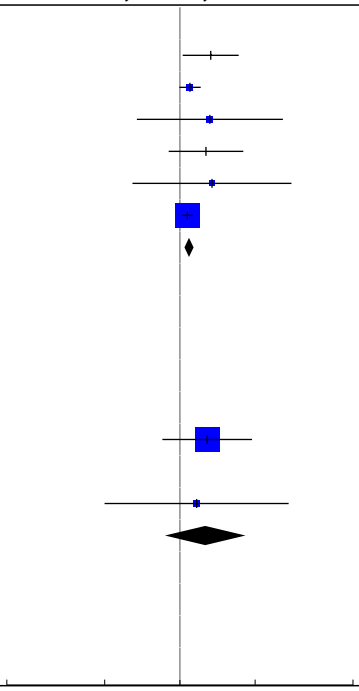
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=1.97(P=0.05)					
Test for subgroup differences: Chi²=2.33, df=1 (P=0.13), I²=57.01%					



Industry less favourable — Industry more favourable

Analysis 4.2. Comparison 4 Subgroup analyses for primary outcomes, Outcome 2 Frequency of favourable conclusions: Cochrane Reviews versus non-Cochrane systematic reviews.

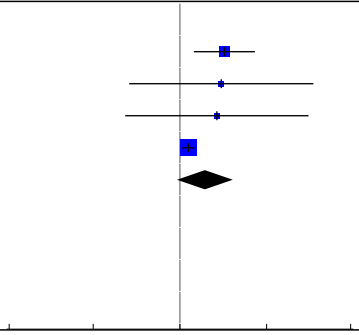
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Non-Cochrane systematic reviews					
Dunn 2014	6/7	4/12		2.73%	2.57[1.09,6.05]
Ebrahim 2016	102/132	17/30		18.76%	1.36[0.98,1.89]
Hartog 2012	1/2	1/5		0.4%	2.5[0.27,23.36]
Jorgensen 2008	4/9	4/20		1.53%	2.22[0.71,6.96]
Wang 2010	1/3	1/8		0.34%	2.67[0.23,30.4]
Yank 2007	45/49	54/74		76.24%	1.26[1.07,1.48]
Subtotal (95% CI)	**202**	**149**		**100%**	**1.32[1.15,1.52]**
Total events: 159 (Industry), 81 (Non-industry)					
Heterogeneity: Tau²=0; Chi²=4.73, df=5(P=0.45); I²=0%					
Test for overall effect: Z=3.86(P=0)					
4.2.2 Cochrane Reviews					
Ebrahim 2016	6/13	2/10		80.84%	2.31[0.59,9.1]
Hartog 2012	0/1	0/4			Not estimable
Jorgensen 2008	0/1	1/9		19.16%	1.67[0.1,27.9]
Subtotal (95% CI)	**15**	**23**		**100%**	**2.17[0.63,7.44]**
Total events: 6 (Industry), 3 (Non-industry)					
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.84); I²=0%					
Test for overall effect: Z=1.23(P=0.22)					
Test for subgroup differences: Chi²=0.61, df=1 (P=0.43), I²=0%					



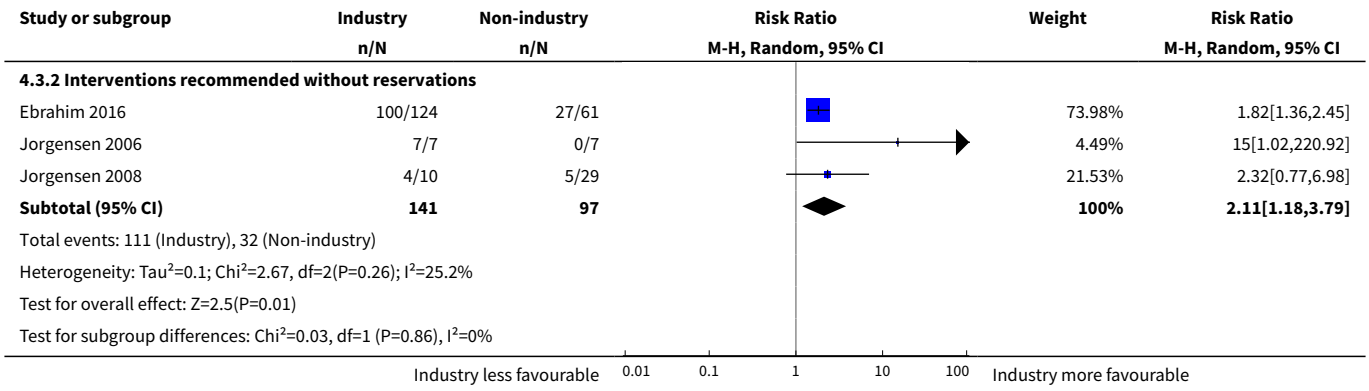
Industry less favourable — Industry more favourable

Analysis 4.3. Comparison 4 Subgroup analyses for primary outcomes, Outcome 3 Frequency of favourable conclusions: recoding favourable conclusions.

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Conclusions in favour of the intervention					
Dunn 2014	6/7	5/19		32.46%	3.26[1.45,7.33]
Hartog 2012	1/3	1/9		7.84%	3[0.26,34.57]
Wang 2010	1/3	1/8		7.9%	2.67[0.23,30.4]
Yank 2007	45/49	55/75		51.8%	1.25[1.07,1.47]
Subtotal (95% CI)	**62**	**111**		**100%**	**1.94[0.93,4.07]**
Total events: 53 (Industry), 62 (Non-industry)					
Heterogeneity: Tau²=0.27; Chi²=6.7, df=3(P=0.08); I²=55.2%					
Test for overall effect: Z=1.75(P=0.08)					



Industry less favourable — Industry more favourable

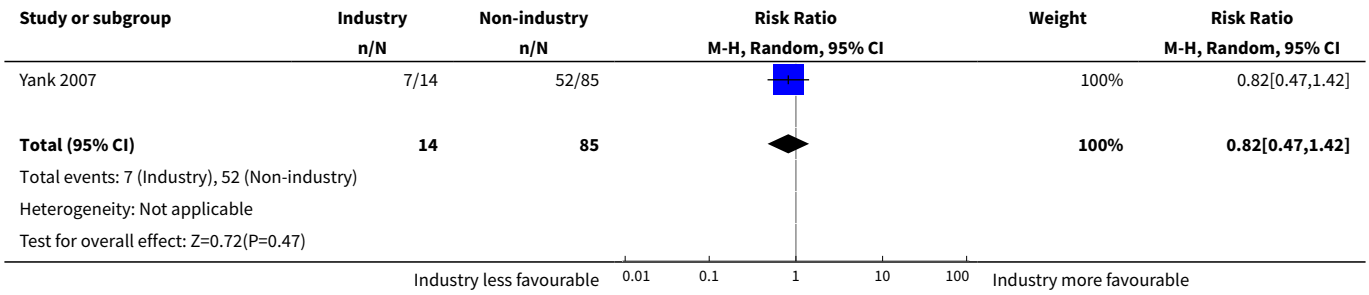


Comparison 5. Sensitivity analyses for primary outcomes

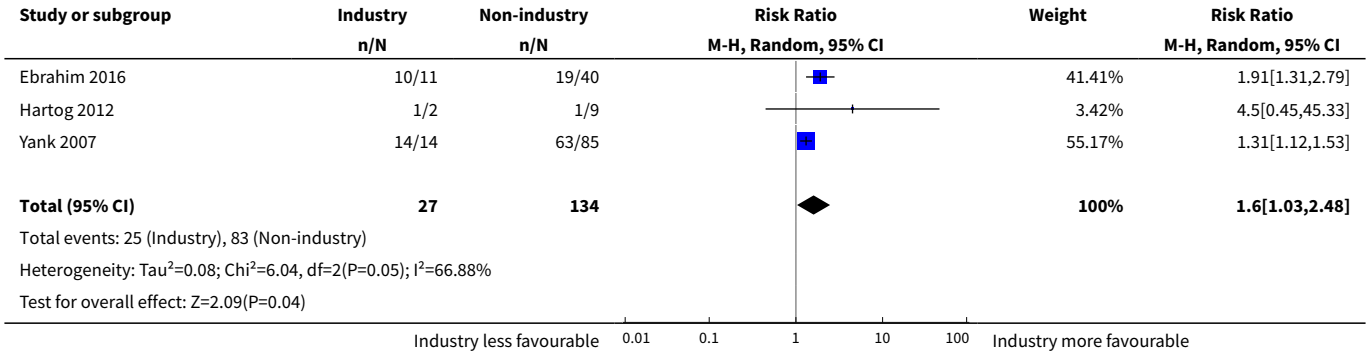
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Re-categorising industry reviews to systematic reviews with industry funding only: frequency of statistically favourable results	1	99	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.47, 1.42]
2 Re-categorising industry reviews to systematic reviews with industry funding only: frequency of favourable conclusions	3	161	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.03, 2.48]
3 Re-categorising industry reviews to systematic reviews with author financial conflicts of interest only: frequency of statistically favourable results	1	101	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.78, 1.63]
4 Re-categorising industry reviews to systematic reviews with author financial conflicts of interest only: frequency of favourable conclusions	3	239	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.08, 1.49]
5 Excluding studies with financial conflicts of interest: frequency of favourable conclusions	6	399	Risk Ratio (M-H, Random, 95% CI)	1.96 [1.23, 3.13]
6 Re-analysing using fixed-effect models: frequency of favourable conclusions	7	411	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [1.43, 1.98]
7 Excluding undeclared conflicts of interest: frequency of statistically favourable results	1	99	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.58, 1.07]
8 Excluding undeclared conflicts of interest: frequency of favourable conclusions	6	345	Risk Ratio (M-H, Random, 95% CI)	1.57 [1.02, 2.41]
9 Excluding one atypical study (Yank 2007): frequency of favourable conclusions	6	287	Risk Ratio (M-H, Random, 95% CI)	2.03 [1.56, 2.64]
10 Restricting to studies with low risk of bias in the comparability criteria or studies performing adjusted regression analyses: frequency of statistically favourable results	1		Odds Ratio (Random, 95% CI)	0.99 [0.44, 2.23]
11 Restricting to studies with low risk of bias in the comparability criteria or studies performing adjusted regression analyses: frequency of favourable conclusions	2		Odds Ratio (Random, 95% CI)	20.28 [0.57, 719.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Financial conflicts of interest related to manufacturer: frequency of favourable conclusions	1	162	Risk Ratio (M-H, Random, 95% CI)	1.61 [1.16, 2.24]
13 Financial conflicts of interest related to any for-profit organisation: frequency of favourable conclusions	7	411	Risk Ratio (M-H, Random, 95% CI)	1.75 [1.16, 2.63]

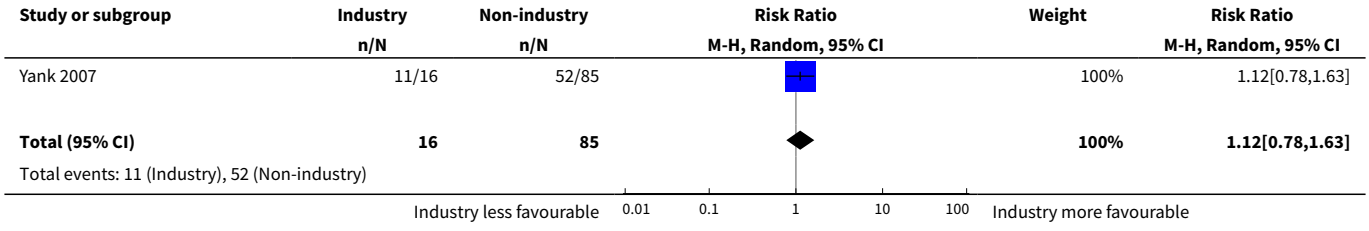
Analysis 5.1. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 1 Re-categorising industry reviews to systematic reviews with industry funding only: frequency of statistically favourable results.

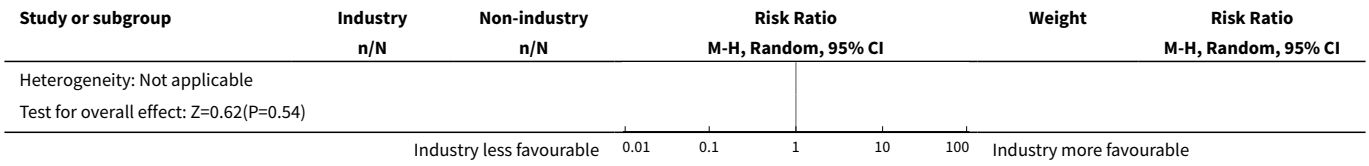


Analysis 5.2. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 2 Re-categorising industry reviews to systematic reviews with industry funding only: frequency of favourable conclusions.

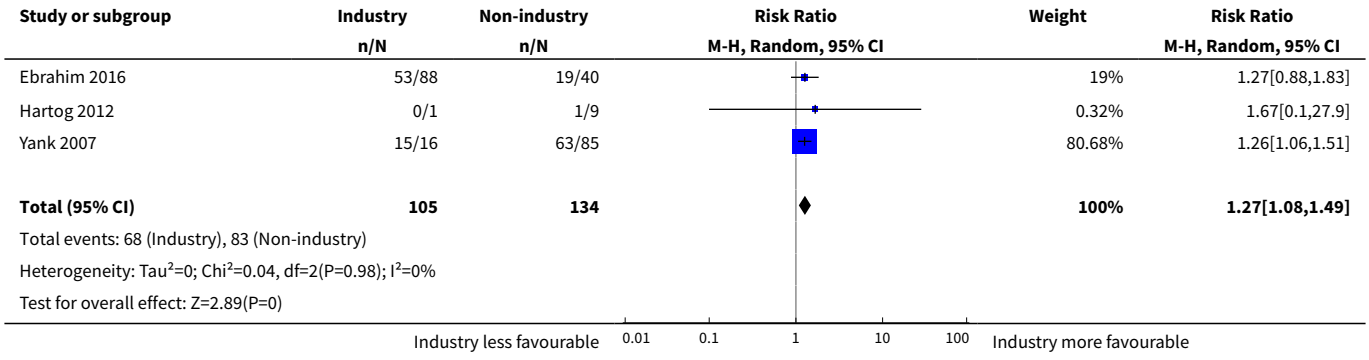


Analysis 5.3. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 3 Re-categorising industry reviews to systematic reviews with author financial conflicts of interest only: frequency of statistically favourable results.

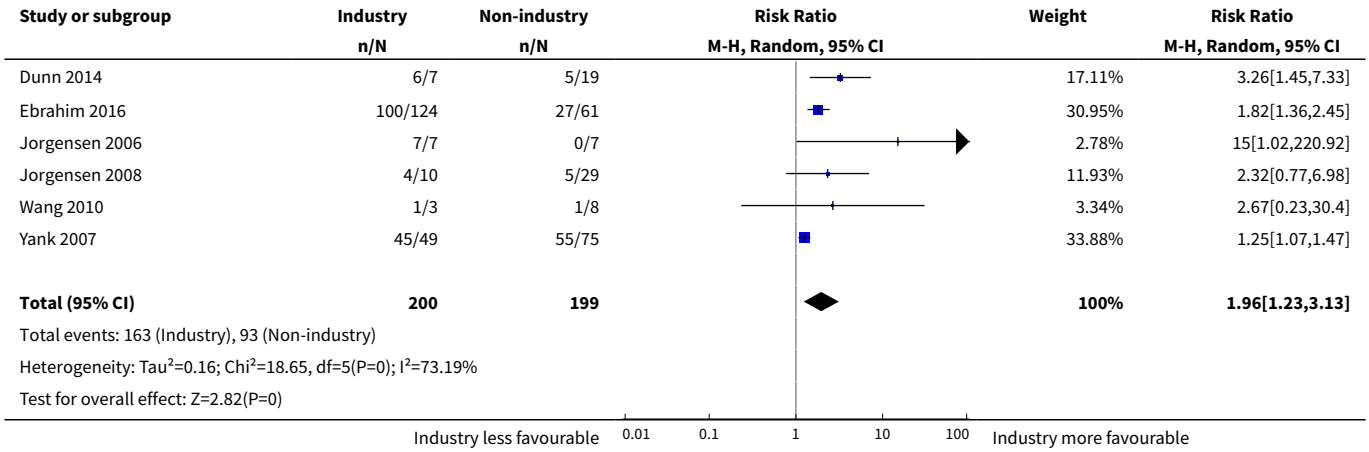




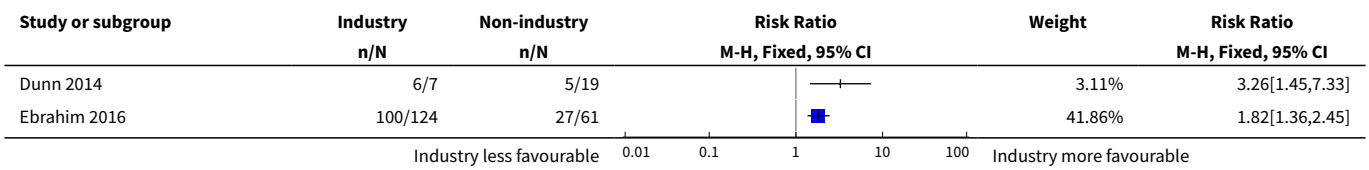
Analysis 5.4. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 4 Re-categorising industry reviews to systematic reviews with author financial conflicts of interest only: frequency of favourable conclusions.

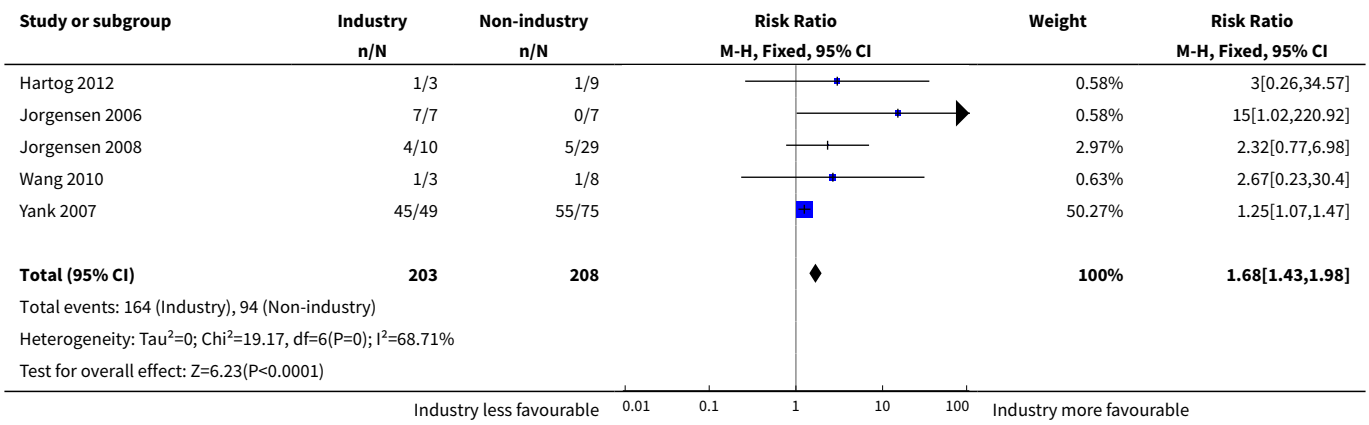


Analysis 5.5. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 5 Excluding studies with financial conflicts of interest: frequency of favourable conclusions.

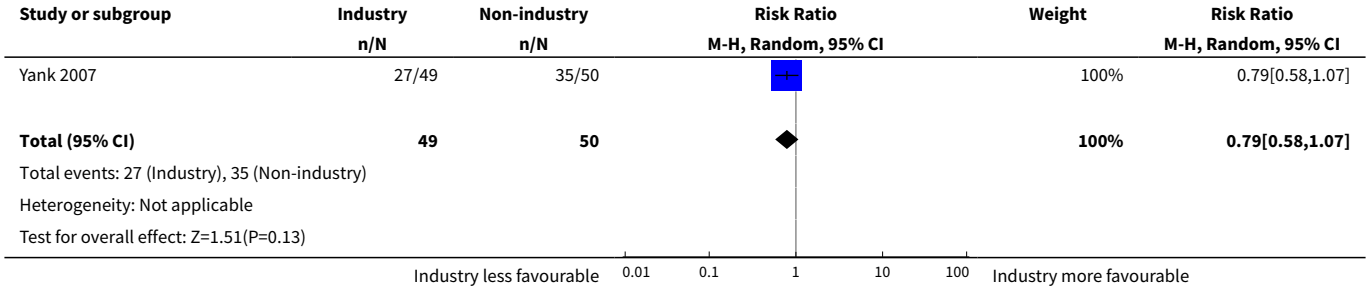


Analysis 5.6. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 6 Re-analysing using fixed-effect models: frequency of favourable conclusions.

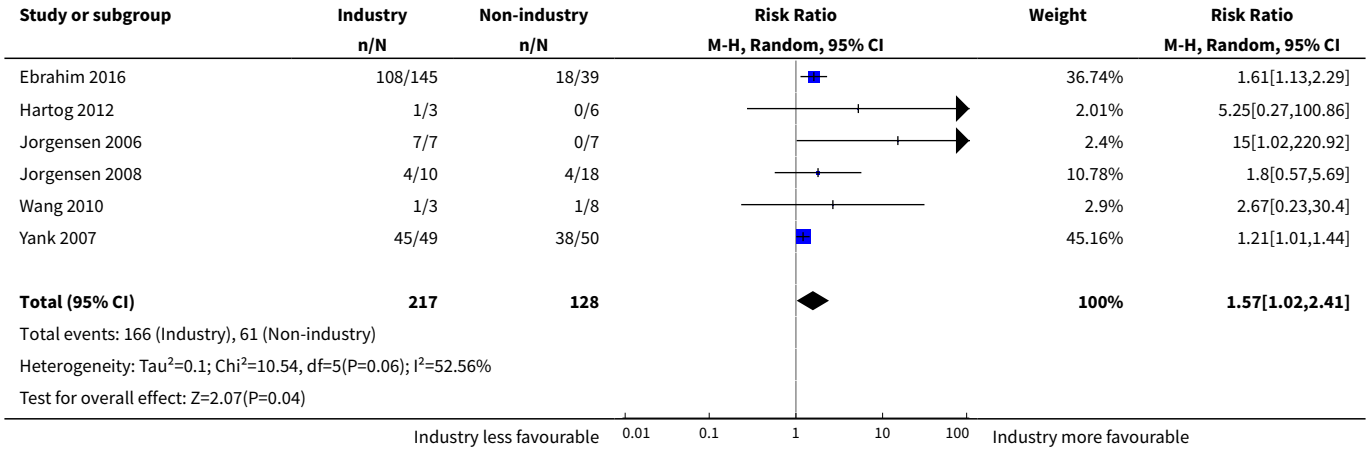




Analysis 5.7. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 7 Excluding undeclared conflicts of interest: frequency of statistically favourable results.

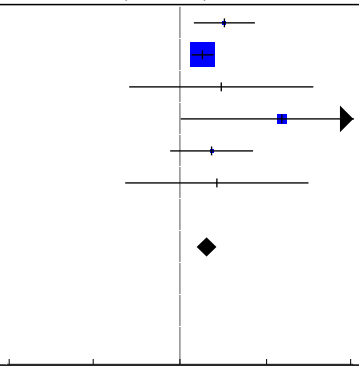


Analysis 5.8. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 8 Excluding undeclared conflicts of interest: frequency of favourable conclusions.



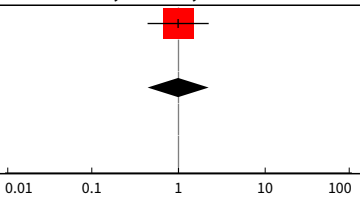
Analysis 5.9. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 9 Excluding one atypical study (Yank 2007): frequency of favourable conclusions.

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Dunn 2014	6/7	5/19		10.6%	3.26[1.45,7.33]
Ebrahim 2016	100/124	27/61		80.35%	1.82[1.36,2.45]
Hartog 2012	1/3	1/9		1.17%	3[0.26,34.57]
Jorgensen 2006	7/7	0/7		0.96%	15[1.02,220.92]
Jorgensen 2008	4/10	5/29		5.75%	2.32[0.77,6.98]
Wang 2010	1/3	1/8		1.18%	2.67[0.23,30.4]
Total (95% CI)	**154**	**133**		**100%**	**2.03[1.56,2.64]**
Total events: 119 (Industry), 39 (Non-industry)					
Heterogeneity: Tau^2=0; Chi^2=4.26, df=5(P=0.51); I^2=0%					
Test for overall effect: Z=5.24(P<0.0001)					



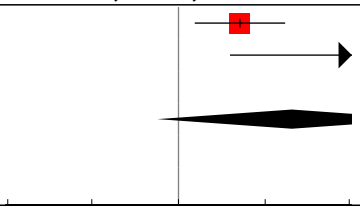
Analysis 5.10. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 10 Restricting to studies with low risk of bias in the comparability criteria or studies performing adjusted regression analyses: frequency of statistically favourable results.

Study or subgroup	Industry N	Non-industry N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
Yank 2007	0	0	-0 (0.414)		100%	0.99[0.44,2.23]
Total (95% CI)					**100%**	**0.99[0.44,2.23]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.02(P=0.98)						

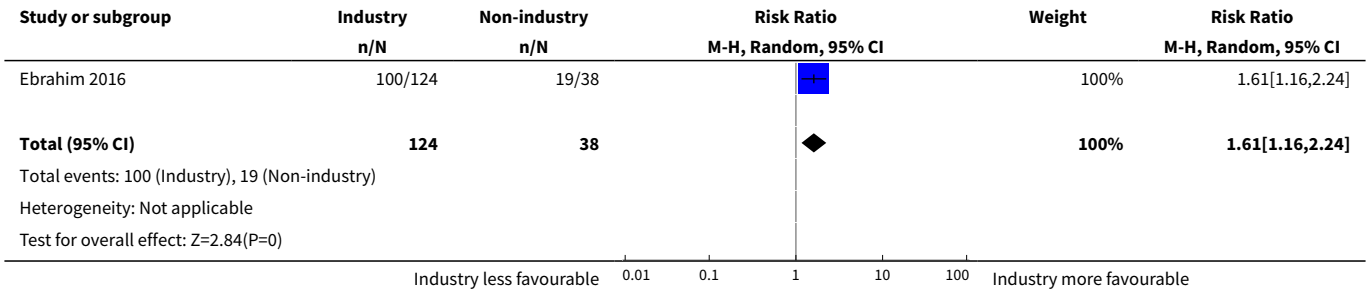


Analysis 5.11. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 11 Restricting to studies with low risk of bias in the comparability criteria or studies performing adjusted regression analyses: frequency of favourable conclusions.

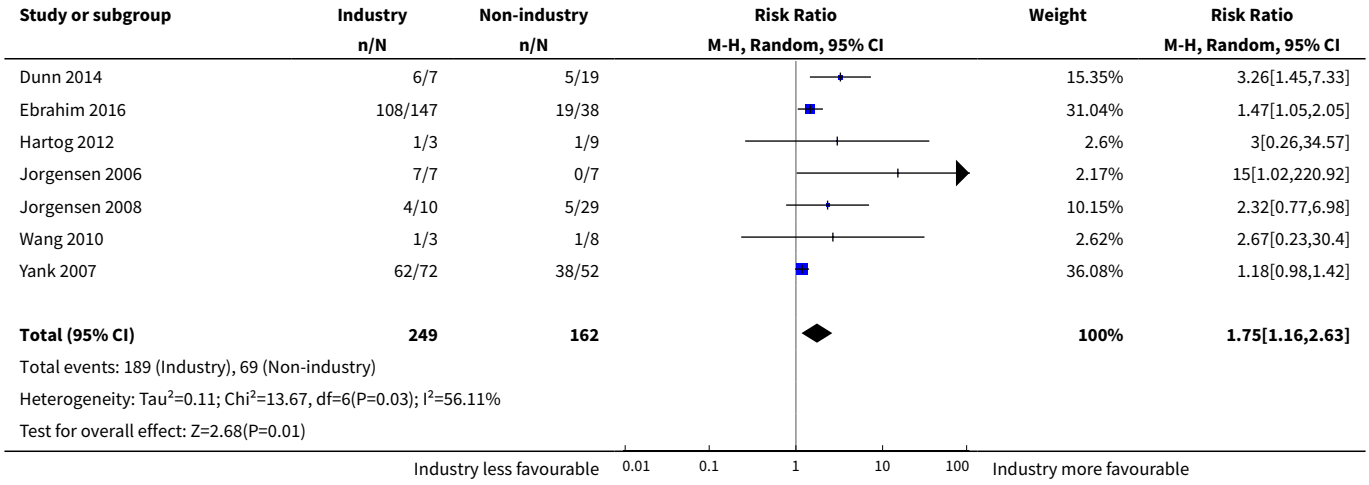
Study or subgroup	Industry N	Non-industry N	log[Odds Ratio] (SE)	Odds Ratio IV, Random, 95% CI	Weight	Odds Ratio IV, Random, 95% CI
Yank 2007	0	0	1.6 (0.612)		63.58%	5.11[1.54,16.96]
Jorgensen 2006	0	0	5.4 (2.066)		36.42%	225[3.93,12895.09]
Total (95% CI)					**100%**	**20.28[0.57,719.88]**
Heterogeneity: Tau^2=4.84; Chi^2=3.09, df=1(P=0.08); I^2=67.6%						
Test for overall effect: Z=1.65(P=0.1)						



Analysis 5.12. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 12 Financial conflicts of interest related to manufacturer: frequency of favourable conclusions.



Analysis 5.13. Comparison 5 Sensitivity analyses for primary outcomes, Outcome 13 Financial conflicts of interest related to any for-profit organisation: frequency of favourable conclusions.

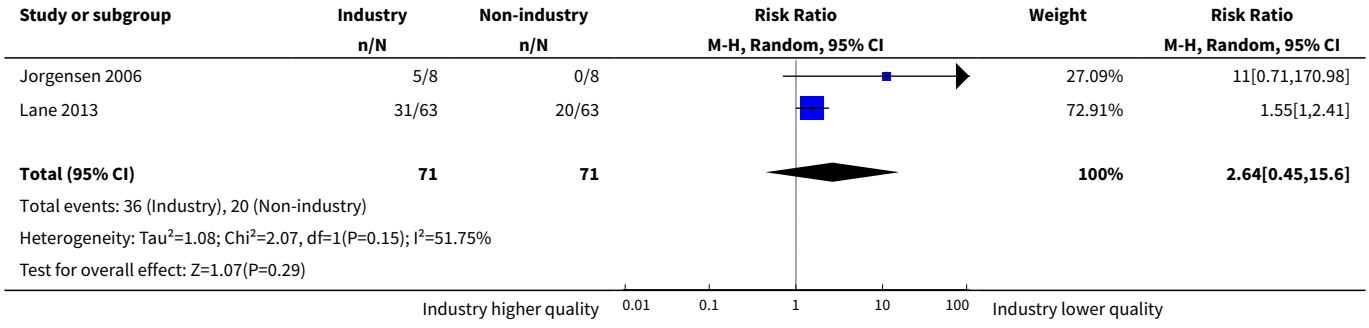


Comparison 6. Sensitivity analysis for secondary outcome

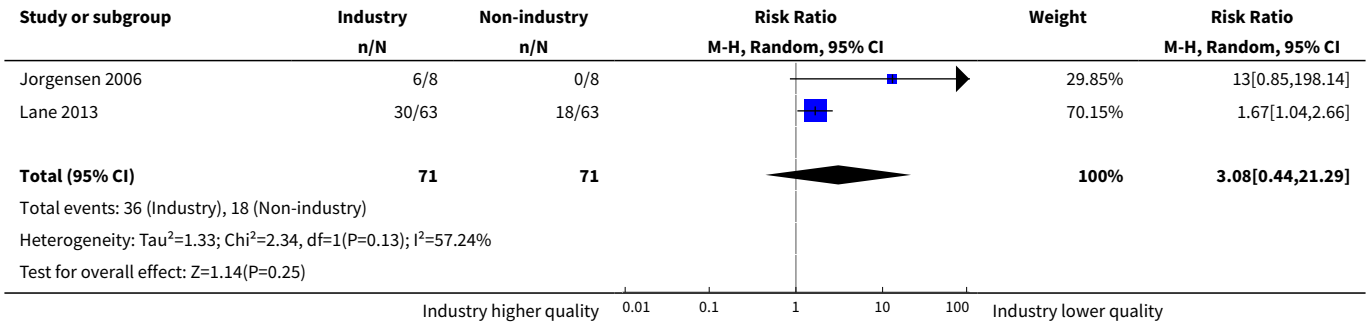
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to search methods	2	142	Risk Ratio (M-H, Random, 95% CI)	2.64 [0.45, 15.60]
2 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to selecting studies	2	142	Risk Ratio (M-H, Random, 95% CI)	3.08 [0.44, 21.29]
3 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to assessing risk of bias	2	142	Risk Ratio (M-H, Random, 95% CI)	4.13 [0.60, 28.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to addressing missing outcome data	1	126	Risk Ratio (M-H, Random, 95% CI)	1.1 [0.94, 1.29]
5 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to analysing individual studies appropriately and without avoidable bias	1	126	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.97, 1.77]
6 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to combining findings of relevant studies using appropriate meta-analysis methods	2	142	Risk Ratio (M-H, Random, 95% CI)	2.05 [0.28, 14.89]
7 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to interpretation of results in light of risk of bias	1	126	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.03, 1.75]
8 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to interpretation of results in light of reporting bias	1	126	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.82, 1.43]
9 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to interpretation of results in light of multiplicity	1	126	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.82, 1.97]
10 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to having conclusions supported by the data	2	142	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.44, 6.55]

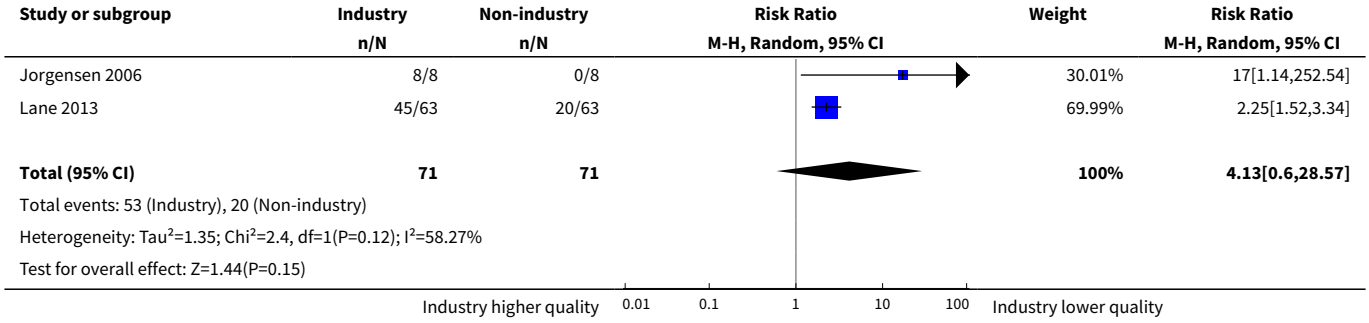
Analysis 6.1. Comparison 6 Sensitivity analysis for secondary outcome, Outcome 1 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to search methods.



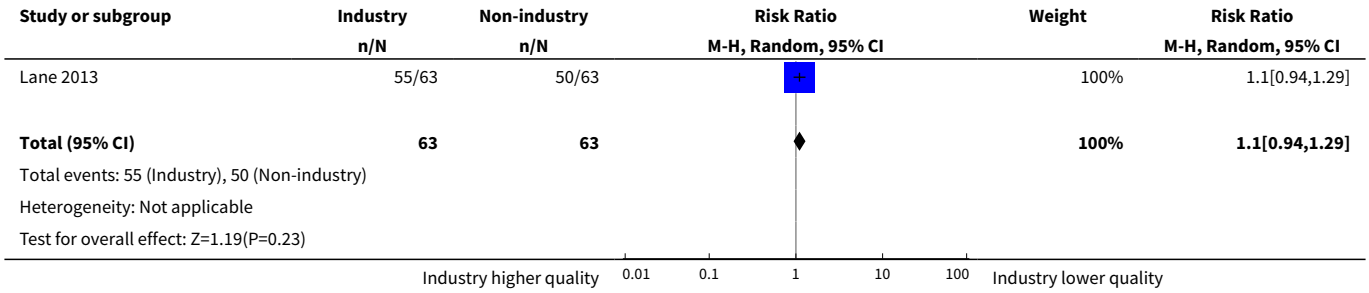
Analysis 6.2. Comparison 6 Sensitivity analysis for secondary outcome, Outcome 2 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to selecting studies.



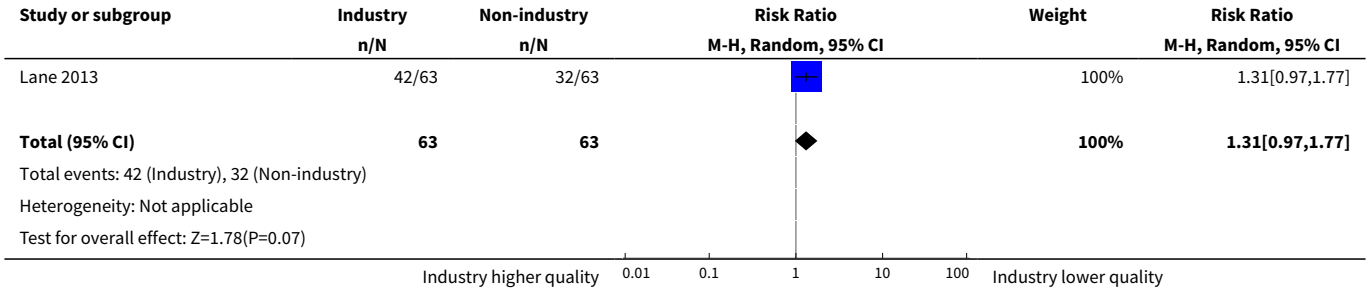
Analysis 6.3. Comparison 6 Sensitivity analysis for secondary outcome, Outcome 3 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to assessing risk of bias.



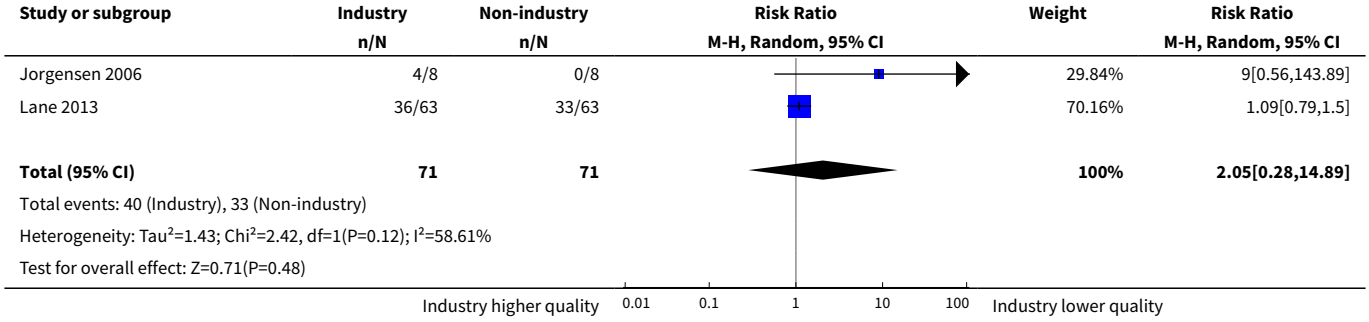
Analysis 6.4. Comparison 6 Sensitivity analysis for secondary outcome, Outcome 4 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to addressing missing outcome data.



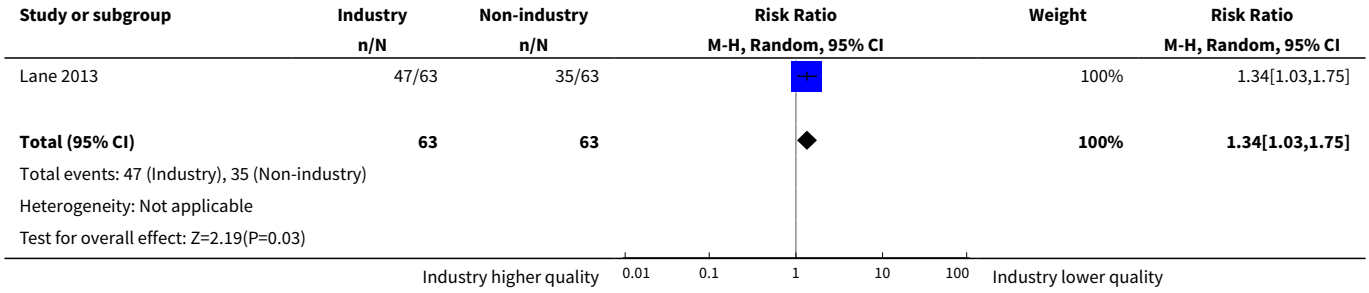
Analysis 6.5. Comparison 6 Sensitivity analysis for secondary outcome, Outcome 5 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to analysing individual studies appropriately and without avoidable bias.



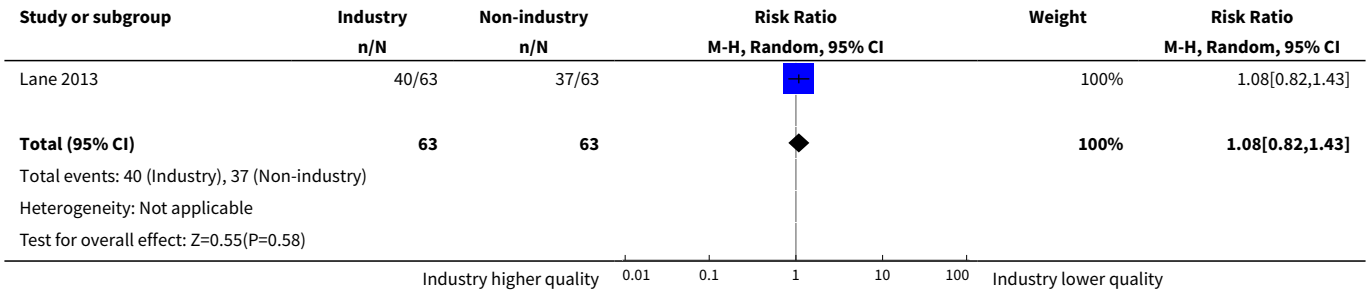
Analysis 6.6. Comparison 6 Sensitivity analysis for secondary outcome, Outcome 6 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to combining findings of relevant studies using appropriate meta-analysis methods.



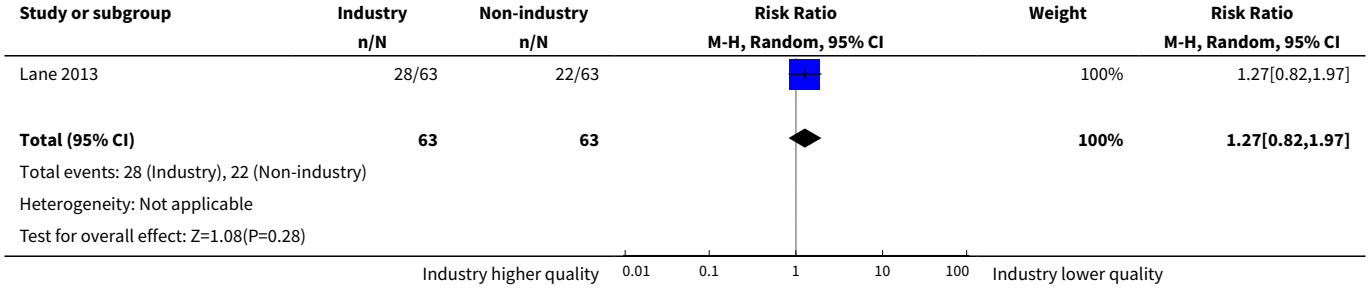
Analysis 6.7. Comparison 6 Sensitivity analysis for secondary outcome, Outcome 7 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to interpretation of results in light of risk of bias.



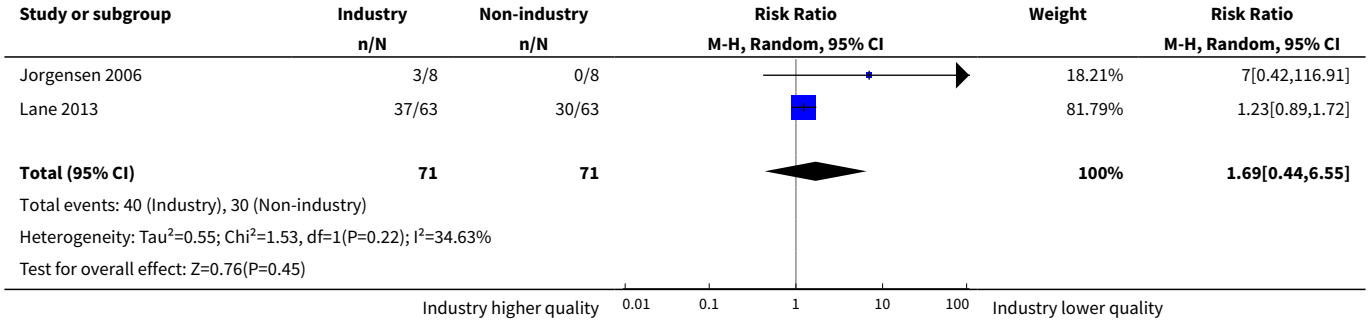
Analysis 6.8. Comparison 6 Sensitivity analysis for secondary outcome, Outcome 8 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to interpretation of results in light of reporting bias.



Analysis 6.9. Comparison 6 Sensitivity analysis for secondary outcome, Outcome 9 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to interpretation of results in light of multiplicity.



Analysis 6.10. Comparison 6 Sensitivity analysis for secondary outcome, Outcome 10 Restricting to studies with low risk of bias in the comparability criteria: low methodological quality related to having conclusions supported by the data.



APPENDICES

Appendix 1. PubMed search strategy

Block 1: drug and device industry

1. Drug Industry (MeSH)

2. (Drug [Title/Abstract] OR drugs[Title/Abstract] OR pharmaceutical[Title/Abstract] OR pharmaceutic [Title/Abstract] OR pharmacological[Title/Abstract] OR pharma*[Title/Abstract] OR biotech*[Title/Abstract] OR biopharma*[Title/Abstract] OR biomed*[Title/Abstract] OR device[Title/Abstract] OR devices[Title/Abstract] OR imaging[Title/Abstract] OR for-profit[Title/Abstract] OR private[Title/Abstract]) AND (industry[Title/Abstract] OR industries[Title/Abstract] OR company[Title/Abstract] OR companies[Title/Abstract] OR manufacturer[Title/Abstract] OR manufacturers[Title/Abstract] OR organisation[Title/Abstract] OR organisations[Title/Abstract] OR organization[Title/Abstract] OR organizations[Title/Abstract] OR agency[Title/Abstract] OR agencies[Title/Abstract] OR sector[Title/Abstract] OR sectors[Title/Abstract])

3. Health[Title/Abstract] AND (industry[Title/Abstract] OR industries[Title/Abstract])

4. 1 OR 2 OR 3

Block 2: conflicts of interest and industry funding

5. Conflict of interest (MeSH)

6. Financial support (MeSH)

7. Research support as topic (MeSH)

8. (Conflict[Title/Abstract] OR conflicts[Title/Abstract] OR conflicting[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])

9. (Competing[Title/Abstract] OR vested[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])

10. (Industry[Title/Abstract] OR industries[Title/Abstract] OR company[Title/Abstract] OR companies[Title/Abstract] OR manufacturer[Title/Abstract] OR manufacturers[Title/Abstract] OR finance[Title/Abstract] OR financial[Title/Abstract]) AND (funded[Title/Abstract] OR funding[Title/Abstract] OR sponsor[Title/Abstract] OR sponsors[Title/Abstract] OR sponsorship[Title/Abstract] OR sponsoring[Title/Abstract] OR support[Title/Abstract] OR supported[Title/Abstract] OR finance[Title/Abstract] OR financial[Title/Abstract] OR involvement[Title/Abstract] OR involving[Title/Abstract] OR payment[Title/Abstract] OR payments[Title/Abstract] OR relationship[Title/Abstract] OR relationships[Title/Abstract] OR relation[Title/Abstract] OR relations[Title/Abstract] OR tie[Title/Abstract] OR ties[Title/Abstract])

11. Industry-funded[Title/Abstract] OR industry-funding[Title/Abstract] OR industry-sponsor*[Title/Abstract] OR company-funded[Title/Abstract] OR company-funding[Title/Abstract] OR company-sponsor*[Title/Abstract] OR industry-support[Title/Abstract] OR industry-supported[Title/Abstract] OR company-support[Title/Abstract] OR company-supported[Title/Abstract]

12. (Commercial-academic[Title/Abstract] OR academic-industry[Title/Abstract] OR commercial-industry[Title/Abstract] OR physician-industry[Title/Abstract]) AND (interface[Title/Abstract] OR interfaces[Title/Abstract] OR interaction[Title/Abstract] OR interactions[Title/Abstract] OR relationship[Title/Abstract] OR relationships[Title/Abstract] OR relation[Title/Abstract] OR relations[Title/Abstract])

13. 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12

Block 3: systematic reviews or meta-analyses

14. Review Literature as Topic (MeSH)

15. Meta-Analysis as Topic (MeSH)

16. Meta-analy*[Title/Abstract] OR metaanal*[Title/Abstract]

17. Meta[Title/Abstract] AND analy*[Title/Abstract]

18. (Systematic[Title/Abstract] OR systematically[Title/Abstract] OR systematical[Title/Abstract] OR Cochrane[Title/Abstract] OR literature[Title/Abstract] OR literatures[Title/Abstract]) AND (review[Title/Abstract] OR reviews[Title/Abstract] OR overview[Title/Abstract] OR overviews[Title/Abstract])

19. 14 OR 15 OR 16 OR 17 OR 18

Combined searches

20. 4 AND 13 AND 19

Appendix 2. Data extraction

Two review authors independently extracted data on the following.

Basic characteristics

1. Title
2. Year published
3. Name of first author
4. Name of journal
5. Primary aim of the study
6. Study design used in the study (cohort, cross-sectional, systematic review or meta-analysis, other)
7. Study domain (i.e. topic of interest) of systematic reviews. Verbatim extraction
8. Study domain coded (specific disease, specific therapy, mixed domain)
9. Sample strategy used to locate systematic reviews or meta-analyses (e.g. search of PubMed and time period covered). Verbatim extraction
10. Types of publications (published/unpublished) included in the systematic reviews or meta-analyses. Verbatim extraction
11. Types of publications included in the systematic reviews or meta-analyses (published only, published and unpublished, not described)
12. Definition of systematic reviews or meta-analyses used in the study. Verbatim extraction
13. Number of systematic reviews or meta-analyses included in the study
14. Types of studies included in systematic review or meta-analysis (e.g. clinical trials or cohort studies)

Outcome data

1. Definition of industry funding used in the study. Verbatim extraction
2. Definition of author conflicts of interest used in the study. Verbatim extraction
3. Definition of effect size estimates used in the study. Verbatim extraction
4. Definition of statistically favourable results (e.g. based on statistical significance) used in the study. Verbatim extraction
5. Definition of favourable conclusions used in the study. Verbatim extraction
6. Definition of methodological quality used in the study. Verbatim extraction
7. Definition of primary analysis used in the study. Verbatim extraction
8. Data on estimates of the association between financial conflicts of interest and estimated treatment effect
9. Data on estimates of the association between financial conflicts of interest and statistically favourable results
10. Data on estimates of the association between financial conflicts of interest and favourable conclusions

Data for informing subgroup analyses or reflection on heterogeneity

1. Types of interventions included in systematic reviews or meta-analyses. Verbatim extraction
2. Types of interventions included in systematic reviews or meta-analyses (drug, device, mixed)
3. Data on estimates of the association between industry funding and estimated treatment effect
4. Data on estimates of the association between author financial conflicts of interest and estimated treatment effect
5. Data on estimates of the association between industry funding and statistically favourable results
6. Data on estimates of the association between author financial conflicts of interest and statistically favourable results
7. Data on estimates of the association between industry funding and favourable conclusions
8. Data on estimates of the association between author financial conflicts of interest and favourable conclusions
9. Data on estimates of the association between industry funding and methodological quality
10. Data on estimates of the association between author financial conflicts of interest and methodological quality
11. Data on estimates of the association between different degrees of financial conflicts of interest (e.g. mild, moderate, and severe) and estimated treatment effect
12. Data on estimates of the association between different degrees of financial conflicts of interest (e.g. mild, moderate, and severe) and statistically favourable results
13. Data on estimates of the association between different degrees of financial conflicts of interest (e.g. mild, moderate, and severe) and favourable conclusions

Additional data

1. Declaration of funding source and other conflicts of interest in the study. Verbatim extraction

2. Additional relevant data

Appendix 3. Dealing with missing data

If the included studies investigated both industry funding and author financial conflicts of interest, but reported them together, we contacted the authors to obtain separate data. If the included studies contained a mixture of systematic reviews and other study designs or mixed domains (e.g. pharmaceutical and nutritional interventions), we contacted the authors to obtain separate data for systematic reviews on drug or device studies. If included studies investigated methodological quality, but reported the overall quality score only, we contacted the authors to obtain data on each item in the measurement tool used. In total, we contacted authors of six studies (Ebrahim 2016; Gomez-Garcia 2017; Hartog 2012; Jorgensen 2008; Wang 2010; Yank 2007) and received data for five of these (Gomez-Garcia 2017; Hartog 2012; Jorgensen 2008; Wang 2010; Yank 2007).

If the included studies did not report their methods in a way that enabled us to conduct our 'Risk of bias' assessment, we contacted the authors in an attempt to clarify these issues. In total, we contacted authors of nine studies and received clarifications for all nine of these (Chambers 2015; Dunn 2014; Ebrahim 2016; Gomez-Garcia 2017; Hartog 2012; Jorgensen 2006; Jorgensen 2008; Wang 2010; Yank 2007).

We contacted authors of included studies in an attempt to obtain published or unpublished protocols for the studies. In total, we contacted authors of all 10 studies. All authors responded, five author teams supplied us with their protocols (Ebrahim 2016; Gomez-Garcia 2017; Jorgensen 2006; Jorgensen 2008; Lane 2013).

Appendix 4. Prediction interval

Formula for prediction interval

To calculate prediction intervals, we used the formula presented in an article by Riley et al.:

$$\hat{u} - t_{k-2} \cdot \sqrt{(T^2 + SE(\hat{u})^2)},\ \hat{u} + t_{k-2} \cdot \sqrt{(T^2 + SE(\hat{u})^2)}$$

Where $\hat{u}$ was the estimate of the average effect measure across studies, $SE(\hat{u})$ was the standard error of $\hat{u}$, T was the estimate of between study standard deviation, and t_{k-2} was the $100(1-(\alpha/2))$ percentile of the t-distribution with k-2 degrees of freedom, where k was the number of observational studies in the meta-analysis and α was 0.05 to give a 95% prediction interval. To meet the assumption on normal distribution, the prediction interval was derived on the natural log scale (Riley 2011). As T^2 is already a measure for the heterogeneity for ln(RR), this was used directly in the calculation (IntHout 2016).

Calculation of prediction interval

As our analyses on estimated treatment effect and frequency of statistically favourable results were based on one study each, calculation of prediction interval was only possible for one of our primary outcomes: frequency of favourable conclusions.

From Analysis 2.1, $\hat{u}$ was given as 1.98 with a 95% CI from 1.26 to 3.11, T^2 and was given as 0.15. The analysis on frequency of favourable conclusions included seven studies, which provided five degrees of freedom according to the formula. The 0.975 percentile of the t distribution with four degrees of freedom was 2.571 (Rosner 2006).

To calculate $SE(\hat{u})$, we used the formula for transforming confidence intervals to the natural log scale from the Cochrane Handbook (Higgins 2011):

lower limit = ln(lower confidence limit given for RR)

upper limit = ln(upper confidence limit given for RR)

Thus, our transformed confidence interval was:

lower limit = ln(1.26) → lower limit = 0.231112

upper limit = ln(3.11) → upper limit = 1.134623

We used the formula for calculating standard errors from the Cochrane Handbook (Higgins 2011):

SE=(upper limit - lower limit) / 3.92

Thus, we calculated the standard error as:

SE=(1.134623-0.231112) / 3.92 → SE=0.230488

Finally, the prediction interval on the natural logarithm scale was calculated:

Prediction interval: ln(1.98) - 2.571· √(0.15+0.230488^2), ln(1.98) + 2.571· √(0.15+0.230488^2) →

Prediction interval: -0.47564-1.84183

Thus, the prediction interval for the risk ratio of frequency of favourable conclusions in industry reviews compared with non-industry reviews was calculated as: 0.62 to 6.31.

Appendix 5. Methodological quality of the systematic reviews

Table A7.1: Methodological quality: Oxman and Guyatt index

Number of systematic reviews assessed as not fulfilled or unclear in each item

	Jorgensen 2006		Jorgensen 2008		Yank 2007	
	Industry N(%)	Non-industry N(%)	Industry N(%)	Non-industry N(%)	Industry N(%)	Non-industry N(%)
1) Were the search methods used to find evidence on the primary question stated?	5 (63)	0 (0)	4 (40)	5 (17)		
2) Was the search for evidence reasonable comprehensive?*	5 (63)	0 (0)	6 (60)	6 (21)		
3) Were the criteria used for deciding which studies to include reported?	3 (38)	0 (0)	5 (50)	2 (7)		
4) Was bias in the selection of studies avoided?*	6 (75)	0 (0)	9 (90)	14 (48)		
5) Were the criteria used for assessing the validity of the included studies reported?	6 (75)	0 (0)	7 (70)	9 (31)		
6) Was the validity of all studies referred to in the text assessed using appropriate criteria?*	8 (100)	0 (0)	9 (90)	18 (62)		
7) Were the methods used to combine the findings of the relevant studies reported?	0 (0)	0 (0)	1 (10)	2 (7)		
8) Were the findings of the relevant studies combined appropriately?*	4 (50)	0 (0)	3 (30)	5 (17)		
9) Were the conclusions made by the author(s) supported by the data reported?*	3 (38)	0 (0)	1 (10)	5 (17)		
Median quality score	2**	7**	2.5**	5**	4***	9***

* Items address methodological quality and were included in pooled analysis

**Score range from 0 to 7

***Score range from 0 to 18, as the authors assigned two points for fulfilling each criteria, one point for partially fulfilling it, and zero points for not fulfilling it (Yank 2007)

Table A7.2: Methodological quality: Lane 2013 (own tool)

(Continued)

Number of systematic reviews assessed as not fulfilled or unclear in each item

	Lane 2013	
	Industry N(%)	Non-industry N(%)
A: Were the review methods adequate such that biases in location and assessment of studies were minimized or able to be identified?*	30 (48)	18 (29)
B: Were the individual studies analysed appropriately and without avoidable bias?*	42 (67)	32 (51)
C: Were the basic meta-analysis methods appropriate?*	36 (57)	33 (52)
D: Are the conclusions justified and the interpretation sound?*	37 (59)	30 (48)
Q8: Was the search for evidence reasonable comprehensive?*	31 (49)	20 (32)
Q11: Was risk of bias (or quality) assessed for each included study?*	45 (71)	20 (32)
Q15 Are adequate methods used to address missing outcome data?*	55 (87)	50 (79)
Q26 Was a sensible strategy used to address statistical heterogeneity in meta-analysis?	42 (67)	32 (51)
Q39: Were results appropriately interpreted in the light of risk of bias in included studies?*	47 (75)	35 (56)
Q40 Were results appropriately interpreted in the light of risk of reporting bias?*	40 (63)	37 (59)
Q41 Were results appropriately interpreted in the light of any multiplicity?*	28 (44)	22 (35)

* Items address methodological quality and were included in pooled analysis

Table A7.3: Methodological quality: AMSTAR

Number of systematic reviews assessed as not fulfilled or unclear in each item

	Gomez-Garcia 2017	
	Industry N(%)	Non-industry N(%)
1) Was an 'a priori' design provided?	31 (48)	39 (68)
2) Was there duplicate study selection and data extraction?*	31 (48)	27 (47)
3) Was a comprehensive literature search performed?*	9 (14)	7 (12)
4) Was the status of publication (i.e. grey literature) used as an inclusion criterion?	33 (52)	31 (54)
5) Was a list of studies (included and excluded) provided?	53 (83)	50 (88)

(Continued)

6) Were the characteristics of the included studies provided?	5 (8)	8 (14)
7) Was the scientific quality of the included studies assessed and documented?*	27 (42)	15 (26)
8) Was the scientific quality of the included studies used appropriately in formulating conclusions?*	31 (48)	16 (28)
9) Were the methods used to combine the findings of studies appropriate?*	27 (42)	27 (47)
10) Was the likelihood of publication bias assessed?*	53 (83)	47 (82)
11) Was the conflict of interest included?	12 (19)	24 (42)

* Items address methodological quality and were included in pooled analysis

Table A7.4: Methodological quality: ISPOR guidance

Number of systematic reviews assessed as not fulfilled or unclear in each item

	Chambers 2015	
	Industry N(%)	Non-industry N(%)
1) Was a Bayesian or a frequentist framework used?	23 (23)	78 (36)
2) Was the risk of bias of included clinical trials assessed? (e.g., using the Cochrane Collaboration's tool for assessing risk of bias or the Jadad scale?)*	45 (46)	47 (22)
3) Did the analysis include adjustments for model covariates?	61 (62)	162 (75)
4) Was a fixed or random-effects model used? Or, were the findings of both fixed and random-effects models presented?	31 (32)	62 (29)
5) Was an assessment of model fit reported?	52 (53)	136 (63)
6) Was a sensitivity analysis performed? (e.g. varied the included clinical studies to evaluate the robustness of the findings)*	41 (42)	95 (44)
7) For studies with at least one closed loop, was the consistency of direct evidence and indirect evidence evaluated? (i.e., presented and compared the findings from the traditional meta-analysis and the network meta-analysis)*	82 (84)	117 (54)
8) Were the search terms reported?	37 (38)	24 (11)
9) Was a network diagram of included treatments presented?	36 (37)	85 (39)
10) Was data from the included clinical studies necessary to reproduce the network meta-analysis presented?	40 (41)	68 (31)
11) Was a table of key clinical study characteristics presented?	9 (9)	20 (9)

(Continued)

12) Was the model code presented or source cited? (reported for studies performed using a Bayesian framework only)	90 (92)	190 (88)
13) Were pairwise comparisons of all included treatments presented?	54 (55)	58 (27)
14) Was the probability of each treatment being best reported? (reported for studies performed using a Bayesian framework only)	73 (74)	155 (71)
15) Was a ranking of treatments in terms of effectiveness reported? (reported for studies performed using a Bayesian framework only)	87 (89)	161 (74)

*Item address methodological quality

Appendix 6. Subgroup analyses

High risk of bias studies versus low risk of bias studies

We planned to compare studies with high and low risk of bias for our primary outcomes. Only one study investigated estimated treatment effect, and only one study investigated statistically favourable results. Thus, our data enabled us to carry out our subgroup analysis for one of our primary outcomes: frequency of favourable conclusions.

We found lower RR for studies assessed as high risk of bias (RR: 1.81, 95% CI: 1.21 to 2.69), than for studies assessed as low risk of bias (RR: 15.00, 95% CI: 1.02 to 220.92). The difference was not statistically significant (P value: 0.13, Analysis 4.1).

The statistical heterogeneity among studies assessed as high risk of bias was substantial (I^2: 64%, Analysis 4.1). However, the effect estimates showed the same directionality and did not differ substantially (RR from 1.25 at the lowest to 3.26 at the highest). Thus, the statistical heterogeneity may be driven by the relatively high number of systematic reviews included in the analysis (n = 411). Only one study assessed as low risk of bias was included in this subgroup analysis.

Cochrane Reviews versus non-Cochrane systematic reviews

The one study investigating estimated treatment effect (Jorgensen 2006) compared Cochrane Reviews with industry reviews, and re-analysing the sample of studies for estimated treatment effect was not meaningful. Furthermore, the one study investigating statistically favourable results (Yank 2007) included only one Cochrane Review and recoding the sample was not considered appropriate for frequency of statistically favourable results. Thus, our data enabled us to carry out this subgroup analysis on one of our primary outcomes: frequency of favourable conclusions.

In total, six studies could be pooled in the subgroup with non-Cochrane Reviews only and three studies could be pooled in a subgroup with Cochrane Reviews only (Jorgensen 2006, Yank 2007 and Dunn 2014 did not include any Cochrane Reviews classified as having authors with financial conflicts of interest or as having received industry funding). Our analysis included a total of 38 Cochrane Reviews, on which 15 Cochrane Reviews were classified as having authors with financial conflicts of interest or as having received industry funding by the authors of the included studies. We found lower RR for non-Cochrane Reviews (RR: 1.32, 95% CI: 1.15 to 1.52) than for Cochrane Reviews (RR: 2.17, 95% CI: 0.63 to 7.44). The difference was not statistically significant (P value: 0.43, Analysis 4.2).

Systematic reviews of drug studies versus systematic reviews of device studies

Only one study (Gomez-Garcia 2017) included systematic reviews of device studies and this study investigated methodological quality only. Our data thereby did not enable us to carry out a subgroup analysis comparing systematic reviews of drug studies with systematic reviews of device studies.

Systematic reviews with major financial conflicts of interest versus systematic reviews with moderate financial conflicts of interest versus systematic reviews with minor financial conflicts of interest according to the definitions used by the authors of the included studies

We planned to compare different degrees of financial conflicts of interest (i.e. severe, moderate, mild). However, none of the included studies graded the degree of financial conflicts of interest therefore, we were not able to carry out this subgroup analysis.

Studies defining favourable conclusions as conclusions in favour of the intervention versus studies defining favourable conclusions as conclusions recommending the intervention without reservations

Our subgroup analysis comparing conclusions in favour of the intervention and conclusions recommending the intervention without reservations showed minor differences between the two groups of favourable conclusions.

We found lower RR for conclusions in favour of the intervention (RR: 1.94, 95% CI: 0.93 to 4.07) than for interventions recommending the intervention without reservations (RR: 2.11, 95% CI: 1.18 to 3.79). The difference was not statistically significant (P value: 0.86). The statistical heterogeneity remained approximately the same (I^2 from 69% to 55%) for conclusions in favour of the intervention, whereas it decreased substantially (I^2 from 69% to 25%) for conclusions recommending the intervention without reservations (Analysis 4.3).

Appendix 7. Sensitivity analyses

Re-categorising industry reviews into systematic reviews with industry funding only (i.e. excluding systematic reviews with author financial conflicts of interest from the industry group) and comparing with non-industry reviews (i.e. systematic reviews without industry funding and author financial conflicts of interest)

We planned to re-categorise industry reviews to systematic reviews with industry funding only. However, as only one study investigated estimated treatment effect and this study restricted the industry group to industry funding only, our data only enabled us to carry out this sensitivity analysis on two of our primary outcomes: frequency of statistically favourable results and frequency of favourable conclusions.

Our re-categorisation showed similar results as our primary analyses, however with wider confidence intervals due to less data. For frequency of statistically favourable results, the effect estimate remained statistically insignificant (RR: 0.82, 95% CI: 0.47 to 1.42, Analysis 5.1). For frequency of favourable conclusions, the effect estimate decreased slightly, but remained statistically significant (RR: 1.60, 95% CI: 1.03 to 2.48, Analysis 5.2).

Re-categorising industry reviews into systematic reviews with author financial conflicts of interest only (i.e. excluding systematic reviews with industry funding from the industry group) and comparing with non-industry reviews (i.e. systematic reviews without author financial conflicts of interest and industry funding)

We planned to re-categorise industry reviews into systematic reviews with author financial conflicts of interest only. However, as only one study investigated estimated treatment effect and this study restricted the industry group to industry funding only, our data only enabled us to carry out this sensitivity analysis on two of our primary outcomes: frequency of statistically favourable results and frequency of favourable conclusions.

Our re-categorisation showed similar results as our primary analyses, however with wider confidence intervals due to less data. For frequency of statistically favourable results, the effect estimate increased, but remained statistically insignificant (RR: 1.12, 95% CI: 0.78 to 1.63, Analysis 5.3). For frequency of favourable conclusions, the effect estimate decreased, but remained statistically significant (RR: 1.27, 95% CI: 1.08 to 1.49, Analysis 5.4).

Excluding included studies with financial conflicts of interest

We planned to re-analyse our primary outcomes excluding studies with financial conflicts of interest according to the declarations. Three studies declared any financial conflicts of interest related to for-profit organisations. Lane 2013 declared that GSK teleconference facilities were used for meetings related to the study and that several authors were employees at pharmaceutical companies at the time the study was conducted. Gomez-Garcia 2017 declared that no funding was received for the study by any pharmaceutical companies, but several authors had received honoraria for research and lecturing from different pharmaceutical companies. Hartog 2012 declared that one author had received research grants, and speaker/consultancy fees from a pharmaceutical company.

Lane 2013 and Gomez-Garcia 2017 solely investigated our secondary outcome, and Hartog and colleagues investigated frequency of favourable conclusions. Therefore, we were able to carry out this sensitivity analysis for one of our outcomes: frequency of favourable conclusions.

Our sensitivity analyses showed similar results as our primary analysis. The effect estimate remained approximately the same and remained statistically significant (RR: 1.96, 95% CI: 1.23 to 3.13, Analysis 5.5).

Re-analysing our data using fixed-effect models

As the analyses for estimated treatment effect and frequency of statistically favourable results included only one study each, our re-analysis of our primary outcomes using fixed-effect models was only carried out for one of our primary outcomes: frequency of favourable conclusions.

Our sensitivity analysis showed similar results as our primary analysis for frequency of favourable conclusions. The effect estimate decreased slightly and remained statistically significant (RR: 1.68, 95% CI: 1.43 to 1.98, Analysis 5.6).

Excluding systematic reviews with unclear or undeclared financial conflicts of interest from the non-industry group

The only study investigating estimated treatment effect included systematic reviews with undeclared financial conflicts of interest in a separate category and these reviews were thereby not included in our primary analysis. Our data, thus, enabled us to exclude systematic reviews with unclear or undeclared financial conflicts of interest for two of our primary outcomes: frequency of statistically favourable results and frequency of favourable conclusions.

Our sensitivity analysis showed similar results as our primary analyses for statistical favourable results and favourable conclusions however with wider confidence intervals due to less data. The effect estimate for frequency of statistically favourable results decreased slightly, but remained statistically insignificant (RR: 0.79, 95% CI: 0.58 to 1.07, Analysis 5.7). The effect estimate for frequency of favourable conclusions decreased slightly, but remained borderline statistically significant (RR: 1.57, 95% CI: 1.02 to 2.41). The statistical heterogeneity deceased slightly compared to our primary analysis (I^2 from 69% to 53%, Analysis 5.8).

Excluding one atypical study (Yank 2007) from our pooled analyses, because it compared industry reviews (financial conflicts of interest with a single drug company) with a group of both industry and non-industry reviews (multiple drug companies, no statement, both drug and non-profit companies, and non-profit companies)

Our primary analyses on estimated treatment effect and frequency of statistically favourable results were based on one study. Thus, we excluded the atypical study from our pooled analysis on frequency of favourable conclusions.

Our sensitivity analysis showed similar results as our primary analysis. When excluding Yank 2007 from the pooled analysis, the effect estimate increased slightly and the statistical heterogeneity disappeared (RR: 2.03, 95% CI: 1.56 to 2.64, I^2: 0%, Analysis 5.9).

Restricting our analyses to studies assessed as low risk of bias in the comparability criteria or studies performing adjusted regression analyses

The only study investigating estimated treatment effect was assessed as low risk of bias in the comparability of systematic reviews, and we did therefore not perform this sensitivity analysis for estimated treatment effect.

For frequency of statistically favourable results, the only study investigating the outcome performed regression analyses adjusted for methodological quality. The authors assessed methodological quality by using the summary scores from the Oxman and Guyatt index. Our analysis based on this study showed similar results as our primary analysis. The effect estimate indicated no difference in frequency of statistically favourable results between industry and non-industry reviews (OR: 0.99, 95% CI: 0.44 to 2.23, Analysis 5.10). As with our primary analysis, the association was not statistically significant.

For frequency of favourable conclusions, one study was assessed as low risk of bias in the comparability of systematic reviews (Jorgensen 2006) and one study performed regression analyses adjusted for methodological quality (Yank 2007). An analysis based on these studies showed similar results as our primary analysis. The effect estimate indicated that industry reviews more often had favourable conclusions compared to non-industry reviews (OR: 20.28, 95% CI: 0.57 to 719.88, Analysis 5.11). Similar to our main analysis the heterogeneity was substantial (I^2: 68%).

Re-categorising industry reviews into reviews with financial conflicts of interest related to any for-profit organisation or to the manufacturer of the investigated intervention in two separate analyses

We planned to distinguish between financial conflicts of interest related to any for-profit organisation and the manufacturer of the investigated intervention. The two studies that investigated estimated treatment effect and frequency of statistically favourable results did not assess whether financial conflicts of interest were related to the manufacturer or any for-profit organisation. Thus, using unpublished data, we were able to investigate financial conflicts of interest related to any for-profit organisation and the manufacturer for frequency of favourable conclusions.

For frequency of favourable conclusions, we found similar impact from financial conflicts of interest related to any for-profit organisation and the manufacturer. In both cases, the effect estimate decreased slightly compared to our primary analysis (RR: 1.61, 95% CI: 1.16 to 2.24 for manufacturer; RR: 1.75, 95% CI: 1.16 to 2.63 for any for-profit organisation; Analysis 5.12; Analysis 5.13).

Sensitivity analysis for methodological quality (secondary outcome): restricting our analyses to studies assessed as low risk of bias in the comparability criteria

Two of the studies that investigated methodological quality used a matched design and were assessed as having low risk of bias in the comparability criteria (Jorgensen 2006; Lane 2013). Together, these studies provided information on 10 of the 11 dimensions of methodological quality.

Ten analyses based on these two studies showed similar results as our primary analysis. For five quality dimensions, the effect estimate increased; for four dimensions, the effect estimate remained the same; and for one dimension, the effect estimate decreased (Analysis 6.1-Analysis 6.10). In the original analysis, three dimensions were statistically significant. In the sensitivity analyses, only one dimension (interpretation of results in light of risk of bias) was statistically significant (RR: 1.34, 95% CI: 1.03 to 1.75, Analysis 6.7).

CONTRIBUTIONS OF AUTHORS

AL conceived the idea for the study. The protocol was developed by CH, AH, and AL. CH and AL developed the search strategy. CH and KR included studies, and CH and AL extracted data and assessed the risk of bias. CH performed the data analysis, and all authors participated in data interpretation. CH wrote the draft review, and all the co-authors contributed in revising the review.

DECLARATIONS OF INTEREST

The review authors have no relevant interests to declare.

SOURCES OF SUPPORT

Internal sources

- Centre for Evidence-Based Medicine Odense (CEBMO), Odense University Hospital and University of Southern Denmark, Denmark.

  CH, AL, and AH were personally salaried by the institution during the period of this review.
- Nordic Cochrane Centre, Rigshospitalet, Denmark.

  CH and KR were personally salaried by the institution during the period of this review.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included one new subgroup analysis (referred to as a post hoc subgroup analysis): recoding frequency of favourable conclusions into conclusions in favour of the intervention and conclusions recommending the intervention without reservations. We also included five new sensitivity analyses (referred to as post hoc sensitivity analyses): 1) excluding systematic reviews with unclear or undeclared financial conflicts of interest, 2) excluding one atypical included study, 3) re-analysing primary outcomes based on observational studies with either low risk of bias in the comparability of systematic reviews or adjusted regression analyses, 4) testing different definitions of financial conflicts of interest (i.e. related to the manufacturer and any for-profit organisation), and 5) re-analysing secondary outcome (i.e. methodological quality) based on included studies with low risk of bias in the comparability criteria.

We initially graded the included studies as providing low certainty in our assessment of the certainty of the evidence.

INDEX TERMS

Medical Subject Headings (MeSH)

*Conflict of Interest; *Nutritional Status

MeSH check words

Humans

Appendix 4. Publication for sub-study II – Cochrane Database of Systematic Reviews

Sub-study II is reported in two co-publications. The first is published in:

Nejstgaard CH, Bero L, Hróbjartsson A, et al. Conflicts of interest in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: associations with recommendations. *Cochrane Database Syst Rev* 2020; Issue 12:MR000040.

Cochrane Library

Cochrane Database of Systematic Reviews

Conflicts of interest in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: associations with recommendations (Review)

Nejstgaard CH, Bero L, Hróbjartsson A, Jørgensen AW, Jørgensen KJ, Le M, Lundh A

Nejstgaard CH, Bero L, Hróbjartsson A, Jørgensen AW, Jørgensen KJ, Le M, Lundh A.
Conflicts of interest in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: associations with recommendations.
Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: MR000040.
DOI: 10.1002/14651858.MR000040.pub3.

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TABLE OF CONTENTS

[Methodology Review]

Conflicts of interest in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: associations with recommendations

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ABSTRACT

Background

Treatment and diagnostic recommendations are often made in clinical guidelines, reports from advisory committee meetings, opinion pieces such as editorials, and narrative reviews. Quite often, the authors or members of advisory committees have industry ties or particular specialty interests which may impact on which interventions are recommended. Similarly, clinical guidelines and narrative reviews may be funded by industry sources resulting in conflicts of interest.

Objectives

To investigate to what degree financial and non-financial conflicts of interest are associated with favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews.

Search methods

We searched PubMed, Embase, and the Cochrane Methodology Register for studies published up to February 2020. We also searched reference lists of included studies, Web of Science for studies citing the included studies, and grey literature sources.

Selection criteria

We included studies comparing the association between conflicts of interest and favourable recommendations of drugs or devices (e.g. recommending a particular drug) in clinical guidelines, advisory committee reports, opinion pieces, or narrative reviews.

Data collection and analysis

Two review authors independently included studies, extracted data, and assessed risk of bias. When a meta-analysis was considered meaningful to synthesise our findings, we used random-effects models to estimate risk ratios (RRs) with 95% confidence intervals (CIs), with RR > 1 indicating that documents (e.g. clinical guidelines) with conflicts of interest more often had favourable recommendations. We analysed associations for financial and non-financial conflicts of interest separately, and analysed the four types of documents both separately (pre-planned analyses) and combined (post hoc analysis).

Main results

We included 21 studies analysing 106 clinical guidelines, 1809 advisory committee reports, 340 opinion pieces, and 497 narrative reviews. We received unpublished data from 11 studies; eight full data sets and three summary data sets. Fifteen studies had a risk of confounding, as they compared documents that may differ in other aspects than conflicts of interest (e.g. documents on different drugs used for different populations). The associations between financial conflicts of interest and favourable recommendations were: clinical guidelines, RR: 1.26, 95% CI: 0.93 to 1.69 (four studies of 86 clinical guidelines); advisory committee reports, RR: 1.20, 95% CI: 0.99 to 1.45 (four studies of 629 advisory committee reports); opinion pieces, RR: 2.62, 95% CI: 0.91 to 7.55 (four studies of 284 opinion pieces); and narrative reviews, RR: 1.20, 95% CI: 0.97 to 1.49 (four studies of 457 narrative reviews). An analysis combining all four document types supported these findings (RR: 1.26, 95% CI: 1.09 to 1.44).

One study investigating specialty interests found that the association between including radiologist guideline authors and recommending routine breast cancer screening was RR: 2.10, 95% CI: 0.92 to 4.77 (12 clinical guidelines).

Authors' conclusions

We interpret our findings to indicate that financial conflicts of interest are associated with favourable recommendations of drugs and devices in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. However, we also stress risk of confounding in the included studies and the statistical imprecision of individual analyses of each document type. It is not certain whether non-financial conflicts of interest impact on recommendations.

PLAIN LANGUAGE SUMMARY

Conflicts of interest and recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews

Which treatments and diagnostic tests doctors offer to their patients are often based on recommendations expressed in a variety of documents. A common example is clinical guidelines, which are statements providing recommendations on how to diagnose and treat patients on the basis of the best available evidence. The treatments that may be offered to patients are also influenced by which drugs are recommended for approval by drug advisory committees at regulatory drug agencies such as the US Food and Drug Administration (FDA). Finally, doctors may also be influenced by recommendations expressed in opinion pieces, such as editorials, or in narrative review papers in medical journals.

Quite often, publications expressing clinical recommendations are written by authors with conflicts of interest related to a specific product, for example when the author acts as a consultant for the company producing the treatment of interest. Such conflicts of interest may impact on the recommendations made. Similarly, authors may have so-called non-financial conflicts of interest such as belonging to a specific profession, for example being an orthopaedic surgeon, which may influence whether a specific intervention is preferred over another. This Cochrane Methodology Review investigated how financial and non-financial conflicts of interest are associated with the recommendations made in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews.

We included 21 studies and we interpreted our findings to indicate that financial conflicts of interest are associated with favourable recommendations in these documents, although there is some uncertainty around the size of the effect. This means that when such publications are written by authors with financial conflicts of interest, they more often have favourable recommendations than publications written by authors without conflicts of interest. Only a single study investigated the impact of non-financial conflicts of interest in clinical guidelines and the results were uncertain, but indicated a similar direction of effect.

We suggest that patients, doctors, and healthcare decision makers primarily use clinical guidelines, opinion pieces, and narrative reviews that have been written by authors without financial conflicts of interest. If that is not possible, users should read and interpret the publications with caution. Furthermore, our findings suggest that if committee members are asked to vote on the recommendation of a drug, they may be more likely to vote in favour of the drug when they have financial conflicts of interest.

BACKGROUND

Recommendations of treatment and diagnostic approaches impact on patient care, especially if they are written by "key opinion leaders" or originate from healthcare authorities. Recommendations may appear in multiple types of documents, for example in clinical guidelines and advisory committee reports (which could include records from meetings in regulatory drug advisory committees or hospital drug and therapeutics committees) as well as in opinion pieces such as editorials, and in narrative reviews.

Quite often, publications with clinical recommendations are written by authors with conflicts of interest related to the drug or device industry. For example, in a sample of 45 clinical guidelines written by 254 authors, Bindslev and colleagues found that 135 (53%) authors had financial conflicts of interest (Bindslev 2013). Similarly, studies report that narrative reviews, editorials and commentaries often (31%) had at least one author with conflicts of interest (Grundy 2018), and around a quarter of committee meetings at the US Food and Drug Administration (FDA) included at least one voting member with financial conflicts of interest (Xu 2017).

Authors may also have non-financial conflicts of interest. For example, if authors of a guideline were also authors of some of the included studies on which recommendations in a guideline were based, the authors may be more likely to favour the interventions that they previously studied (Akl 2014). Whereas financial conflicts of interest are relatively simple to characterise (i.e. any financial relationship with a party with an interest in the direction of a recommendation), it is more unclear and debated which interests and relationships constitute a non-financial conflict of interest and whether the term is appropriate (Bero 2016). This lack of consensus regarding non-financial conflicts of interest is also reflected in journal disclosure policies. Shawwa and colleagues found that only 57% of core clinical journals specifically required disclosure of non-financial conflicts of interest, and that there was large variation in how journals defined such conflicts (Shawwa 2016).

Numerous studies have investigated the impact of financial conflicts of interest on the interpretation of the results of primary research studies, mainly clinical trials. An updated Cochrane Methodology Review reported an association between industry funding and favourable conclusions in primary research studies (Lundh 2017). This association has been attributed to various factors, including the sponsor's influence on framing the question, study design, and reporting of results (Bero 1996; Bero 2007; Fabbri 2018). Similarly, another Cochrane Methodology Review reported an association between financial conflicts of interest and favourable conclusions in systematic reviews (Hansen 2019a). In contrast, few studies have investigated the association between conflicts of interest and favourable recommendations in clinical guidelines (Norris 2012), advisory committee reports (Pham-Kanter 2014), opinion pieces (Bariani 2013), and narrative reviews (Dunn 2016). Furthermore, the evidence from such studies has to our knowledge not previously been synthesised in a methodological systematic review. This review fills that gap and is based on the previously published protocol (Hansen 2019b).

How these methods might work

Financial conflicts of interest such as honoraria, consultancies, grants, or advisory board membership can provide a substantial income for physicians and academic researchers. Such relationships may therefore affect how the benefits and harms of the companies' products are perceived by authors and thereby whether they are recommended in publications by the authors. Similarly, non-financial interests, such as authors' professional affiliations and personal relationships, may influence the recommendation of a particular intervention.

In contrast to primary research papers and systematic reviews, clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews typically provide specific recommendations concerning treatments and diagnostics. However, the methodological rigour behind such recommendations differs between the types of publications. Clinical guidelines are increasingly based on systematic searches of existing evidence and may follow standardised procedures for grading evidence and recommendations (Guyatt 2011). In contrast, authors of opinion pieces are free to selectively cite studies and interpret the evidence, and editorials often focus on results from a single primary study. Clinical guidelines are also typically written by a broad group of authors who may have differing viewpoints, whereas opinion pieces are often written by single authors. Thus, clinical guidelines may be less susceptible to influence from conflicts of interest compared to opinion pieces. Committee reports and narrative reviews are conducted using more or less systematic procedures, but also involve subjective elements and may therefore be more susceptible to influence from conflicts of interest than clinical guidelines, but less than opinion pieces.

Why it is important to do this review

Recommendations in journal papers or guidelines and decisions about which interventions are approved by regulatory authorities have substantial impact on the interventions offered to patients. It is therefore important that such recommendations are evidence-based and as little influenced by conflicts of interest as possible. Individual studies have investigated the associations between conflicts of interest and favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews, but these studies differ in methods and conclusions. Despite conflicts of interest being recognised as an important source of influence on clinical recommendations, these studies have, to our knowledge, not previously been summarised in a systematic review. Findings from this review may provide patients, clinicians, and policymakers with guidance on how to interpret recommendations in light of conflicts of interest and may assist journal editors, guideline issuing organisations, and public authorities with managing such conflicts.

OBJECTIVES

Our objectives were to investigate to what degree financial and non-financial conflicts of interests are associated with favourable recommendations in:

- clinical guidelines;
- advisory committee reports (e.g. records from the Food and Drug Administration (FDA) advisory committee on oncological drugs or hospital drug and therapeutics committees);

- opinion pieces (e.g. editorials and commentaries);
- narrative reviews.

Terminology

We used the definitions below. All definitions are described in more detail in Appendix 1.

Conflicts of interest: any financial or non-financial conflicts of interest as specified below.

Financial conflicts of interest: any funding of clinical guidelines, opinion pieces, or narrative reviews by drug or device companies or any authors or committee members with ties to such companies (e.g. advisory board membership).

Non-financial conflicts of interest: any relationships that differ from what is typically regarded as financial conflicts of interest (i.e. relationships with the drug or device industry). Regardless of the definitions used by the authors of the included studies, we do not focus on studies investigating beliefs (e.g. political or religious), personal experience (e.g. abuse or trauma), or institutional conflicts of interest (Bero 2016).

Drugs: medications that require approval from a regulatory authority.

Devices: instruments used in diagnosis, treatment, or prevention of disease (FDA 2017). This term also includes medical imaging technologies.

Clinical guidelines: *"Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances"* (Institute of Medicine 1990).

Advisory committee reports: reports from meetings held in committees, boards, councils, or similar formalised groups that are established to advise an organisation and provide a recommendation concerning an intervention (e.g. the FDA advisory committee on oncological drugs).

Opinion pieces: publications that are not research studies in which an author expresses a personal opinion about a specific intervention (e.g. editorials, commentaries, and letters to the editor).

Narrative reviews: literature reviews without a systematic search of the literature with clear eligibility criteria.

Documents: clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews.

METHODS

Criteria for considering studies for this review

Types of studies

We included published and unpublished studies of any design (e.g. cross-sectional studies) that assessed the association between conflicts of interest and favourable recommendations made in clinical guidelines, advisory committee reports, opinion pieces, or narrative reviews concerning drug or device interventions (which include diagnostic tests for the purposes of this review, see Appendix 1).

Studies in all languages were eligible.

Types of data

We included studies with dichotomous (e.g. favourable or unfavourable recommendations) or continuous data (e.g. percentages) on the association between conflicts of interest and recommendations in favour of the intervention in question.

Types of methods

We included studies that investigated documents with conflicts of interest versus documents without conflicts of interest. For financial conflicts of interest, we included studies regardless of the type of financial conflict. For non-financial conflicts of interest, we included studies on intellectual, academic, professional, or specialty interests, and personal or professional relationships.

We excluded studies concerning:

- financial conflicts of interest not related to the drug or device industry (e.g. tobacco or nutrition industry);
- beliefs (e.g. religious) or personal experiences (e.g. suffering from the medical condition), even if the original authors defined these as non-financial conflicts of interest;
- membership of certain groups (e.g. gender or ethnicity), even if the original authors defined this as non-financial conflicts of interest;
- both financial and non-financial conflicts of interest at the level of an institution;
- conflicts of interest related to reports from scientific grant committees.

Types of outcome measures

Primary outcomes

Our primary outcome was the type of recommendation in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. We defined 'favourable recommendations' according to the definitions used by the authors of the included studies.

Search methods for identification of studies

Electronic searches

We searched PubMed, Embase, and the Cochrane Methodology Register (up to February 2020). We searched Web of Science (up to March 2020) for studies that cited any of the included studies.

Search strategy

Our search strategy was based on search terms used in a PubMed search from two previous Cochrane Methodology Reviews on financial conflicts of interest in primary research studies and systematic reviews (Lundh 2017; Hansen 2019a), and tailored it for this review (Appendix 2). The PubMed strategy was adapted for Embase and The Cochrane Methodology Register. All search strategies were developed in collaboration with information specialists.

Searching other resources

Grey literature

Our electronic search in the Cochrane Methodology Register identified relevant grey literature because the database includes conference abstracts. Additionally, we searched for conference abstracts from Peer Review Congresses (American Medical Association 2017), Cochrane Colloquia (Cochrane Community 2017), and Evidence Live (Centre for Evidence-Based Medicine 2017) (search of all conferences up to February 2020). We searched PROSPERO (up to February 2020) for registered systematic reviews and the ProQuest database (up to February 2020) for dissertations and theses.

Additional searches

We used Google Scholar (up to March 2020) to search for additional eligible studies. We based our search on core search terms from the search strategy defined in Appendix 2 and screened the first 20 records for each search. We searched PubMed for publications by the first and last author of the included studies (up to March 2020). Other sources of data included the files of the authors of this review and checking reference lists of included studies (Horsley 2011).

Data collection and analysis

Selection of studies

One review author (CHN) screened titles and abstracts of all retrieved records for obvious exclusions. Two review authors (CHN and either AWJ or AL) independently assessed potentially eligible studies based on full text. We resolved any disagreements by discussion and used arbitration by a third review author (AL or AH) when needed.

Reasons for exclusion of studies are described in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors (CHN and either AWJ, ML, or AL) independently extracted data from included studies. We resolved any differences in data extraction by discussion and used arbitration by a third review author (AH or AL) when needed.

We extracted data on basic characteristics of the included studies and data on the association between conflicts of interest and favourable recommendations. We extracted data for documents with and without conflicts of interest based on the definitions used by the authors of the included studies. When reported, we also extracted effect measures and confidence intervals (CIs) or the raw data to calculate them. We also extracted information on funding sources and conflicts of interest disclosures of authors of the included studies. The full plan for data extraction is reported in Appendix 3.

Assessment of risk of bias in included studies

As there are no published assessment tools for investigating bias in these types of studies, we developed our own criteria based on those used in previous Cochrane Methodology Reviews on financial conflicts of interest in primary research studies and systematic reviews (Lundh 2017; Hansen 2019a). In accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020) we use the term 'risk of bias' in contrast to 'methodological quality'. However, we recognise that some of the included items are more related to methodological quality than risk of bias and that inadequate methodological quality (e.g. coding of conflicts of interest information by a single author) is not necessarily biased. In our risk of bias assessment we therefore focused on whether study methodology was appropriate (i.e. appropriate methodology resulted in low risk of bias).

Two review authors (CHN and either AWJ, ML, or AL) independently assessed included studies for risk of bias. We resolved any disagreements by discussion and used arbitration by a third review author (AL or AH) when needed. We used the following criteria.

- Whether there was a risk of bias in the inclusion of documents (low risk of bias may, for example, include reporting of clear inclusion criteria with two or more assessors independently selecting documents).
- Whether there was a risk of bias in the coding of conflicts of interest (low risk of bias may, for example, include coding done by two or more assessors based on multiple sources of information).
- Whether there was a risk of bias in the coding of recommendations (low risk of bias may, for example, include coding done by two or more assessors blinded to the status of conflicts of interest).
- Whether there was a risk of confounding (low risk of confounding may, for example, include documents with and without conflicts of interest discussing the same treatment used in similar groups of patients). The documents included in a study may differ on key aspects (e.g. in a sample of clinical guidelines, the guidelines may differ in relation to types of patients and conditions, interventions, the quality of the underlying evidence, and the quality of the guidelines), which could potentially confound the association between conflicts of interest and favourable recommendations.

In assessing risk of bias, our primary aim was to differentiate between studies with higher and lower risk of bias. Thus, we coded, by default, a study as low risk of bias if all criteria were assessed as low risk of bias; otherwise, we coded it as high risk of bias.

Dealing with missing data

We contacted authors of the included studies in an attempt to obtain unpublished data, to clarify issues on our 'Risk of bias' assessments, or to receive copies of unpublished protocols (Appendix 4). When we received unpublished data, we analysed the data according to the methods used in the original studies.

We included one study that investigated a mixture of opinion pieces and narrative reviews, but which did not report results stratified by document type. However, coding of financial conflicts of interest and recommendations were reported separately for each document (Hayes 2019). As the type of document (e.g. opinion piece) was not coded in the original study, two review authors (CHN and AL) independently coded the type of documents to enable inclusion in our meta-analyses.

Assessment of heterogeneity

Statistical heterogeneity was described using the I^2 statistic.

To further address statistical heterogeneity, we calculated prediction intervals for our primary analyses. We only calculated prediction intervals when at least four studies were included in the pooled analysis, because intervals will be imprecise when the effect estimates are based on only a few studies. A prediction interval presents the expected range of true effects in similar studies, is not influenced by sample size, and shows whether the study effects are dispersed over a wide range (IntHout 2016). A prediction interval thereby shows the range of risk ratios (RRs) that can be expected from similar studies, and, thus, a broad prediction interval indicates heterogeneity and uncertainty. To calculate prediction intervals, we used the formula presented by Riley and colleagues (Riley 2011) (Appendix 5).

Data synthesis

Data management of individual studies

In our primary analyses, we used the definitions and coding of recommendations and conflicts of interest used by the authors of the included studies. If an ordinal scale was used to grade recommendations (e.g. highly positive, positive, neutral, negative, and highly negative), we recoded recommendations into two categories (i.e. favourable versus neutral/unfavourable recommendations).

If the sample of documents included in a study contained a mixture of types of documents (e.g. both clinical guidelines and research papers), we only included the study in our pooled analyses if we could get separate data for the types of documents relevant for our review.

In our analyses on clinical guidelines, we included one study that investigated 13 guidelines that each included recommendations on 24 different drugs (Norris 2013). To allow for this type of panel data, we used Poisson Generalised Estimating Equations to calculate effect estimates we could include in our pooled analyses (Lumley 2006).

In our analyses on advisory committee reports, we included studies with two types of analysis units: committee members and their individual votes (individual level) and committee reports and the overall voting outcome (meeting level). In our primary analysis, we analysed data on meeting level as this level of analysis was most comparable to recommendations in the other types of documents (e.g. clinical guidelines).

In some cases the same document was included in two separate studies. When we had access to unpublished data it was possible to remove the duplicate documents and we chose to remove it from the study with the latest publication date. We included two studies that investigated some of the same FDA advisory committee reports (Ackerley 2009; Lurie 2006) and removed duplicates from the study by Ackerley and colleagues (Ackerley 2009). We included two studies that investigated editorials published in some of the same oncology journals in overlapping time periods (Bariani 2013; Lerner 2012) and removed duplicates from the study by Bariani and colleagues (Bariani 2013).

Primary analysis

Due to expected clinical and methodological heterogeneity among the included studies, we used inverse variance random-effects models to estimate RRs with 95% CIs. We compared recommendations between documents with and without conflicts of interest and ensured uniform directionality so RR > 1 indicated that documents with conflicts of interest more often had favourable recommendations than documents without conflicts of interest. We analysed financial and non-financial conflicts of interests separately, and analysed clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews separately.

Using the methods for calculating a Number Needed to Treat, we calculated a Number Needed to Read for each document type (Appendix 6) (Schünemann 2020). We defined Number Needed to Read as the expected number of documents with conflicts of interest needed to be read rather than documents without conflicts of interest for one additional document having a favourable recommendation. As describing the 95% CI is difficult for Number Needed to Read when the CI of the RR crosses the boundary of no difference (Altman 1998), we report the 95% CI of the Number Needed to Read in Appendix 6.

Secondary analyses

We analysed advisory committee reports on an individual level.

In a post-hoc analysis, we combined all four types of documents (i.e. clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews) in an analysis of financial conflicts of interest.

Subgroup analysis and investigation of heterogeneity

We planned to conduct the following pre-planned subgroup analyses for our primary analyses for all document types (Appendix 7):

- Documents stratified by different types of financial conflicts of interest (e.g. funding, investigator, author grants, honorarium, consulting, speaker's bureau, equity/stock, gifts)
- Studies assessed as high risk of bias versus studies assessed as low risk of bias

We planned to conduct the following pre-planned subgroup analysis for our primary analysis on clinical guidelines only:

- Clinical guidelines developed using standardised methods (e.g. GRADE (Guyatt 2011) or USPSTF (U.S. Preventive Services Task Force 2015)) versus clinical guidelines not developed using standardised methods. For the stratification of documents, we relied on the coding done by the authors of the included studies

In addition, we conducted the following post-hoc subgroup analyses for our primary analyses.

- Documents stratified by degree of financial conflicts of interest: we compared major financial conflicts of interest (defined as at least half of the authors/committee members having financial conflicts of interest) with minor financial conflicts of interest (defined as less than half of the authors/committee members with financial conflicts of interest). The purpose of this subgroup analysis was to investigate a potential dose-response relationship between financial conflicts of interest and recommendations.

We only carried out the subgroup analyses when we had sufficient data (i.e. at least five documents in the groups with and without conflicts of interest in the included studies combined).

Sensitivity analysis

We planned to conduct the following pre-planned sensitivity analyses for our primary analyses (Appendix 8).

- Excluding documents with unclear or undisclosed conflicts of interest.
- Excluding documents with neutral recommendations.
- Excluding all studies which disclosed a relevant conflict of interest. For example, if one of the included studies was funded by a drug company, we excluded the study and re-analysed our data.
- Re-analysing our primary analyses using a fixed-effect model.

In addition, we conducted the following post-hoc sensitivity analyses for our primary analyses.

- Re-categorising documents with financial conflicts of interest into documents with financial conflicts of interest related to the manufacturer of the drug or device of interest or to any for-profit organisation in two separate analyses.

We only carried out the sensitivity analyses when we had sufficient data (i.e. at least five documents in the groups with and without conflicts of interest in the included studies combined).

We conducted all analyses in Review Manager (RevMan 5.4) and Stata 15.

Assessment of the certainty of the evidence

Based on prior experience, using formal systems such as GRADE for assessing the certainty of evidence from methodological studies is challenging. We therefore focused on interpreting our results in the context of the statistical precision of our estimates (i.e. width of CIs) and risk of confounding. In Appendix 9, we report GRADE assessments employing both an approach similar to observational intervention studies and to prognostic studies (Guyatt 2008; Foroutan 2020).

RESULTS

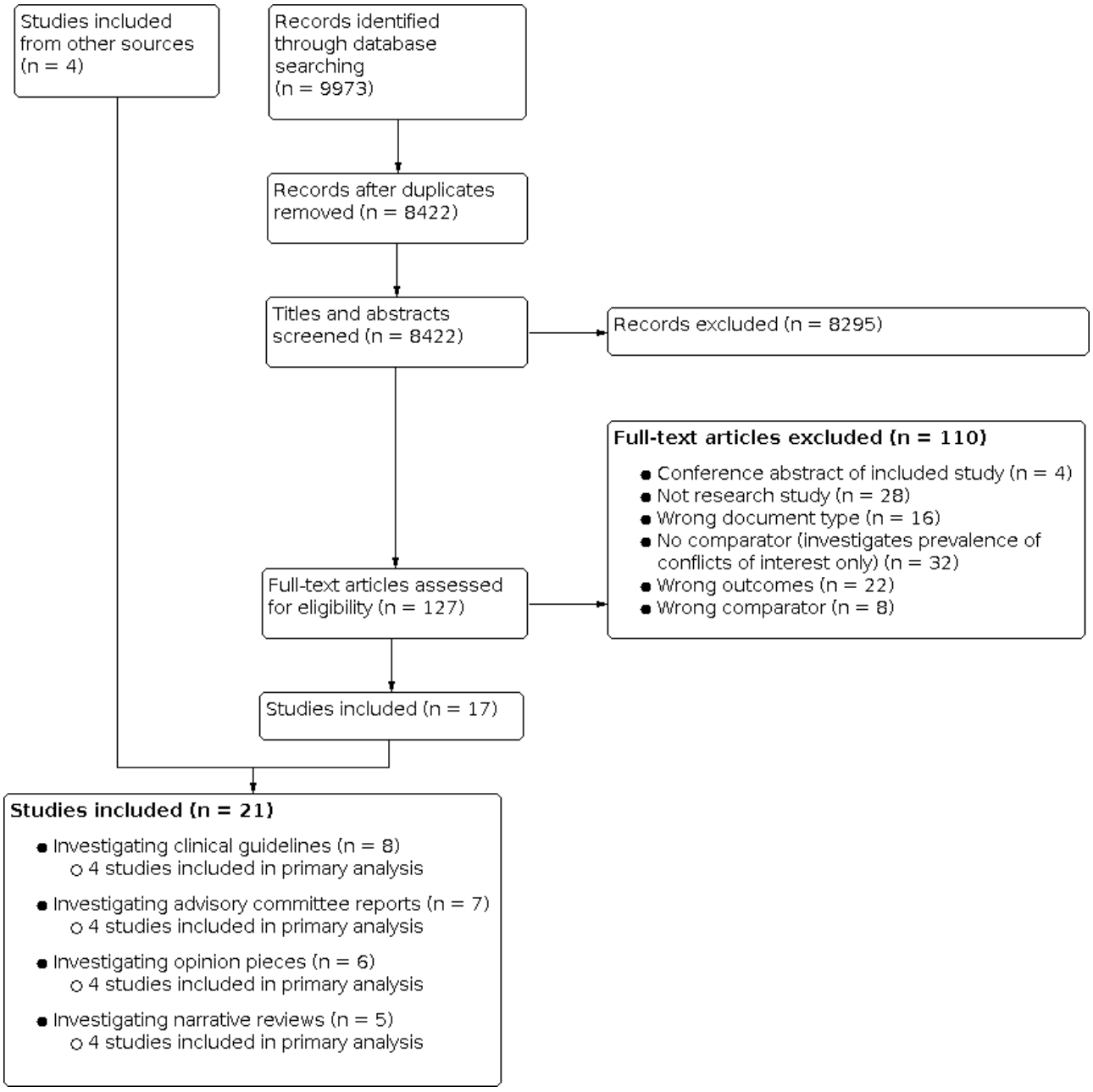
Description of studies

See: Characteristics of included studies.

Results of the search

See: Figure 1

Figure 1. Study flow diagram.



In total, 9973 records were identified through our database searches. After removing duplicates, we screened 8422 records based on titles and abstracts and assessed 127 full-text papers for inclusion. In total, we included 21 studies. We did not identify any unpublished studies or protocols for planned studies.

Included studies

See: Characteristics of included studies.

The 21 studies were published between 1998 and 2019. Eight studies investigated clinical guidelines (median number of clinical guidelines: nine, range: 2 to 50), seven studies investigated FDA drug and/or device advisory committee reports (median number of advisory committee reports: 376, range: 79 to 416), six studies investigated opinion pieces (editorials, commentaries, and letters; median number of opinion pieces: 44, range: 8 to 131), and five studies investigated narrative reviews (median number of narrative reviews: 84, range: 7 to 213). Sixteen studies investigated documents on drugs, three studies investigated documents on devices, and two studies investigated documents on both drugs and devices. Twenty studies only investigated financial conflicts of interest and one study investigated both financial conflicts of interest and specialty affiliations among guideline authors (i.e. non-financial conflicts of interest). None of the included studies reported industry funding, but six studies did not report funding information. Seven of the included studies investigating documents with and without financial conflicts of interest were

conducted by authors who themselves had financial conflicts of interest.

We received unpublished data from 11 studies. In eight cases, we obtained full unpublished data sets (Ackerley 2009; Bariani 2013; Dunn 2016; Hartog 2012; Lerner 2012; Lurie 2006; Wang 2010; Zhang 2019), and in three cases we obtained additional summary data (Pham-Kanter 2014; Tibau 2015; Tibau 2016).

Risk of bias in included studies

See: Figure 2; Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

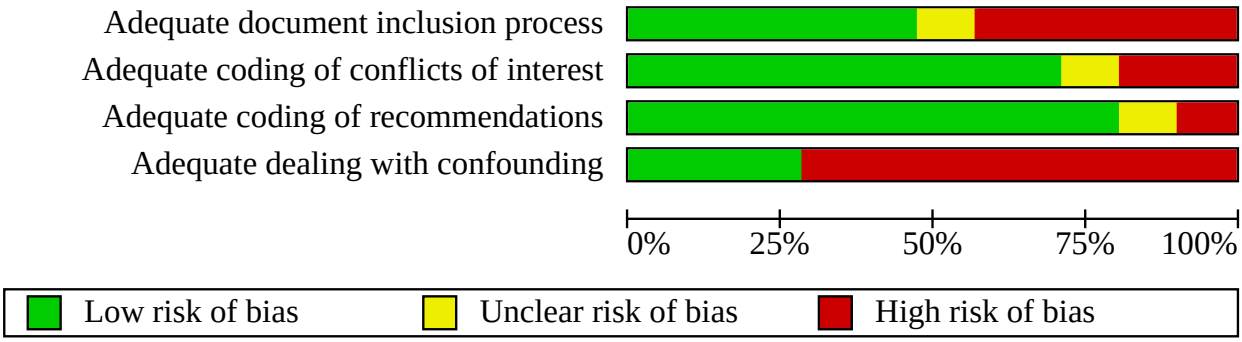
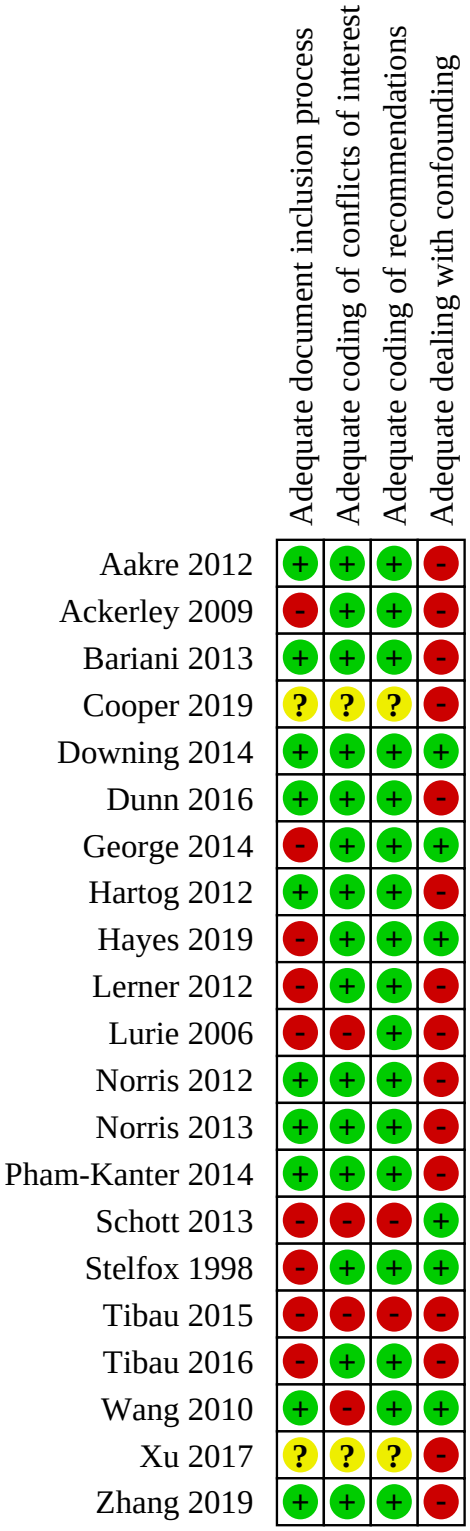


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



We assessed 20 studies as overall high risk of bias and one study as low risk of bias. Around half of the included studies had low risk of bias in the document inclusion process (n = 10) and the majority had low risk of bias in the coding of conflicts of interest (n = 15) and recommendations (n = 17). We assessed six studies to be low risk of confounding and 15 to be high risk of confounding, because they included documents of different topics (e.g. various cancer drugs for different indications), or included documents on the same drug used for different indications (e.g. antidiabetic drugs used in adults, children, or pregnant women).

We found no published protocols and only received unpublished protocols for two studies (Downing 2014; Lurie 2006). We found no discrepancies between outcomes in these protocols and study publications. Nine of 21 author teams replied that no protocol existed for their study, and two author teams supplied us with reports that we did not consider to be protocols (Appendix 4).

Effect of methods

Financial conflicts of interest: differences in recommendations

Clinical guidelines

Eight studies investigated a total of 106 clinical guidelines and data from four of these studies including 86 clinical guidelines could be used in our pooled primary analysis (Aakre 2012; Norris 2013; Tibau 2015; Wang 2010). The association between financial conflicts of interest and favourable recommendations in clinical guidelines was RR: 1.26, 95% CI: 0.93 to 1.69, I^2: 0% (Analysis 1.1). The Number Needed to Read for clinical guidelines was 9.1 (Appendix 6).

The prediction interval for the RR was 0.65 to 2.43 (Appendix 5). Thus, one can expect that clinical guidelines with financial conflicts of interest more often have favourable recommendations compared with clinical guidelines without financial conflicts of interest, but for an individual study of clinical guidelines the association may be reversed.

Four included studies did not report data in a way that enabled us to include them in our pooled analysis. Two studies each investigated one clinical guideline with financial conflicts of interest and one without. In both of these studies the clinical guidelines with financial conflicts of interest had a favourable recommendation, whereas the clinical guidelines without had a unfavourable recommendation (George 2014; Schott 2013). One study investigated 12 clinical guidelines, but only reported the percentage of authors with financial conflicts of interest in each guideline. Three out of eight clinical guidelines with favourable recommendations included authors with financial conflicts of interest (prevalence from 12% to 53%), and two out of four clinical guidelines with unfavourable recommendations included authors with financial conflicts of interest (prevalence 9% and 11%) (Norris 2012). The remaining study investigated a mixture of four clinical guidelines, 23 editorials and commentaries, and 40 reviews (mainly narrative) commenting on a randomised trial on fenofibrate use. The authors found that documents written by authors with conflicts of interest more often recommended fibrate use (RR: 1.69, 95% CI: 1.07 to 2.67) (Downing 2014).

One of the studies included in our pooled analysis adjusted for the specific drug that was evaluated in the guideline (thereby reducing the risk of confounding). The authors found no association between financial conflicts of interest and recommendations of a drug, but did not report any effect estimates in the study publication (Norris 2013).

Advisory committee reports

Seven studies investigated a total of 1809 advisory committee reports and data from five studies could be included in our pooled analyses (Ackerley 2009; Lurie 2006; Pham-Kanter 2014; Tibau 2016; Zhang 2019). In our primary analysis, including four studies of 629 advisory committee reports, the association between any advisory committee report with members with financial conflicts of interest and voting in favour of approving a drug or device was RR: 1.20, 95% CI: 0.99 to 1.45, I^2: 24% (Analysis 1.1). The Number Needed to Read for advisory committee reports was 7.7 (Appendix 6). In our secondary analysis, including three studies of 17,816 votes, the association between financial conflicts of interest of individual advisory committee members and voting in favour of approving a drug or device was RR: 1.14, 95% CI: 1.07 to 1.21, I^2: 35% (Analysis 2.1).

The prediction interval for the RR was 0.66 to 2.19 (Appendix 5). Thus, one can expect that advisory committee reports with financial conflicts of interest more often have favourable recommendations compared with advisory committee reports without financial conflicts of interest, but for an individual study of advisory committee reports the association may be reversed.

Two included studies did not report data in a way that enabled us to include them in our pooled analysis. One of the studies investigated the association between conflicts of interest and voting behaviour of 1482 members from 385 advisory committee reports. The authors reported that they found no association between conflicts of interest and voting outcome among members, but did not report any effect estimates on the association (Xu 2017). The remaining study investigated 1483 members from 416 advisory committee reports. The authors found that committee members with financial conflicts of interest had 14.3% greater odds of voting for approval compared with committee members without financial conflicts of interest. However, the estimate was not statistically significant (P value: 0.12) (Cooper 2019).

One of the studies included in the pooled analysis adjusted for medical product and advisory committee meeting characteristics (thereby reducing the risk of confounding) and the association between financial conflicts of interest related to the manufacturing company and favourable recommendations was odds ratio (OR): 4.66, 95% CI: 0.64 to 33.6 (Zhang 2019).

Opinion pieces

Six studies investigated a total of 340 opinion pieces (Bariani 2013; Downing 2014; Hayes 2019; Lerner 2012; Stelfox 1998; Wang 2010) and data from four of these studies including 284 opinion pieces could be included in our pooled primary analysis. The association between financial conflicts of interest and favourable recommendations in opinion pieces was RR: 2.62, 95% CI: 0.91 to 7.55, I^2: 78% (Analysis 1.1). The Number Needed to Read for opinion pieces was 2.3 (Appendix 6).

The prediction interval for the RR was 0.03 to 220.56 (Appendix 5). Thus, one can expect that opinion pieces with financial conflicts of interest more often have favourable recommendations compared

with opinion pieces without financial conflicts of interest, but for an individual study of opinion pieces the association may be reversed.

Two included studies did not report data in a way that enabled us to include them in our pooled analysis. One study investigated a mixture of 69 authors of original research papers, review articles, and letters. The study found that authors with financial conflicts of interest related to the drug manufacturer more often had favourable recommendations than authors without financial conflicts of interest (RR: 13.91, 95% CI: 1.99 to 96.97) (Stelfox 1998). The remaining study investigated a mixture of four clinical guidelines, 23 editorials and commentaries, and 40 reviews (mainly narrative) and found that documents written by authors with conflicts of interest more often recommended fibrate use (RR: 1.69, 95% CI: 1.07 to 2.67) (Downing 2014).

One of the studies included in the pooled analysis adjusted for characteristics of the trial (e.g. type of intervention and trial conclusion) the editorial commented on (thereby reducing the risk of confounding) and the association between financial conflicts of interest and favourable recommendations was OR: 1.39, 95% CI: 0.52 to 3.70 (Bariani 2013).

Narrative reviews

Five studies investigated a total of 497 narrative reviews and data from four of these studies investigating 457 narrative reviews could be included in our pooled primary analysis (Dunn 2016; Hartog 2012; Hayes 2019; Wang 2010). The association between financial conflicts of interest and favourable recommendations in narrative reviews was RR: 1.20, 95% CI: 0.97 to 1.49, I^2: 39% (Analysis 1.1). The Number Needed to Read for narrative reviews was 8.3 (Appendix 6).

The prediction interval for the RR of was 0.56 to 2.59 (Appendix 5). Thus, one can expect that narrative reviews with financial conflicts of interest more often have favourable recommendations compared with narrative reviews without financial conflicts of interest, but for an individual study of narrative reviews the association may be reversed.

One included study did not report data in a way that enabled us to include it in our pooled analysis. The study investigated a mixture of four clinical guidelines, 23 editorials and commentaries, and 40 reviews (mainly narrative). The authors found that documents written by authors with conflicts of interest more often recommended fibrate use (RR: 1.69, 95% CI: 1.07 to 2.67) (Downing 2014).

Post-hoc analysis combining all document types. Financial conflicts of interest: differences in recommendations

In a post-hoc analysis, we combined all types of documents and the association between financial conflicts of interest and favourable recommendations was RR: 1.26, 95% CI: 1.09 to 1.44, I^2: 38% (Analysis 1.1). The Number Needed to Read was 7.1 (Appendix 6).

The prediction interval for the RR was 0.88 to 1.80 (Appendix 5). Thus, one can expect that documents with financial conflicts of interest more often have favourable recommendations compared with documents without financial conflicts of interest, but for an individual study the association may be reversed.

Non-financial conflicts of interest: differences in recommendations

One study investigated specialty interests and included 12 clinical guidelines on mammography screening. The focus was whether the guideline author team included a radiologist (Norris 2012). In our analysis based on this study, the association between having radiologists in the guideline panel and recommending routine screening for breast cancer was RR: 2.10, 95% CI: 0.92 to 4.77. The Number Needed to Read was 2.1 (Appendix 6).

Subgroup and sensitivity analyses

We found no differences in effect estimates in relation to the type of financial conflicts of interest or the degree of financial conflicts of interest for any document type. We were not able to conduct the planned subgroup analyses in relation to risk of bias in included studies for all document types and development methods for clinical guidelines (Appendix 7).

Sensitivity analyses were robust in 20 of 23 analyses of financial conflicts of interest and in three analyses the association between financial conflicts of interest and favourable recommendations became stronger (Appendix 8).

Assessment of certainty of the evidence

The evidence on financial conflicts of interest in all four types of documents and non-financial conflicts of interest in clinical guidelines should be interpreted with some caution as the majority of the studies (15 out of 21) had a risk of confounding and all effect estimates of the primary analyses lacked statistical precision. Using the GRADE approaches for intervention and prognostic studies resulted in low to very low certainty of the evidence depending on type of document and the GRADE system used (Appendix 9).

DISCUSSION

Summary of main results

We included 21 studies investigating 106 clinical guidelines, 1809 advisory committee reports, 340 opinion pieces, and 497 narrative reviews. We found an association between financial conflicts of interest and favourable recommendations of drugs and devices in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. Our four primary analyses pointed in a consistent direction and provided a fairly similar magnitude of effect, but each with varying degrees of statistical precision. Our post hoc analysis combining all document types confirmed these findings and increased the statistical precision. Our findings on the impact of non-financial conflicts of interest on recommendations were limited to evidence from a single study of breast cancer screening guidelines with involvement of radiologist authors, with statistically imprecise results. It is therefore uncertain whether specialty interests or other types of non-financial conflicts of interest impact on recommendations.

Quality of the evidence

All but one of the included studies were assessed as having high risk of bias, mainly due to a high risk of confounding. Documents differed in other aspects than conflicts of interest (e.g. they investigated different drugs used for different patient groups) which could have introduced confounding. For example, if a study included editorials in oncology commenting on numerous drugs. If some drugs are more likely to have editorials written by authors with conflicts of interest (e.g. developed by major drug companies),

and if such drugs are more likely to have favourable trial results (i.e. thereby receiving a favourable recommendation in an editorial), this could confound the association between financial conflicts of interest and favourable recommendations.

Strengths and limitations

A major strength of our study is the inclusion of unpublished data from 11 of 21 studies. We retrieved eight full datasets and unpublished summary data for three additional studies which enabled us to ensure high data quality and to conduct comprehensive analyses thereby increasing statistical precision and minimising reporting bias. Furthermore, we did a thorough search for grey literature and attempted to identify published and unpublished protocols. We only obtained two protocols (Downing 2014; Lurie 2006) and a comparison of outcomes in the protocols with outcomes in the study publications gave no indication of selective outcome reporting.

However, six of 21 included studies were reported in a format that did not allow inclusion in meta-analysis. Four of these studies reported results similar to our meta-analysis. Two of the four studies combined different types of documents without stratifying results, with estimates RR: 1.69, 95% CI: 1.07 to 2.67 and RR: 13.91, 95% CI: 1.99 to 96.97) in line with our primary analysis (Downing 2014; Stelfox 1998). The other two of the four studies sampled a single pair of clinical guidelines with and without financial conflicts of interest and in both cases guidelines with conflicts were favourable (George 2014; Schott 2013). The last two of the six studies (29% of all documents) (Cooper 2019; Xu 2017) sampled FDA committee reports from the same period as the studies included in our meta-analysis, implying a considerable risk of overlapping documents between the studies. The two studies reported no results for our primary analysis and if we had access to raw data we would likely have had to exclude a considerable proportion of the documents from our analyses to avoid double-counting. Thus, we find it unlikely that our result would have been qualitatively different had the six studies reported results in a format suitable for meta-analysis.

Furthermore, our findings on the influence of financial conflicts of interest were robust in most of our sensitivity analyses. When our analyses were not robust, the sensitivity analyses generally showed a stronger association between financial conflicts of interest and favourable recommendations.

Nevertheless, there are some challenges. First, the different types of documents were described using various terms in the included studies and despite using a comprehensive search strategy we might have missed relevant studies. Furthermore, only four studies were included in each of our four primary analyses. Therefore, our effect estimates have some degree of statistical imprecision and none of our primary analyses were statistically significant at the conventional 5% level. However, the sizes of the effect estimates were similar for clinical guidelines, advisory committee reports, and narrative reviews and slightly higher for opinion pieces, and when we combined all document types in a post hoc analysis including 13 studies, we increased the statistical precision and found a statistically significant association with moderate heterogeneity.

Second, our criteria for assessment of risk of bias in relation to confounding might be viewed as quite strict and others may interpret the risk of bias in studies differently. Nevertheless, the majority of studies had a risk of confounding as they compared documents that may differ in other aspects than conflicts of interest (e.g. documents on different drugs used for different patient groups). While confounding could have influenced our estimates, the association between conflicts of interest and recommendations was fairly consistent across document types despite some studies including quite comparable documents (e.g. clinical guidelines on efalizumab for treatment of psoriasis (Schott 2013)), and others including quite different documents (e.g. advisory committee reports on a wide range of different drugs (Pham-Kanter 2014)). Moreover, recommendations in guidelines and narrative reviews could have been influenced by conflicts of interest in the underlying evidence. For example, in certain clinical fields such as oncology (Andreatos 2017), conflicts of interest are highly frequent which could have impacted the conclusions of clinical trials and systematic reviews (Lundh 2017; Hansen 2019a) and thereby indirectly affected guideline recommendations and potentially result in effect modification. Furthermore, how conflicts of interest in the primary clinical trials and systematic reviews underpinning a guideline are interpreted could be associated with the conflicts of interest of the guideline authors.

Third, the number of authors with financial conflicts of interest may influence recommendations in a document. Our subgroup analyses comparing documents with the majority of authors with financial conflicts of interest versus a minority of authors found no difference in effect. However, the analyses were somehow simplistic and based on few data with statistically imprecise results. Another important aspect is the role of the author with financial conflicts of interest. For example, the chair of a guideline committee or the lead author of a narrative review likely has greater influence on recommendations than an author with a less prominent role. Unfortunately, none of the included studies reported data that allowed such a comparison.

Fourth, 11 of the 21 included studies relied solely on disclosed information in the included documents for coding conflicts of interest. This could have led to an underestimation of our effect estimates, as conflicts of interest are often underreported in various publication types, including clinical guidelines (Bindslev 2013).

Finally, the interpretation of our results can be debated. There is no published guidance specifically tailored for summarising and interpreting evidence from methodological studies. One approach could be to use the GRADE system (Guyatt 2008), but it is questionable whether using GRADE for observational intervention studies or prognostic studies is best suited for methodological studies, since the methodology of studies or the presence of conflicts of interest cannot be randomised. In Appendix 9, we report assessments using both strategies which resulted in low to very low certainty of evidence depending on type of documents and the system used. Using the GRADE approach for intervention studies resulted in a more conservative interpretation of the certainty of the evidence.

Agreements and disagreements with other studies or reviews

Other systematic reviews have focused on financial conflicts of interest in other types of publications and have reported similar findings. A recent updated Cochrane Methodology Review focused on primary research, mainly trials, and found that industry-funded

studies more often had favourable conclusions compared with non-industry-funded studies (RR: 1.34, 95% CI: 1.19 to 1.51) (Lundh 2017). Similarly, another recent Cochrane Methodology Review focused on systematic reviews and found that systematic reviews with industry funding or by authors with financial conflicts of interest more often had favourable conclusions compared with systematic reviews without financial conflicts of interest (RR: 1.98, 95% CI: 1.26 to 3.11) (Hansen 2019a).

Financial conflicts of interest have also been investigated in relation to other industries and in a systematic review, Chartres and colleagues reported that industry-funded nutrition studies and reviews more often had favourable conclusions than non-industry-funded nutrition studies and reviews (RR: 1.31, 95% CI: 0.99 to 1.72) (Chartres 2016).

Meaning of our review

For our analyses, we included studies of four types of documents that both were fairly common and involved authors' interpretation of external evidence (involving methods less stringent than in a systematic review). Although we had anticipated potential differences between the various types of documents, we found a fairly consistent association between financial conflicts of interest and favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. One reason could be that authors with conflicts of interest are more prone to confirm prior beliefs by selectively citing and interpreting the literature (DuBroff 2018). This could also explain the somewhat stronger association found in opinion pieces which to some degree allow authors more room for interpretation than narrative reviews, which undergo peer review, and clinical guidelines, which are increasingly done using standardised methods. On an absolute scale, the association between conflicts of interest and recommendations was particularly strong for opinion pieces and specialty interest in clinical guidelines with Numbers Needed to Read of only 2.3 and 2.1, respectively, although the estimates had considerable statistical imprecision.

AUTHORS' CONCLUSIONS

Implication for systematic reviews and evaluations of healthcare

We interpreted our findings to indicate that financial conflicts of interest are associated with favourable recommendations of drugs and devices in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. Although the magnitude of effect is fairly consistent across document types, most studies had a risk of confounding and our individual analyses of each document type had some degree of statistical imprecision. It is more uncertain whether non-financial conflicts of interest impact on recommendations.

Our findings support conflicts of interest policies from major guideline issuing organisations such as the National Institute for Health and Care Excellence, the US Preventive Services Task Force, and the World Health Organization (NICE 2019; U.S. Preventive Services Task Force 2018; WHO 2014). These policies aim to minimise the number and role of guideline authors with conflicts of interest. Similarly, some high impact journals manage conflicts of interest beyond disclosure, for example *New England Journal of Medicine* prohibits narrative reviews and editorials with significant financial conflicts of interest (> US$ 10,000), and *The Lancet* prohibits commentaries, seminars, reviews, and series by authors with relevant stock ownership, employment, or company board membership (Bero 2018; Lundh 2020). Other journals should consider introducing such polices in order to minimise the influence from conflicts of interest on journal content.

In line with this, the FDA introduced more stringent criteria on which types of conflicts of interest where allowed for committee members in 2008 (Ackerley 2009). This could be a possible explanation as to why the study by Zhang and colleagues (Zhang 2019), which exclusively sampled advisory committee reports from 2008 and onwards, found a somewhat weaker association between financial conflicts of interest and recommendations in advisory committee reports than the three other studies included in our pooled analyses (Ackerley 2009; Lurie 2006; Tibau 2016).

To minimise influence from conflicts of interest we suggest that patients, clinicians, and healthcare decision makers primarily use clinical guidelines that are based on rigorous methodology and have clear policies of how to manage conflicts of interest, such as excluding or minimising the role of members with conflicts and ensuring a broad skill set in the panel. If such guidelines are not available, users should interpret such guidelines with caution. Similarly, journal readers should prefer publications written by authors without conflicts of interest.

Implication for methodological research

Ideally, future studies should try to minimise the risk of confounding, e.g. by using a matched study design (Jørgensen 2006). However, identifying editorials commenting on the same study or guidelines addressing the same question and developed using similar methods might be a challenge. Furthermore, future research could focus on investigating whether specific types of financial conflicts of interest (e.g. advisory board membership) or conflicts of interest related to specific companies (e.g. drug manufacturer) have a greater impact than others. Moreover, the included studies used various definitions of financial conflicts of interest and recommendations, and use of a standardised terminology would be helpful.

Investigating the impact of non-financial conflicts of interest is challenging because no uniform definition exists. On one hand, a multitude of interests such as specialty interests, intellectual interests, personal beliefs, and personal relationships can be viewed as non-financial conflicts of interest (The PLoS Medicine Editors 2008; Viswanathan 2014). On the other hand, labelling personal beliefs and theoretical schools of thoughts as conflicts of interest risks muddying the waters since no researcher is completely interest free or free from intellectual pre-conceptions (Bero 2014; Bero 2016; Bero 2017). Furthermore, the distinction between financial and non-financial conflicts of interest is not always clear. For example, in relation to the included study on mammography screening guidelines (Norris 2012), it can be debated whether being a radiologist should be considered a purely non-financial conflict of interest because radiologists may have direct financial income from breast cancer screening. Future studies could focus on investigating the impact of the various types of non-financial conflicts of interest on favourable recommendations and on the impact of managing such interests using guideline panels with a broad range of skill sets, rather than mainly content area experts.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aakre 2012

Study characteristics	
Methods	To explore to what extent current clinical practice guideline recommendations about use of self-monitoring blood glucose in patients with diabetes who do not use insulin are based on the principles of evidence-based medicine. Guidelines published between 1999 and 2011
Data	18 guidelines
Comparisons	Clinical guidelines with financial conflicts of interest (defined as funding by industry) and clinical guidelines without financial conflicts of interest
Outcomes	Recommendations (classified by a scale of 1-4: grade 1, strongly against self-monitoring; grade 2, weekly against self-monitoring; grade 3, weakly in favour of self-monitoring; grade 4, strongly in favour of self-monitoring)
Funding source	The study was funded by the European Federation of Clinical Chemistry and no additional funding related to any for-profit organisation was disclosed
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit organisation
Notes	

Risk of bias		
Item	**Authors' judgement**	**Support for judgement**
Adequate document inclusion process	Yes	Two pairs of authors independently assessed clinical guidelines for inclusion
Adequate coding of conflicts of interest	Yes	One author extracted data, three authors independently coded each guideline (according to personal correspondence with lead author)
Adequate coding of recommendations	Yes	Three authors independently coded the recommendations of each guideline

Aakre 2012 *(Continued)*

Adequate dealing with confounding	No	Compared clinical guidelines of different types of self-monitoring with wide range of publication years (1999-2011)

Ackerley 2009

Study characteristics

Methods	To analyse whether advisory committee members tend to vote in a manner that is relevant to their financial conflicts-of-interest. FDA drug, radiology, device, and biologic advisory committee meetings held between January 2001 and first quarter of 2008.
Data	98 advisory committee reports and 1191 committee members (611 advisory committee reports included in study (not all had data available in a format for inclusion in analysis) and 221 duplicates also included in Lurie 2006 removed).
Comparisons	Advisory committee reports with financial conflicts of interest (defined as at least one committee member with financial ties to the product manufacturer or competitor) and advisory committee meetings without financial conflicts of interest Advisory committee members with financial conflicts of interest (defined as financial ties to the product manufacturer or competitor) and advisory committee members without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as votes in favour of the drug)
Funding source	The study was commissioned by Eastern Research Group (ERG) and no additional funding related to any for-profit organisation was disclosed
Declaration of conflicts of interest	Conflicts of interest not described
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	No	Only one author assessed committee meetings for inclusion (according to personal correspondence with lead author)
Adequate coding of conflicts of interest	Yes	The dataset was reviewed by multiple team members (according to personal correspondence with lead author)
Adequate coding of recommendations	Yes	The dataset was reviewed by multiple team members (according to personal correspondence with lead author)
Adequate dealing with confounding	No	Compared committee meetings of different drugs used for different diseases

Bariani 2013

Study characteristics

Bariani 2013 *(Continued)*

Methods	To identify whether there was any association between conclusions of authors of editorials and self-reported conflicts of interest or sponsorship. Editorials commenting on phase III oncology clinical trials and published between January 2008 and October 2011 in six clinical oncology journals
Data	131 editorials (131 opinion pieces included in analysis after removing 19 duplicates also included in the Lerner 2012 study)
Comparisons	Editorials with financial conflicts of interest (defined as at least one author with any self-reported financial ties with a pharmaceutical company) and editorials without financial conflicts of interest
Outcomes	Recommendations (classified as highly positive, positive, neutral, negative, or highly negative)
Funding source	Funding source not described
Declaration of conflicts of interest	MKK (fourth author) has a consultant or advisory role at Bayer Pharmaceuticals, has received honoraria from Novartis, Sanofi-Aventis, and AstraZeneca, and has received research funding from AstraZeneca, Novartis, and Exelixis. RPR (last author) has a consultant or advisory role at Novartis, has received honoraria from Novartis, Merck Serono, and Roche, has received research funding from Novartis, and has received other remuneration from Merck Serono, Ipsen, Novartis, Bayer Pharmaceuticals, and Roche
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	Yes	Two authors independently assessed editorials for inclusion (according to personal correspondence with corresponding author)
Adequate coding of conflicts of interest	Yes	Two authors independently coded each editorial (according to personal correspondence with corresponding author)
Adequate coding of recommendations	Yes	Two authors independently coded the recommendations of each editorial
Adequate dealing with confounding	No	Compared editorials of different interventions and outcomes. In regression analyses, the authors adjusted for type of outcome and type of intervention

Cooper 2019

Study characteristics

Methods	To investigate whether financial ties to drug companies bias FDA drug advisory committee members' voting on drug approval recommendations. FDA advisory committee meeting held between 1997 and 2012
Data	416 advisory committee reports and 1483 advisory committee members
Comparisons	Advisory committee members with financial conflicts of interest (defined as financial ties to any drug company) and advisory committee members without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as votes in favour of the drug)
Funding source	The study received support from the Searle Civil Justice Institute and no additional funding related to any for-profit organisation was disclosed

Cooper 2019 *(Continued)*

Declaration of conflicts of interest	Conflicts of interest not described
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	Unclear	Not possible to determine
Adequate coding of conflicts of interest	Unclear	Not possible to determine
Adequate coding of recommendations	Unclear	Not possible to determine
Adequate dealing with confounding	No	Compared committee meetings of different drugs used for different diseases

Downing 2014

Study characteristics

Methods	To examine whether there was an association between authors' financial relationships with pharmaceutical companies invested in fenofibrate's commercial success and their interpretation. Clinical guidelines, opinion pieces, and narrative reviews commenting on a randomised trial of fenofibrate (the ACCORD-Lipid trial) and published in 2010 and 2011.
Data	4 clinical guidelines; 23 editorials and commentaries; 40 reviews (mainly narrative) (5 clinical guidelines, 24 editorials and commentaries, and 70 reviews included in the study, but not all had data available in a format for inclusion in analysis).
Comparisons	Documents with financial conflicts of interest (defined as at least one author with financial ties to the manufacturer of fenofibrate or any other drug company with a commercial interest in fenofibrate) and documents without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as recommending use of fibrates)
Funding source	No funding was received for the study
Declaration of conflicts of interest	HMK (third author) and JSR (last author) have received support from Medtronic and Johnson and Johnson to develop methods of clinical trial data sharing
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	Yes	Two authors independently assessed documents for inclusion

Downing 2014 *(Continued)*

Adequate coding of conflicts of interest	Yes	Two authors independently coded conflicts of interest in each document
Adequate coding of recommendations	Yes	Two authors independently coded the recommendations of each document
Adequate dealing with confounding	Yes	Compared documents commenting on the same trial and published within a short period of time

Dunn 2016

Study characteristics	
Methods	To examine the association between author financial competing interests and the conclusions of narrative reviews about neuroaminidase inhibitors. Narrative reviews published between January 2005 and April 2015
Data	213 narrative reviews
Comparisons	Narrative reviews with financial conflicts of interest (defined as at least one author with employment, research funding, consulting fees, or speaker fees provided by a pharmaceutical company manufacturing any of the neuraminidase inhibitors of interest) and narrative reviews without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as concluding that one or more of the neuraminidase inhibitors were safe and effective for use in the prophylaxis or treatment of influenza)
Funding source	The study was funded by the National Health and Medical Research Council and no additional funding related to any for-profit organisation was disclosed
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit organisation
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	Yes	Up to three authors independently assessed narrative reviews for inclusion (according to personal correspondence with lead author)
Adequate coding of conflicts of interest	Yes	One author extracted data, and two author independently coded any ambiguous narrative reviews (according to personal correspondence with lead author)
Adequate coding of recommendations	Yes	Two authors independently coded the recommendations of each narrative review
Adequate dealing with confounding	No	Compared narrative reviews of different drugs (all neuraminidase inhibitors), used for different indications (prophylaxis and treatment), and different publication years

George 2014

Study characteristics	
Methods	To compare the methods and outcomes of two guidelines on diagnosis and treatment of primary immune thrombocytopenia published in close proximity
Data	Two clinical guidelines
Comparisons	One clinical guideline with financial conflicts of interest (defined as unrestricted grants from pharmaceutical companies and financial associations among the authors with companies that manufacture products related to primary immune thrombocytopenia) and one clinical guideline without financial conflicts of interest
Outcomes	Recommendations (classified by two different scales: 1) A, strong; B, intermediate; C, weak; or 2) 1, strong; 2, weak)
Funding source	No funding was received for the study
Declaration of conflicts of interest	JNG (lead author) has been a consultant, receiving honoraria, and receiving research funding from pharmaceutical companies. SKV (second author) has served as a biostatistician on an industry funded study
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	No	No systematic search for guidelines
Adequate coding of conflicts of interest	Yes	Three authors agreed that the information provided in the reporting of the two guidelines was concise and clear, and the authors of the study reported this information (according to personal correspondence with lead author)
Adequate coding of recommendations	Yes	The two included guidelines graded the recommendations made and the authors of the study reported this grading (according to personal correspondence with lead author)
Adequate dealing with confounding	Yes	Compared clinical guidelines of the same disease published within one year of each other in the same scientific journal

Hartog 2012

Study characteristics	
Methods	To examine the relationship between authors' potential conflicts of interest and the recommendations made in narrative reviews on clinical use of hydroxyethyl starch. Narrative reviews published between 1960 and 21 May 2010
Data	153 narrative reviews
Comparisons	Narrative reviews with financial conflicts of interest (defined as at least one author with financial relationships or other kind of support from a manufacturer of any commercially available intravenous fluids) and narrative reviews without financial conflicts of interest

Hartog 2012 *(Continued)*

Outcomes	Recommendations (favourable recommendations defined as recommending hydroxyethyl starch use over other fluids)
Funding source	The study was funded by the Intramural Research Program of the U.S. National Institutes of Health and no additional funding related to any for-profit organisation was disclosed
Declaration of conflicts of interest	KR (last author) has received grants and speaker's and consultancy fees from B. Braun
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	Yes	Two authors independently assessed narrative reviews for inclusion
Adequate coding of conflicts of interest	Yes	Two authors independently coded each narrative review
Adequate coding of recommendations	Yes	Two authors independently coded the recommendations of each narrative review
Adequate dealing with confounding	No	Compared narrative reviews of hydroxyethyl starch used for many different indications (outcomes may vary) in different populations with different publication years

Hayes 2019

Study characteristics

Methods	To investigate the association between authors' financial conflict-of-interest and position on the clinical application of a medical device utilising tumour-treating fields for the treatment of Glioblastoma. Opinion pieces and narrative reviews published up to 2018
Data	8 opinion pieces and 7 narrative reviews
Comparisons	Documents with financial conflicts of interest (defined as at least one author with financial ties to the manufacturer of tumour-treating fields therapy) and documents without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as supporting tumour-treating fields without caveat)
Funding source	The work of VP (last author) is funded by the Laura and John Arnold Foundation and no additional funding related to any for-profit organisation was disclosed
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit organisation
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement

Hayes 2019 *(Continued)*

Adequate document inclusion process	No	Only one author assessed documents for inclusion (according to personal correspondence with corresponding author)
Adequate coding of conflicts of interest	Yes	Two authors independently coded conflicts of interest in each document
Adequate coding of recommendations	Yes	Two authors independently coded the recommendations of each document
Adequate dealing with confounding	Yes	Compared documents commenting on the same trial

Lerner 2012

Study characteristics	
Methods	To investigate the possible association between the presence of personal conflicts of interest and favourable opinions. Editorials commenting on phase III clinical trials published between January 2007 and December 2009 in four major oncology journals
Data	54 editorials
Comparisons	Editorials with financial conflicts of interest (defined as at least one author with financial relationships to a for-profit organisation) and editorials without financial conflicts of interest
Outcomes	Recommendations (classified as favourable, neutral, and unfavourable)
Funding source	No funding was received for the study
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit organisation
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	No	Only one author assessed editorials for inclusion (according to personal correspondence with corresponding author)
Adequate coding of conflicts of interest	Yes	Three authors independently coded each editorial
Adequate coding of recommendations	Yes	Two authors independently coded the recommendations of each editorial
Adequate dealing with confounding	No	Compared editorials of different drugs with different publication years

Lurie 2006

Study characteristics	
Methods	To assess the relationship between conflicts of interest and voting behavior at drug-related meetings. All FDA Drug Advisory Committee meetings held between January 2001 and December 2004
Data	76 advisory committee reports and 886 advisory committee members from (221 advisory committee reports included in the study, but not all had data available in a format for inclusion in analysis)
Comparisons	Advisory committee reports with financial conflicts of interest (defined as at least one committee member with current investments, employment, patents, contracts, grants, cooperative research, development agreements, consulting, speaking/writing arrangements with any for-profit company within the last 12 months) and advisory committee reports without financial conflicts of interest Advisory committee members with financial conflicts of interest (defined as current investments, employment, patents, contracts, grants, cooperative research, development agreements, consulting, speaking/writing arrangements with any for-profit company within the last 12 months) and advisory committee members without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as votes in favour of the drug)
Funding source	Funding source not described
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit organisation
Notes	

Risk of bias		
Item	**Authors' judgement**	**Support for judgement**
Adequate document inclusion process	No	Only one author assessed advisory committee reports for inclusion based on criteria developed by three authors (according to personal correspondence with lead author)
Adequate coding of conflicts of interest	No	Only one author coded each advisory committee report
Adequate coding of recommendations	Yes	Two authors developed criteria for which votes to include, then one author extracted the yes/no votes. No interpretation of text
Adequate dealing with confounding	No	Compared advisory committee reports of different drugs used for different diseases

Norris 2012

Study characteristics	
Methods	To examine the relationship between guideline recommendations on routine mammography screening and 1) specialty of physician guideline authors and 2) financial disclosures of physician authors. Clinical guidelines published between January 2005 and June 2011
Data	12 clinical guidelines
Comparisons	Clinical guidelines with varying percentages of authors with financial conflicts of interest (defined as disclosure of any financial conflicts of interest)

Norris 2012 *(Continued)*

	Clinical guidelines with at least one radiologists in the guideline author team and clinical guidelines without radiologists in the guideline author team
Outcomes	Recommendations (favourable recommendations defined as recommending routine screening)
Funding source	The study was funded by the Agency for Healthcare Research and Quality and no additional funding related to any for-profit organisation was disclosed
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit organisation
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	Yes	Two authors independently assessed clinical guidelines for inclusion
Adequate coding of conflicts of interest	Yes	Two authors independently coded each clinical guideline (according to personal lead with corresponding author)
Adequate coding of recommendations	Yes	Two author independently coded the recommendations of each clinical guideline (according to personal correspondence with lead author)
Adequate dealing with confounding	No	Compared clinical guidelines of the same topic (mammography screening), but with various publication years. Mammography screening is a controversial topic that evolves over time

Norris 2013

Study characteristics

Methods	To explore whether financial conflicts interests among authors of clinical guidelines on drugs for glycaemic control in type 2 diabetes are associated with recommendation of specific drugs. Clinical guidelines published between February 2012 and June 2012
Data	13 clinical guidelines
Comparisons	Clinical guidelines with financial conflicts of interest (defined as having at least one author with financial interests in companies that manufacture the drugs recommended in the clinical guidelines) and clinical guidelines without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as recommending a drug in the guidance portion of the guideline)
Funding source	The study was funded by the Agency for Healthcare Research and Quality and no additional funding related to any for-profit organisation was disclosed
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit organisation
Notes	

Norris 2013 *(Continued)*

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	Yes	Two authors independently assessed clinical guidelines for inclusion (according to personal correspondence with lead author)
Adequate coding of conflicts of interest	Yes	Two authors independently coded each clinical guideline. A third author checked the coding of a sample of the included clinical guidelines and looked through any outliers or notable information (according to personal correspondence with lead author)
Adequate coding of recommendations	Yes	Two authors independently coded the recommendations of each clinical guideline
Adequate dealing with confounding	No	Compared clinical guidelines of the same drugs, but used for different populations (adults, children, pregnant women)

Pham-Kanter 2014

Study characteristics	
Methods	To examine the association between financial conflicts of interest among FDA Center for Drug Evaluation and Research advisory committee members and voting behavior. FDA drug advisory committee reports from February 1997 to December 2011
Data	379 advisory committee reports and 15,739 advisory committee members
Comparisons	Adviosory committee members with financial conflicts of interest (defined as financial interests in the sponsoring firm, in a firm competing with the sponsor, or in both the sponsoring firm and any of its competitors) and advisory committee members without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as votes favourable to the sponsoring firm)
Funding source	The study was funded by the Edmond J. Safra Philanthropic Foundation and no additional funding related to any for-profit organisation was disclosed
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit organisation
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	Yes	Three research assistants assessed advisory committee reports for inclusion (according to personal correspondence with lead author)
Adequate coding of conflicts of interest	Yes	One research assistant extracted data and coded each advisory committee report. One author reviewed and audited all data (according to personal correspondence with lead author)

Pham-Kanter 2014 *(Continued)*

Adequate coding of recommendations	Yes	One research assistant coded the recommendations of each advisory committee report. One author reviewed and audited all data (according to personal correspondence with lead author)
Adequate dealing with confounding	No	Compared advisory committee reports of different drugs, used for different diseases, and held within a large time span

Schott 2013

Study characteristics		
Methods	To investigate the association between conflicts of interest among guideline authors and the guidelines' recommendations in two clinical guidelines on treatment of psoriasis by gabapentin versus efalizumab	
Data	Two clinical guidelines	
Comparisons	One clinical guideline with financial conflicts of interest (defined as at least one author with financial ties to drug companies) and one clinical guideline without financial conflicts of interest	
Outcomes	Recommendations (favourable recommendations defined as efalizumab being judged more favourable)	
Funding source	Funding source not described	
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit organisation	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Support for judgement**
Adequate document inclusion process	No	No systematic search for guidelines
Adequate coding of conflicts of interest	No	Only one author coded each guideline
Adequate coding of recommendations	No	No systematic procedure for coding the recommendations of each guideline
Adequate dealing with confounding	Yes	Compared two guidelines of the same drug used for the same disease and published in the same year

Stelfox 1998

Study characteristics	
Methods	To investigate the association between authors' positions on the safety of calcium-channel antagonists and their financial relationships with the pharmaceutical industry. Reports of original research,

Stelfox 1998 *(Continued)*

	reviews, and letters to the editor on calcium-channel antagonists published between March 1995 and September 1996
Data	33 letters, 5 research studies, and 32 review articles
Comparisons	Authors of letters to the editors, original research, and review articles with financial conflicts of interest (defined as authors receiving any the following types of funding in the past five years: support to attend a symposium, honoraria, support to organise an educational program, research support, employment, or consultation) and letters to the editor, original research, and review articles without financial conflicts of interest
Outcomes	Recommendations (classified as critical, neutral, and supportive)
Funding source	The authors disclosed that the study was not funded by the pharmaceutical industry
Declaration of conflicts of interest	HTS (lead author) has attended educational rounds sponsored by pharmaceutical manufacturers GC (second author) has received travel fees from manufacturers of calcium-channel antagonists and manufacturers of competing products. KO (third author) has attended industry-sponsored functions, when invited by clinicians. ASD (last author) has received honoraria for speeches, consulting fees from manufacturers of calcium-channel antagonists and manufacturers of competing products, and has received research grants from Rhone-Poulenc Rorer Pharmaceuticals, Searle, and SmithKline Beecham Pharmaceuticals.
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	No	Only one author assessed articles for inclusion (according to personal correspondence with corresponding author)
Adequate coding of conflicts of interest	Yes	Conflicts of interest were assessed using a detailed questionnaire
Adequate coding of recommendations	Yes	Two authors independently coded the recommendations of each article (according to personal correspondence with corresponding author)
Adequate dealing with confounding	Yes	Compared documents commenting of the same controversy and published in a narrow time span

Tibau 2015

Study characteristics

Methods	To explore whether financial conflicts of interest were associated with greater probability of endorsement of specific anticancer drugs. Clinical guidelines on anticancer drugs for breast, colorectal, lung, and prostate cancers published between January 2003 and October 2013
Data	50 clinical guidelines (91 clinical guidelines included in the study, but not all had data available in a format for inclusion in analysis)
Comparisons	Clinical guidelines with financial conflicts of interest (defined as at least one authors with employment, stock ownership, participation in speakers bureaus, consultancy, honoraria, research funding, and expert testimony) and clinical guidelines without financial conflicts of interest

Tibau 2015 *(Continued)*

Outcomes	Recommendations (favourable recommendations defined as endorsement of a drug)
Funding source	Funding source not described
Declaration of conflicts of interest	BS (eight author) has received honoraria from Astellas, Janssen Oncology, Novartis, and Sanofi, and has a consulting or advisory role at Astellas, Sanofi, and Janssen Oncology
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	No	Only one author assessed clinical guidelines for inclusion (according to personal correspondence with corresponding author)
Adequate coding of conflicts of interest	No	Only one author coded each clinical guideline
Adequate coding of recommendations	No	Only one author coded the recommendations of each clinical guideline (according to personal correspondence with corresponding author)
Adequate dealing with confounding	No	Compared clinical guidelines of different cancer drugs used for different types of cancers

Tibau 2016

Study characteristics

Methods	To explore the influence from Drug Advisory Commitee members' financial conflicts of interest on the meeting recommendations. FDA Oncologic Drugs Advisory Committee meetings between January 2000 and December 2004
Data	79 advisory committee reports (82 advisory committee reports included in the study, but not all had data available in a format for inclusion in analysis)
Comparisons	Advisory committee reports with financial conflicts of interest (defined as at least one committee members with investments, employment, consultancy, advisory capacity, research funding, speakers' bureau activities, or lectures) and advisory committee reports without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as votes in favour of drug approval)
Funding source	Funding source not described
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit organisation
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	No	Only one author assessed advisory committee reports for inclusion (according to personal correspondence with corresponding author)

Tibau 2016 *(Continued)*

Adequate coding of conflicts of interest	Yes	One author coded each committee member, and another author verified all data
Adequate coding of recommendations	Yes	One author coded the recommendations of each advisory committee report, and another author verified all data
Adequate dealing with confounding	No	Compared advisory committee reports of different oncology drugs

Wang 2010

Study characteristics	
Methods	To explore the association between authors' financial conflicts of interest and their position on the association between rosiglitazone in patients with diabetes and cardiovascular events
Data	5 clinical guidelines, 91 opinion pieces (letters, editorials, commentaries), and 84 narrative reviews
Comparisons	Documents with financial conflicts of interest (defined as at least one author with funding of the document, employment, consultancy, advisory board membership, speaker or lecture feeds, travel grants, stock ownership or honoraria from pharmaceutical companies) and documents without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as recommending the use of rosiglitazone)
Funding source	No funding was received for the study
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related to any for-profit company
Notes	

Risk of bias

Item	**Authors' judgement**	**Support for judgement**
Adequate document inclusion process	Yes	Two authors independently assessed documents for inclusion (according to personal correspondence with corresponding author)
Adequate coding of conflicts of interest	No	Only one author coded each document
Adequate coding of recommendations	Yes	Two review authors independently coded the recommendations of each document
Adequate dealing with confounding	Yes	Compared documents on the same drug used for the same disease

Xu 2017

Study characteristics

Xu 2017 *(Continued)*

Methods	To examine the association between conflicts of interest and voting behaviour at the FDA advisory committee reports. Committee meetings on drugs and devices held between 2008 and 2014
Data	385 advisory committee reports
Comparisons	Advisory committee members with financial conflicts of interest (defined as financial interests or personal and business relationships) and advisory committee members without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined as votes favourable to the product)
Funding source	Funding source not described
Declaration of conflicts of interest	The authors disclosed no conflicts of interest related any for-profit company
Notes	

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	Unclear	Not possible to determine
Adequate coding of conflicts of interest	Unclear	Not possible to determine
Adequate coding of recommendations	Unclear	Not possible to determine
Adequate dealing with confounding	No	Compared advisory committee reports of different drugs and devices

Zhang 2019

Study characteristics	
Methods	To understand how the FDA interprets the recommendations of its advisory committees and to explore potential contributing factors to cases in which the FDA as an agency disagreed with its advisory committees' recommendations. FDA advisory committee meetings held between 2008 and 2015
Data	376 advisory committee reports
Comparisons	Advisory committee reports with financial conflicts of interest (defined as at least one committee members with financial ties to the drug manufacturer or competitor) and advisory committee reports without financial conflicts of interest
Outcomes	Recommendations (favourable recommendations defined committee votes in favour of the drug)
Funding source	No funding was received for the study
Declaration of conflicts of interest	JSR (last author) has received support from Johnson and Johnson to develop methods of clinical trial data sharing and from Medtronic to develop methods for postmarket surveillance of medical devices

Zhang 2019 *(Continued)*

Notes

Risk of bias

Item	Authors' judgement	Support for judgement
Adequate document inclusion process	Yes	Two authors developed inclusion criteria, one author primarily assessed committee reports for inclusion, any uncertainties were discussed between two authors (according to personal correspondence with corresponding author)
Adequate coding of conflicts of interest	Yes	One author primarily coded conflicts of interest for each committee report, any uncertainties were discussed between two authors (according to personal correspondence with corresponding author)
Adequate coding of recommendations	Yes	One author primarily coded recommendations for each committee report, any uncertainties were discussed between two authors (according to personal correspondence with corresponding author)
Adequate dealing with confounding	No	Compared committee meetings of different drugs and devices

FDA: Food and Drug Administration

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abola 2016	Not research study
Abramson 2005	Not research study
Aidara-Kane 2018	Wrong document type (includes studies on food-producing animals)
Akl 2014	No comparator (investigates prevalence of conflicts of interest only)
Alhazzani 2018	No comparator (investigates prevalence of conflicts of interest only)
Allan 2015	Wrong outcomes
Allan 2015a	Wrong outcomes
American Journal of Hospital Pharmacy 1993	Wrong document type (includes conflicts of interest policies)
American Medical Association 1993	Wrong document type (includes conflicts of interest policies)
Bachmann 2019	No comparator (investigates prevalence of conflicts of interest only)
Banks 2005	Not research study
Bariani 2012	Conference abstract of included study
Barriocanal 2013	Wrong outcomes

Study	Reason for exclusion
Bastian 2016	Not research study
Bekelman 2003	Wrong document type (includes systematic reviews and cross-sectional surveys)
Bellomo 2020	Wrong document type (includes primary research articles)
Bennett 2011	Wrong outcomes
Bennett 2019	Wrong comparator
Bero 2014	Not research study
Bhargava 2007	No comparator (investigates prevalence of conflicts of interest only)
Bindslev 2013	No comparator (investigates prevalence of conflicts of interest only)
Biomedical Ethics Committee 1990	Not research study
Bion 2009	Wrong document type (includes studies investigating conflicts of interest)
Burda 2011	Conference abstract of included study
Burki 2016	Not research study
Burklow 1998	Not research study
Campsall 2016	Wrong outcomes
Carlisle 2018	No comparator (investigates prevalence of conflicts of interest only)
Checketts 2017	Wrong outcomes
Choudhry 2002	No comparator (investigates prevalence of conflicts of interest only)
Chren 1994	Not research study
Combs 2018	No comparator (investigates prevalence of conflicts of interest only)
Combs 2019	No comparator (investigates prevalence of conflicts of interest only)
Cosgrove 2006	Wrong outcomes
Cosgrove 2009	No comparator (investigates prevalence of conflicts of interest only)
Cosgrove 2013	Not research study
Cosgrove 2013a	Wrong outcomes
Cosgrove 2014	Wrong document type (includes randomised trials)
Cosgrove 2017	Wrong outcomes
Council on Ethical and Judicial Affairs 1991	Not research study

Study	Reason for exclusion
Council on Ethical and Judicial Affairs 1992	Wrong document type (includes conflicts of interest policies)
Coyne 2007	Not research study
DeJong 2018	Not research study
Desai 2019	No comparator (investigates prevalence of conflicts of interest only)
Dillon 2016	Wrong outcomes
DuBroff 2018	Not research study
Editors of Annals of Internal Medicine 2004	Not research study
Editors of Canadian Medical Association Journal	Not research study
Ferket 2011	Wrong comparator
Finucane 2004	Wrong document type (includes abstracts, posters, and presentations from a medical conference)
Friesen 2019	Not research study
Gasparyan 2013	Not research study
Glazer 2018	Not research study
Graham 2001	Wrong comparator
Greenberg 2012	Wrong document type (includes conflicts of interest policies)
Grindal 2019	No comparator (investigates prevalence of conflicts of interest only)
Hart 2019	Not research study
Hayes 2018	Not research study
Holloway 2008	Wrong outcomes
Horn 2018	No comparator (investigates prevalence of conflicts of interest only)
Hu 2013	Wrong comparator
Irwig 2018	No comparator (investigates prevalence of conflicts of interest only)
Janssen 2015	Wrong document type (includes medical journal editorial boards)
Ji 2018	No comparator (investigates prevalence of conflicts of interest only)
Johnson 2020	Wrong document type (includes public speakers)
Jones 2011	Wrong outcomes

Study	Reason for exclusion
Khalil 2012	Wrong outcomes
Khan 2018	Not research study
Klikova 2013	No comparator (investigates prevalence of conflicts of interest only)
Langer 2012	No comparator (investigates prevalence of conflicts of interest only)
Lexchin 2019	No comparator (investigates prevalence of conflicts of interest only)
Lexchin 2019a	Wrong document type (includes clinicians making submissions to the pan-Canadian Oncology Drug Review)
Liu 2019	Wrong outcomes
Lopez-Olivo 2017	Wrong outcomes
Lu 2017	Wrong outcomes
Lurie 2006a	Not research study
Lurie 2015	Wrong comparator
MacKenzie 2015	Wrong comparator
Madadi 2012	No comparator (investigates prevalence of conflicts of interest only)
McCoy 2018	Wrong document type (includes public speakers)
Mehlman 2017	Wrong document type (includes physician editors)
Miranda 2011	Conference abstract of included study
Mitchell 2016	No comparator (investigates prevalence of conflicts of interest only)
Mitchell 2019	Not research study
Moynihan 2013	Wrong outcomes
Napierala 2018	No comparator (investigates prevalence of conflicts of interest only)
Neuman 2011	Wrong outcomes
Neuman 2011a	Wrong outcomes
Newton 2016	No comparator (investigates prevalence of conflicts of interest only)
Niforatos 2019	Wrong outcomes
Norris 2011	No comparator (investigates prevalence of conflicts of interest only)
Papanikolaou 2001	Wrong outcomes
Pharmaceutical Journal 2005	Not research study

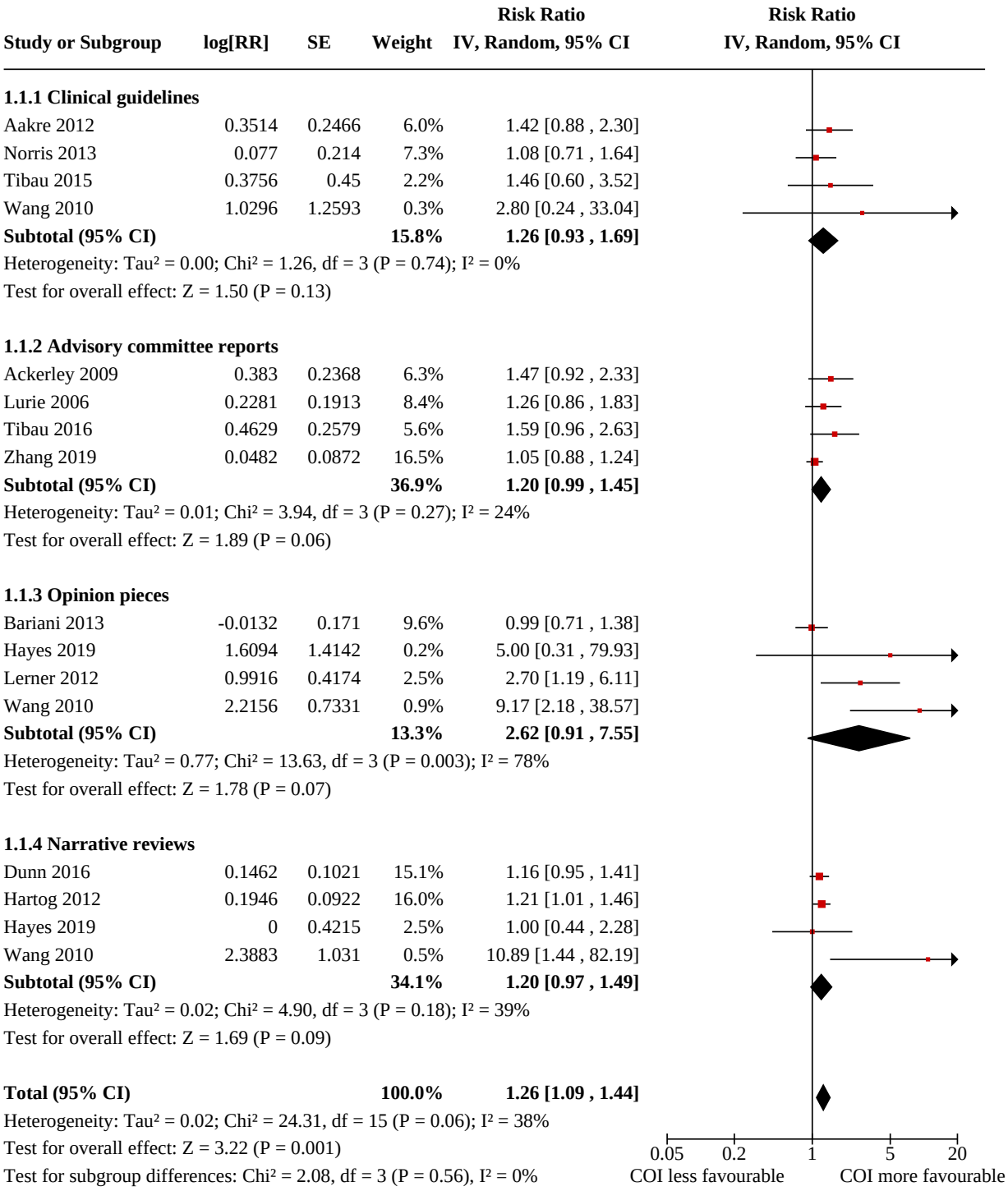
Study	Reason for exclusion
Riechelmann 2007	Wrong outcomes
Roberts 2020	Wrong document type (includes public speakers)
Roland 2009	Wrong comparator
Roundtree 2009	No comparator (investigates prevalence of conflicts of interest only)
Saito 2019	Not research study
Saito 2019a	No comparator (investigates prevalence of conflicts of interest only)
Saleh 2019	No comparator (investigates prevalence of conflicts of interest only)
Shapiro 2003	Wrong comparator
Shimada 2019	No comparator (investigates prevalence of conflicts of interest only)
Shnier 2016	No comparator (investigates prevalence of conflicts of interest only)
Spithoff 2020	No comparator (investigates prevalence of conflicts of interest only)
Steinbrook 2005	Not research study
Traynor 2002	Not research study
Verma 2017	No comparator (investigates prevalence of conflicts of interest only)
Wang 2010a	Conference abstract of included study
Wayant 2019	No comparator (investigates prevalence of conflicts of interest only)

DATA AND ANALYSES

Comparison 1. Primary analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Financial conflicts of interest	13		Risk Ratio (IV, Random, 95% CI)	1.26 [1.09, 1.44]
1.1.1 Clinical guidelines	4		Risk Ratio (IV, Random, 95% CI)	1.26 [0.93, 1.69]
1.1.2 Advisory committee reports	4		Risk Ratio (IV, Random, 95% CI)	1.20 [0.99, 1.45]
1.1.3 Opinion pieces	4		Risk Ratio (IV, Random, 95% CI)	2.62 [0.91, 7.55]
1.1.4 Narrative reviews	4		Risk Ratio (IV, Random, 95% CI)	1.20 [0.97, 1.49]

Analysis 1.1. Comparison 1: Primary analyses, Outcome 1: Financial conflicts of interest



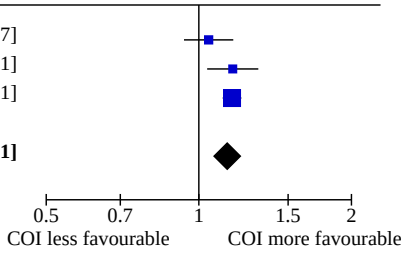
Comparison 2. Secondary analysis: using individual voting level in the analysis on advisory committee reports

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Financial conflicts of interest	3	17816	Risk Ratio (IV, Random, 95% CI)	1.14 [1.07, 1.21]

Analysis 2.1. Comparison 2: Secondary analysis: using individual voting level in the analysis on advisory committee reports, Outcome 1: Financial conflicts of interest

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Ackerley 2009	140	220	591	971	21.2%	1.05 [0.93 , 1.17]
Lurie 2006	97	132	475	754	20.0%	1.17 [1.04 , 1.31]
Pham-Kanter 2014	820	1239	8254	14500	58.8%	1.16 [1.11 , 1.21]
Total (95% CI)		**1591**		**16225**	**100.0%**	**1.14 [1.07 , 1.21]**
Total events:	1057		9320			

Heterogeneity: Tau² = 0.00; Chi² = 3.10, df = 2 (P = 0.21); I² = 35%
Test for overall effect: Z = 4.24 (P < 0.0001)
Test for subgroup differences: Not applicable

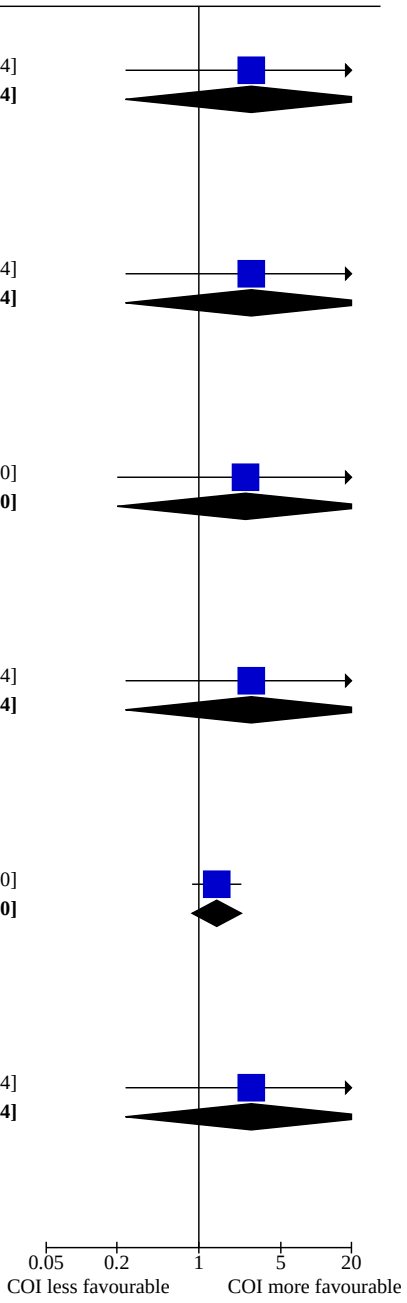


Comparison 3. Subgroup analyses for clinical guidelines

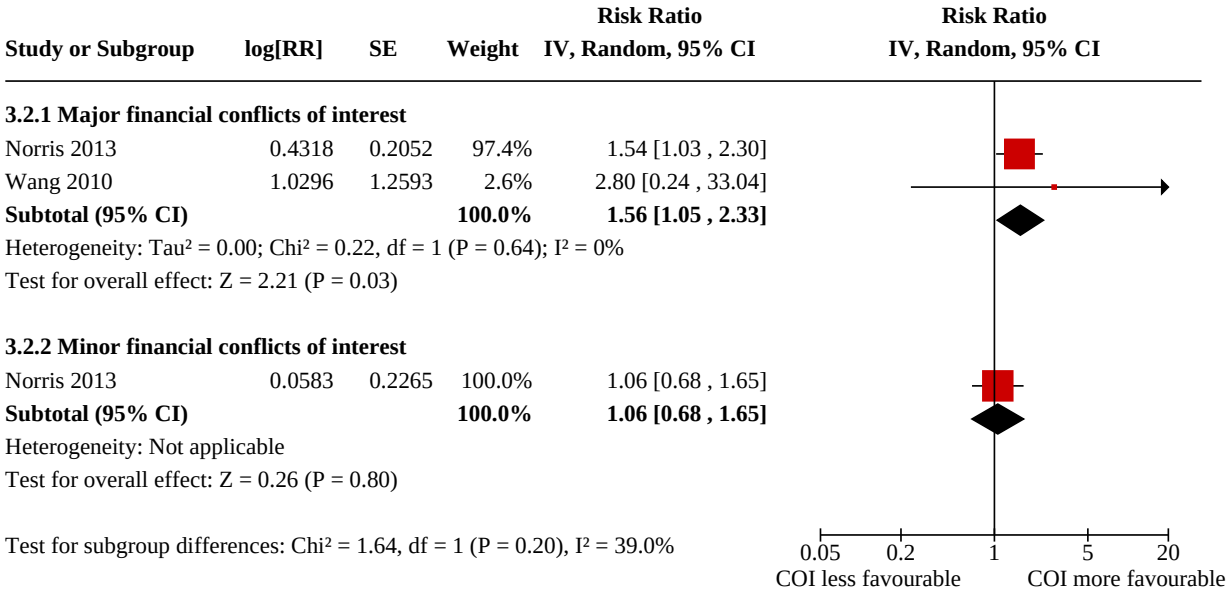
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Different types of financial conflicts of interest	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.1.1 Advisory board membership	1	5	Risk Ratio (IV, Random, 95% CI)	2.80 [0.24, 33.04]
3.1.2 Consultancy	1	5	Risk Ratio (IV, Random, 95% CI)	2.80 [0.24, 33.04]
3.1.3 Grants	1	4	Risk Ratio (IV, Random, 95% CI)	2.50 [0.20, 31.00]
3.1.4 Honoraria	1	5	Risk Ratio (IV, Random, 95% CI)	2.80 [0.24, 33.04]
3.1.5 Industry funding of the clinical guideline	1	18	Risk Ratio (IV, Random, 95% CI)	1.42 [0.88, 2.30]
3.1.6 Speaker fees	1	5	Risk Ratio (IV, Random, 95% CI)	2.80 [0.24, 33.04]
3.2 Clinical guidelines with major financial conflicts of interest versus clinical guidelines with minor financial conflicts of interest	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.2.1 Major financial conflicts of interest	2		Risk Ratio (IV, Random, 95% CI)	1.56 [1.05, 2.33]
3.2.2 Minor financial conflicts of interest	1		Risk Ratio (IV, Random, 95% CI)	1.06 [0.68, 1.65]

Analysis 3.1. Comparison 3: Subgroup analyses for clinical guidelines, Outcome 1: Different types of financial conflicts of interest

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Advisory board membership						
Wang 2010	3	4	0	1	100.0%	2.80 [0.24 , 33.04]
Subtotal (95% CI)		**4**		**1**	**100.0%**	**2.80 [0.24 , 33.04]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
3.1.2 Consultancy						
Wang 2010	3	4	0	1	100.0%	2.80 [0.24 , 33.04]
Subtotal (95% CI)		**4**		**1**	**100.0%**	**2.80 [0.24 , 33.04]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
3.1.3 Grants						
Wang 2010	2	3	0	1	100.0%	2.50 [0.20 , 31.00]
Subtotal (95% CI)		**3**		**1**	**100.0%**	**2.50 [0.20 , 31.00]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
3.1.4 Honoraria						
Wang 2010	3	4	0	1	100.0%	2.80 [0.24 , 33.04]
Subtotal (95% CI)		**4**		**1**	**100.0%**	**2.80 [0.24 , 33.04]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
3.1.5 Industry funding of the clinical guideline						
Aakre 2012	4	4	9	14	100.0%	1.42 [0.88 , 2.30]
Subtotal (95% CI)		**4**		**14**	**100.0%**	**1.42 [0.88 , 2.30]**
Total events:	4		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.15)						
3.1.6 Speaker fees						
Wang 2010	3	4	0	1	100.0%	2.80 [0.24 , 33.04]
Subtotal (95% CI)		**4**		**1**	**100.0%**	**2.80 [0.24 , 33.04]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
Test for subgroup differences: Chi^2 = 1.14, df = 5 (P = 0.95), I^2 = 0%						



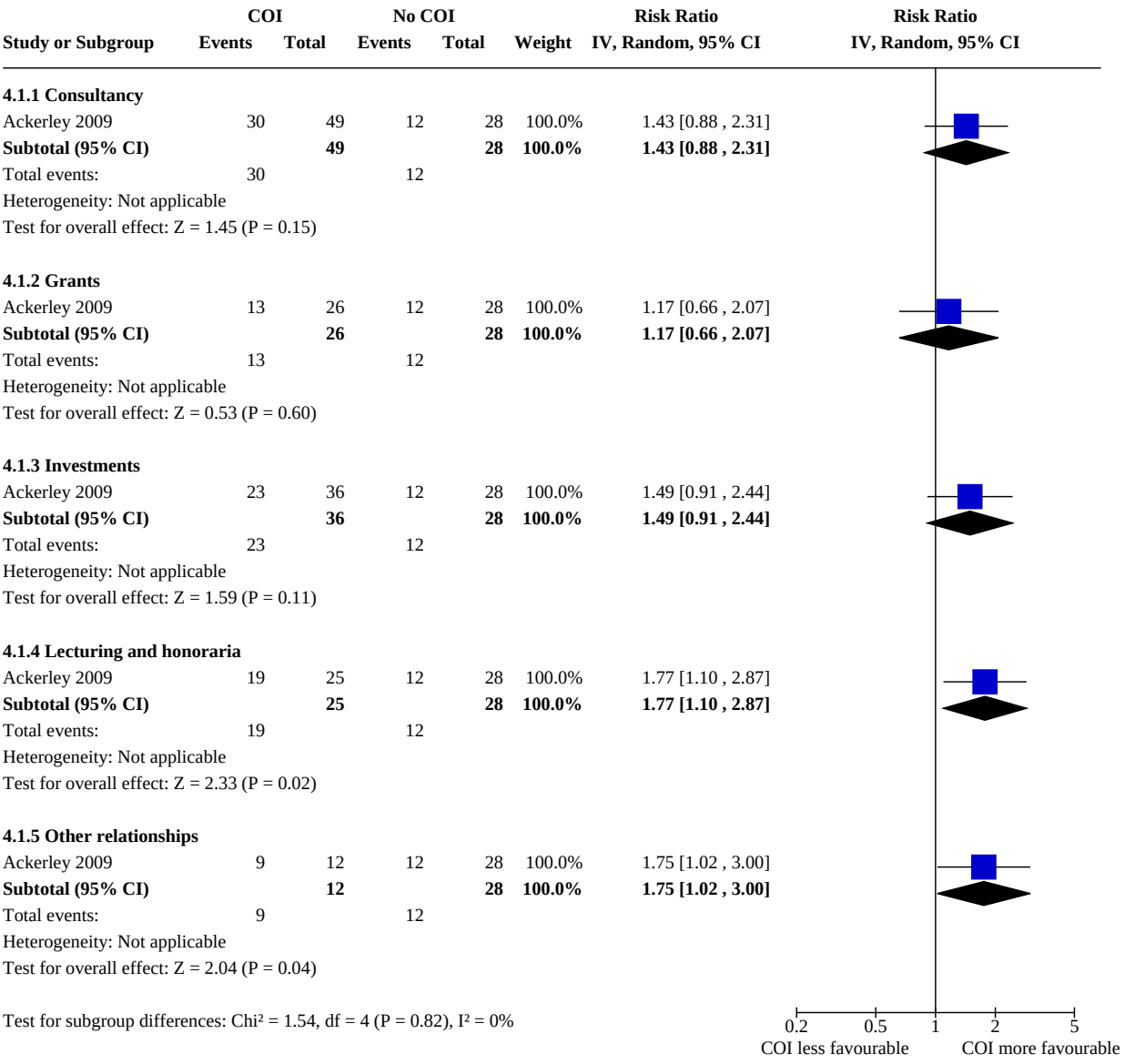
Analysis 3.2. Comparison 3: Subgroup analyses for clinical guidelines, Outcome 2: Clinical guidelines with major financial conflicts of interest versus clinical guidelines with minor financial conflicts of interest



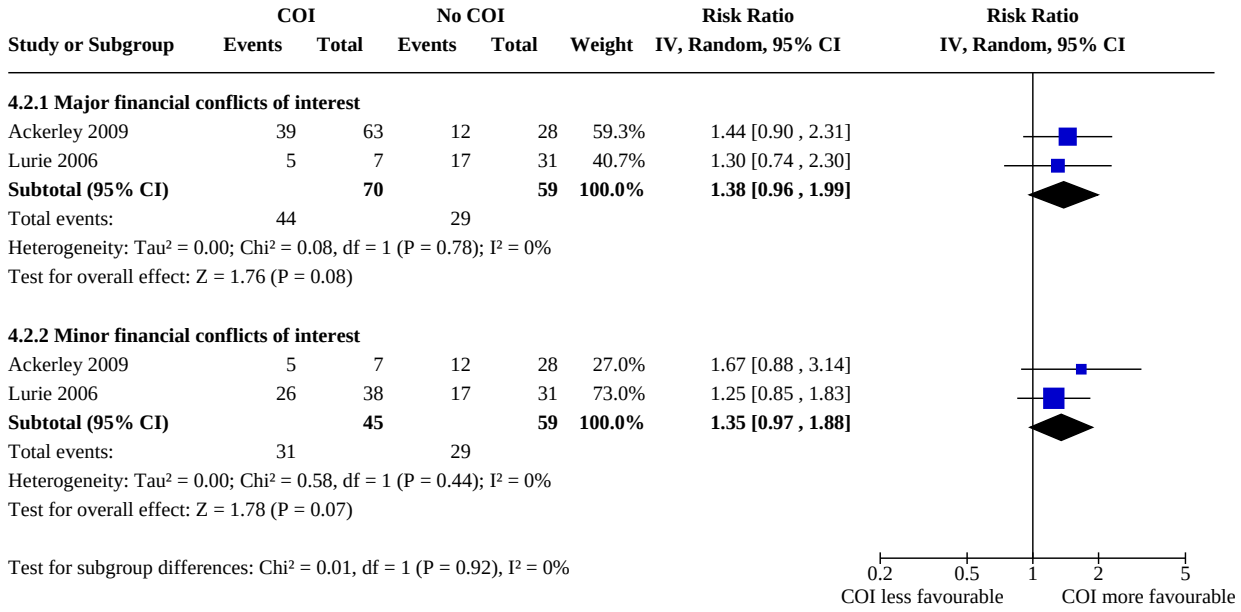
Comparison 4. Subgroup analyses for advisory committee reports

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Different types of financial conflicts of interest	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.1.1 Consultancy	1	77	Risk Ratio (IV, Random, 95% CI)	1.43 [0.88, 2.31]
4.1.2 Grants	1	54	Risk Ratio (IV, Random, 95% CI)	1.17 [0.66, 2.07]
4.1.3 Investments	1	64	Risk Ratio (IV, Random, 95% CI)	1.49 [0.91, 2.44]
4.1.4 Lecturing and honoraria	1	53	Risk Ratio (IV, Random, 95% CI)	1.77 [1.10, 2.87]
4.1.5 Other relationships	1	40	Risk Ratio (IV, Random, 95% CI)	1.75 [1.02, 3.00]
4.2 Advisory committee reports with major financial conflicts of interest versus advisory committee reports with minor financial conflicts of interest	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
4.2.1 Major financial conflicts of interest	2	129	Risk Ratio (IV, Random, 95% CI)	1.38 [0.96, 1.99]
4.2.2 Minor financial conflicts of interest	2	104	Risk Ratio (IV, Random, 95% CI)	1.35 [0.97, 1.88]

Analysis 4.1. Comparison 4: Subgroup analyses for advisory committee reports, Outcome 1: Different types of financial conflicts of interest



Analysis 4.2. Comparison 4: Subgroup analyses for advisory committee reports, Outcome 2: Advisory committee reports with major financial conflicts of interest versus advisory committee reports with minor financial conflicts of interest

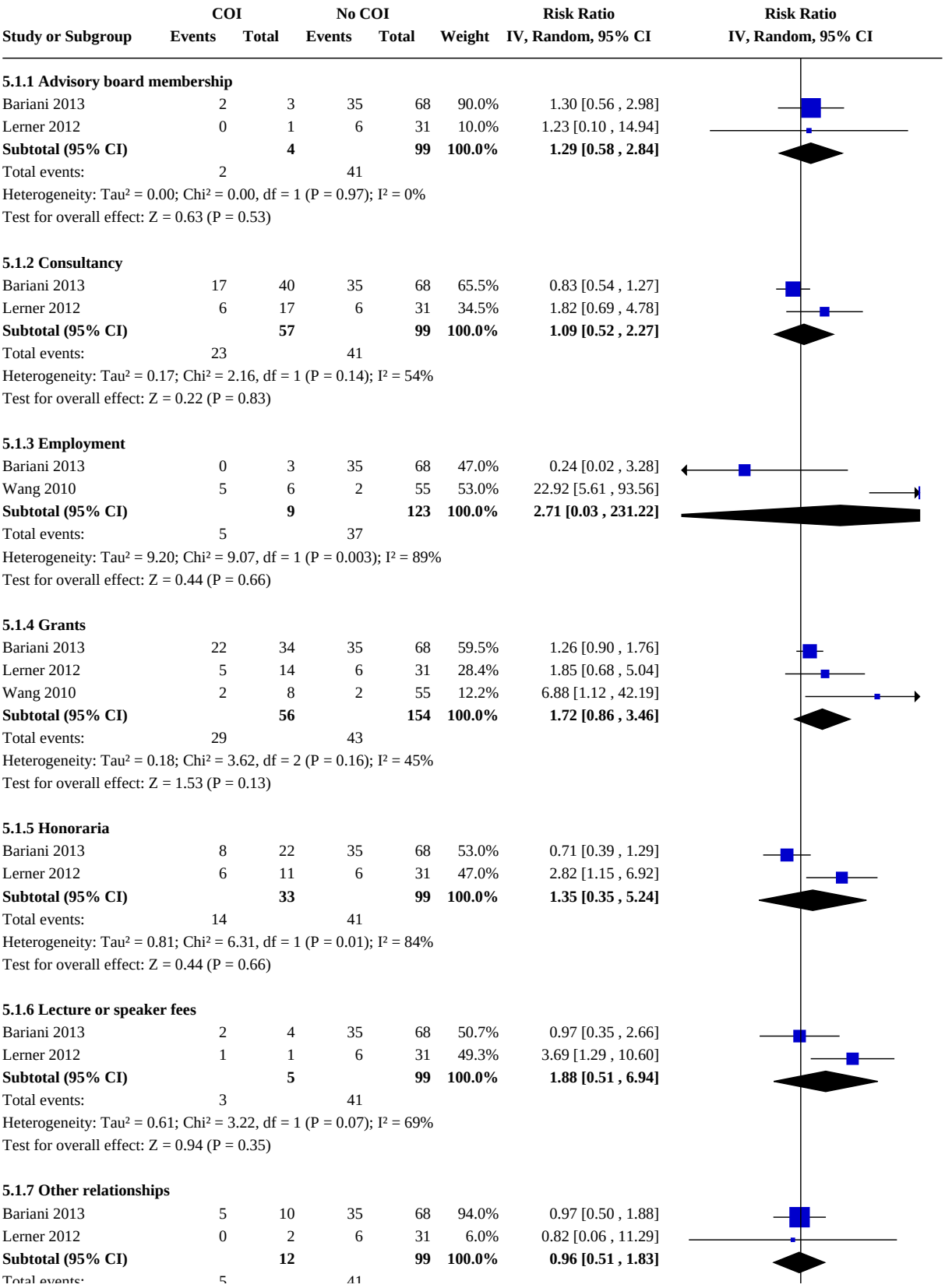


Comparison 5. Subgroup analyses for opinion pieces

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Different types of financial conflicts of interest	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
5.1.1 Advisory board membership	2	103	Risk Ratio (IV, Random, 95% CI)	1.29 [0.58, 2.84]
5.1.2 Consultancy	2	156	Risk Ratio (IV, Random, 95% CI)	1.09 [0.52, 2.27]
5.1.3 Employment	2	132	Risk Ratio (IV, Random, 95% CI)	2.71 [0.03, 231.22]
5.1.4 Grants	3	210	Risk Ratio (IV, Random, 95% CI)	1.72 [0.86, 3.46]
5.1.5 Honoraria	2	132	Risk Ratio (IV, Random, 95% CI)	1.35 [0.35, 5.24]
5.1.6 Lecture or speaker fees	2	104	Risk Ratio (IV, Random, 95% CI)	1.88 [0.51, 6.94]
5.1.7 Other relationships	2	111	Risk Ratio (IV, Random, 95% CI)	0.96 [0.51, 1.83]
5.1.8 Stock ownership	2	107	Risk Ratio (IV, Random, 95% CI)	0.64 [0.22, 1.89]
5.2 Opinion pieces with major financial conflicts of interest versus opinion pieces with minor financial conflicts of interest	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

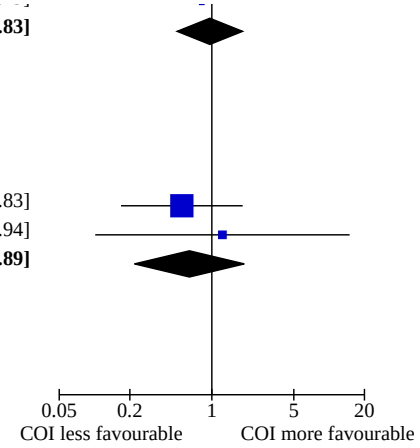
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2.1 Major financial conflicts of interest	1	90	Risk Ratio (IV, Random, 95% CI)	9.43 [2.24, 39.62]
5.2.2 Minor financial conflicts of interest	1	56	Risk Ratio (IV, Random, 95% CI)	5.60 [0.38, 82.41]

Analysis 5.1. Comparison 5: Subgroup analyses for opinion pieces, Outcome 1: Different types of financial conflicts of interest



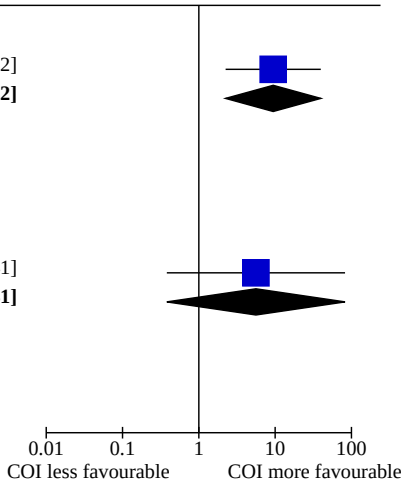
Analysis 5.1. (Continued)

Subtotal (95% CI)		**12**		**99**	**100.0%**	**0.96 [0.51 , 1.83]**
Total events:	5		41			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
5.1.8 Stock ownership						
Bariani 2013	2	7	35	68	81.4%	0.56 [0.17 , 1.83]
Lerner 2012	0	1	6	31	18.6%	1.23 [0.10 , 14.94]
Subtotal (95% CI)		**8**		**99**	**100.0%**	**0.64 [0.22 , 1.89]**
Total events:	2		41			
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Test for subgroup differences: Chi² = 3.49, df = 7 (P = 0.84), I² = 0%						



Analysis 5.2. Comparison 5: Subgroup analyses for opinion pieces, Outcome 2: Opinion pieces with major financial conflicts of interest versus opinion pieces with minor financial conflicts of interest

	COI		No COI			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
5.2.1 Major financial conflicts of interest							
Wang 2010	12	35	2	55	100.0%	9.43 [2.24 , 39.62]	
Subtotal (95% CI)		**35**		**55**	**100.0%**	**9.43 [2.24 , 39.62]**	
Total events:	12		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.06 (P = 0.002)							
5.2.2 Minor financial conflicts of interest							
Wang 2010	0	1	2	55	100.0%	5.60 [0.38 , 82.41]	
Subtotal (95% CI)		**1**		**55**	**100.0%**	**5.60 [0.38 , 82.41]**	
Total events:	0		2				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.26 (P = 0.21)							
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%							



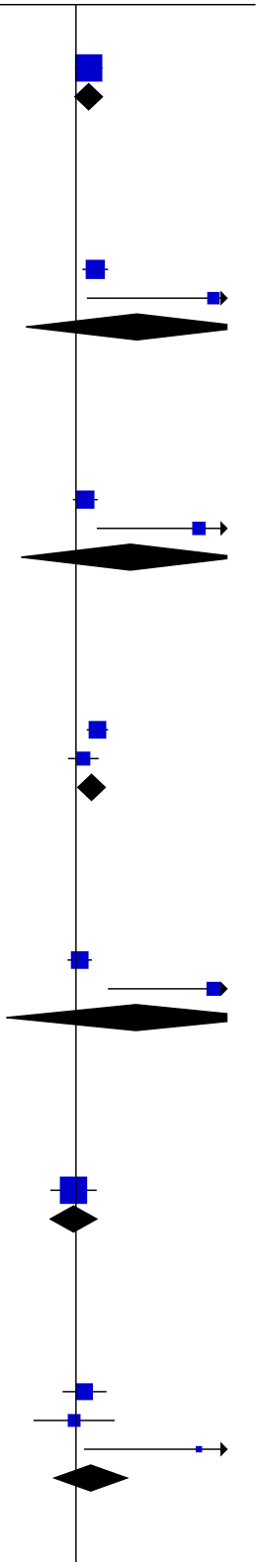
Comparison 6. Subgroup analyses for narrative reviews

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Different types of financial conflicts of interest	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.1.1 Advisory board membership	1	130	Risk Ratio (IV, Random, 95% CI)	1.29 [0.98, 1.69]
6.1.2 Assistance provided by industry	2	169	Risk Ratio (IV, Random, 95% CI)	3.35 [0.37, 30.16]
6.1.3 Consultancy	2	228	Risk Ratio (IV, Random, 95% CI)	2.94 [0.34, 25.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1.4 Employment	2	275	Risk Ratio (IV, Random, 95% CI)	1.36 [1.04, 1.79]
6.1.5 Grants	2	229	Risk Ratio (IV, Random, 95% CI)	3.29 [0.25, 42.87]
6.1.6 Honoraria	1	121	Risk Ratio (IV, Random, 95% CI)	0.95 [0.60, 1.51]
6.1.7 Industry funding of the review	3	315	Risk Ratio (IV, Random, 95% CI)	1.34 [0.65, 2.75]
6.1.8 Lecture or speaker fees	1	122	Risk Ratio (IV, Random, 95% CI)	1.39 [1.06, 1.83]
6.1.9 Other relationships	1	122	Risk Ratio (IV, Random, 95% CI)	1.39 [1.06, 1.83]
6.1.10 Travel grants	1	125	Risk Ratio (IV, Random, 95% CI)	1.27 [0.94, 1.71]
6.2 Narrative reviews with major financial conflicts of interest versus narrative reviews with minor financial conflicts of interest	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
6.2.1 Major financial conflicts of interest	2	277	Risk Ratio (IV, Random, 95% CI)	3.00 [0.34, 26.81]
6.2.2 Minor financial conflicts of interest	2	171	Risk Ratio (IV, Random, 95% CI)	1.21 [0.86, 1.71]

Analysis 6.1. Comparison 6: Subgroup analyses for narrative reviews, Outcome 1: Different types of financial conflicts of interest

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
6.1.1 Advisory board membership						
Dunn 2016	19	25	62	105	100.0%	1.29 [0.98 , 1.69]
Subtotal (95% CI)		**25**		**105**	**100.0%**	**1.29 [0.98 , 1.69]**
Total events:	19		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.82 (P = 0.07)						
6.1.2 Assistance provided by industry						
Dunn 2016	13	15	62	105	64.8%	1.47 [1.14 , 1.89]
Wang 2010	1	3	1	46	35.2%	15.33 [1.24 , 189.38]
Subtotal (95% CI)		**18**		**151**	**100.0%**	**3.35 [0.37 , 30.16]**
Total events:	14		63			
Heterogeneity: Tau² = 1.92; Chi² = 3.31, df = 1 (P = 0.07); I² = 70%						
Test for overall effect: Z = 1.08 (P = 0.28)						
6.1.3 Consultancy						
Dunn 2016	32	45	62	105	60.4%	1.20 [0.94 , 1.54]
Wang 2010	8	32	1	46	39.6%	11.50 [1.51 , 87.50]
Subtotal (95% CI)		**77**		**151**	**100.0%**	**2.94 [0.34 , 25.62]**
Total events:	40		63			
Heterogeneity: Tau² = 2.00; Chi² = 4.68, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 0.98 (P = 0.33)						
6.1.4 Employment						
Dunn 2016	19	21	62	105	58.0%	1.53 [1.24 , 1.89]
Hartog 2012	4	4	113	145	42.0%	1.16 [0.85 , 1.57]
Subtotal (95% CI)		**25**		**250**	**100.0%**	**1.36 [1.04 , 1.79]**
Total events:	23		175			
Heterogeneity: Tau² = 0.02; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%						
Test for overall effect: Z = 2.23 (P = 0.03)						
6.1.5 Grants						
Dunn 2016	42	66	62	105	58.0%	1.08 [0.85 , 1.37]
Wang 2010	4	12	1	46	42.0%	15.33 [1.88 , 124.86]
Subtotal (95% CI)		**78**		**151**	**100.0%**	**3.29 [0.25 , 42.87]**
Total events:	46		63			
Heterogeneity: Tau² = 2.94; Chi² = 6.08, df = 1 (P = 0.01); I² = 84%						
Test for overall effect: Z = 0.91 (P = 0.36)						
6.1.6 Honoraria						
Dunn 2016	9	16	62	105	100.0%	0.95 [0.60 , 1.51]
Subtotal (95% CI)		**16**		**105**	**100.0%**	**0.95 [0.60 , 1.51]**
Total events:	9		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						
6.1.7 Industry funding of the review						
Dunn 2016	7	10	62	105	54.5%	1.19 [0.77 , 1.83]
Hartog 2012	1	1	113	145	36.8%	0.96 [0.43 , 2.16]
Wang 2010	2	8	1	46	8.7%	11.50 [1.18 , 112.43]
Subtotal (95% CI)		**19**		**296**	**100.0%**	**1.34 [0.65 , 2.75]**
Total events:	10		176			
Heterogeneity: Tau² = 0.20; Chi² = 4.06, df = 2 (P = 0.13); I² = 51%						
Test for overall effect: Z = 0.79 (P = 0.43)						



Analysis 6.1. (Continued)

Heterogeneity: Tau² = 0.20; Chi² = 4.06, df = 2 (P = 0.13); I² = 51%
Test for overall effect: Z = 0.79 (P = 0.43)

6.1.8 Lecture or speaker fees

Dunn 2016	14	17	62	105	100.0%	1.39 [1.06 , 1.83]
Subtotal (95% CI)		**17**		**105**	**100.0%**	**1.39 [1.06 , 1.83]**
Total events:	14		62			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.40 (P = 0.02)

6.1.9 Other relationships

Dunn 2016	14	17	62	105	100.0%	1.39 [1.06 , 1.83]
Subtotal (95% CI)		**17**		**105**	**100.0%**	**1.39 [1.06 , 1.83]**
Total events:	14		62			

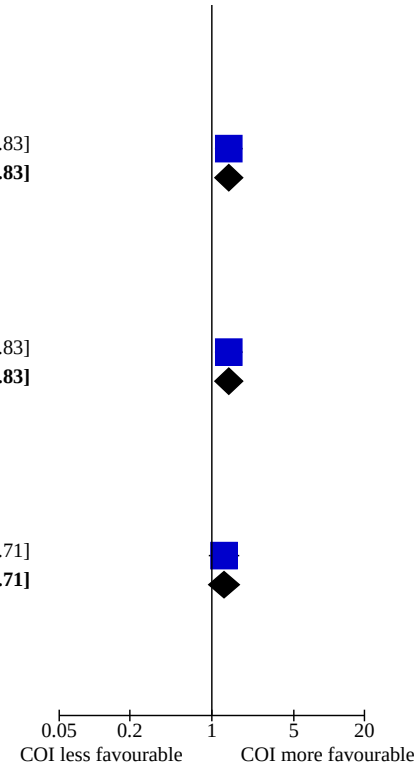
Heterogeneity: Not applicable
Test for overall effect: Z = 2.40 (P = 0.02)

6.1.10 Travel grants

Dunn 2016	15	20	62	105	100.0%	1.27 [0.94 , 1.71]
Subtotal (95% CI)		**20**		**105**	**100.0%**	**1.27 [0.94 , 1.71]**
Total events:	15		62			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)

Test for subgroup differences: Chi² = 4.10, df = 9 (P = 0.90), I² = 0%



Analysis 6.2. Comparison 6: Subgroup analyses for narrative reviews, Outcome 2: Narrative reviews with major financial conflicts of interest versus narrative reviews with minor financial conflicts of interest

	COI		No COI			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
6.2.1 Major financial conflicts of interest							
Dunn 2016	65	91	62	105	60.1%	1.21 [0.98 , 1.49]	
Wang 2010	9	35	1	46	39.9%	11.83 [1.57 , 89.05]	
Subtotal (95% CI)		**126**		**151**	**100.0%**	**3.00 [0.34 , 26.81]**	
Total events:	74		63				

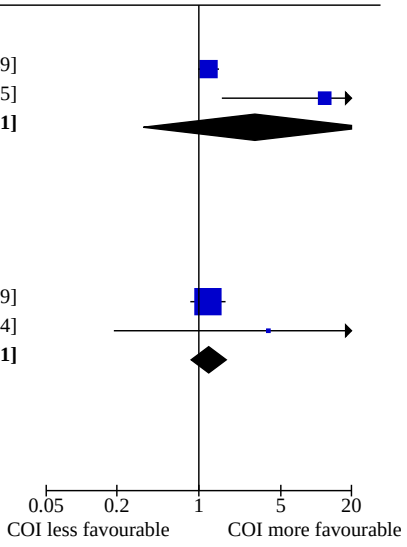
Heterogeneity: Tau² = 2.06; Chi² = 4.85, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 0.99 (P = 0.32)

6.2.2 Minor financial conflicts of interest

Dunn 2016	12	17	62	105	98.7%	1.20 [0.85 , 1.69]
Wang 2010	0	3	1	46	1.3%	3.92 [0.19 , 81.34]
Subtotal (95% CI)		**20**		**151**	**100.0%**	**1.21 [0.86 , 1.71]**
Total events:	12		63			

Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)

Test for subgroup differences: Chi² = 0.64, df = 1 (P = 0.42), I² = 0%

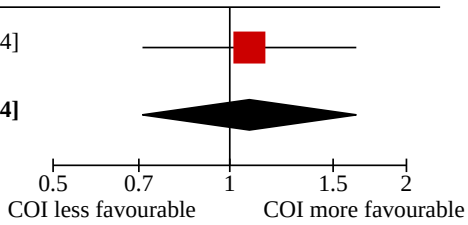


Comparison 7. Sensitivity analyses for clinical guidelines

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Excluding clinical guidelines with unclear or undisclosed financial conflicts of interest	1		Risk Ratio (IV, Random, 95% CI)	1.08 [0.71, 1.64]
7.2 Excluding clinical guidelines with neutral recommendations	1		Risk Ratio (IV, Random, 95% CI)	1.08 [0.71, 1.64]
7.3 Excluding all studies of clinical guidelines which disclosed a relevant conflict of interest of study authors	3		Risk Ratio (IV, Random, 95% CI)	1.23 [0.90, 1.69]
7.4 Re-analysing our primary analyses using fixed-effect meta-analyses	4		Risk Ratio (IV, Fixed, 95% CI)	1.26 [0.93, 1.69]
7.5 Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer	1		Risk Ratio (IV, Random, 95% CI)	1.08 [0.71, 1.64]
7.6 Re-categorising financial conflicts of interest into financial conflicts of interest related to any for-profit company	3		Risk Ratio (IV, Random, 95% CI)	1.46 [0.96, 2.21]

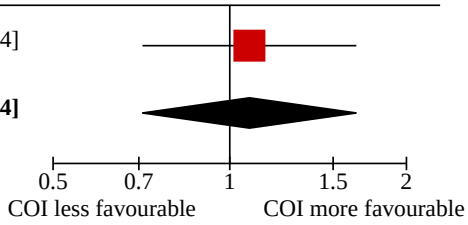
Analysis 7.1. Comparison 7: Sensitivity analyses for clinical guidelines, Outcome 1: Excluding clinical guidelines with unclear or undisclosed financial conflicts of interest

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Norris 2013	0.077	0.214	100.0%	1.08 [0.71 , 1.64]
Total (95% CI)			**100.0%**	**1.08 [0.71 , 1.64]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.36 (P = 0.72)				
Test for subgroup differences: Not applicable				



Analysis 7.2. Comparison 7: Sensitivity analyses for clinical guidelines, Outcome 2: Excluding clinical guidelines with neutral recommendations

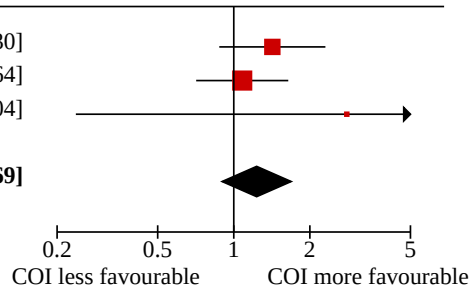
Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Norris 2013	0.077	0.214	100.0%	1.08 [0.71 , 1.64]
Total (95% CI)			**100.0%**	**1.08 [0.71 , 1.64]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.36 (P = 0.72)				
Test for subgroup differences: Not applicable				



Analysis 7.3. Comparison 7: Sensitivity analyses for clinical guidelines, Outcome 3: Excluding all studies of clinical guidelines which disclosed a relevant conflict of interest of study authors

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Aakre 2012	0.3514	0.2466	42.3%	1.42 [0.88 , 2.30]
Norris 2013	0.077	0.214	56.1%	1.08 [0.71 , 1.64]
Wang 2010	1.0296	1.2593	1.6%	2.80 [0.24 , 33.04]
Total (95% CI)			**100.0%**	**1.23 [0.90 , 1.69]**

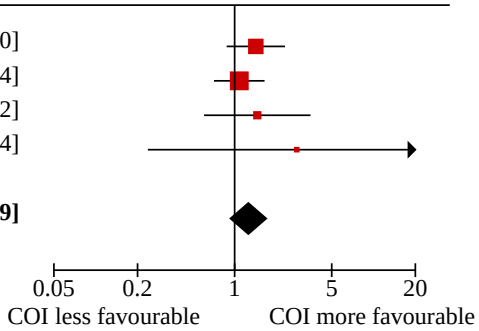
Heterogeneity: Tau² = 0.00; Chi² = 1.14, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)
Test for subgroup differences: Not applicable



Analysis 7.4. Comparison 7: Sensitivity analyses for clinical guidelines, Outcome 4: Re-analysing our primary analyses using fixed-effect meta-analyses

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Aakre 2012	0.3514	0.2466	37.5%	1.42 [0.88 , 2.30]
Norris 2013	0.077	0.214	49.8%	1.08 [0.71 , 1.64]
Tibau 2015	0.3756	0.45	11.3%	1.46 [0.60 , 3.52]
Wang 2010	1.0296	1.2593	1.4%	2.80 [0.24 , 33.04]
Total (95% CI)			**100.0%**	**1.26 [0.93 , 1.69]**

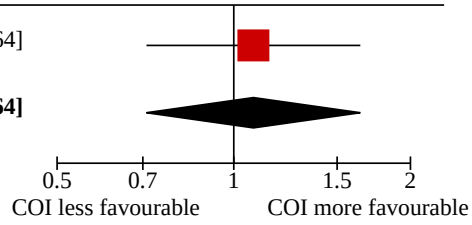
Heterogeneity: Chi² = 1.26, df = 3 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 7.5. Comparison 7: Sensitivity analyses for clinical guidelines, Outcome 5: Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Norris 2013	0.077	0.214	100.0%	1.08 [0.71 , 1.64]
Total (95% CI)			**100.0%**	**1.08 [0.71 , 1.64]**

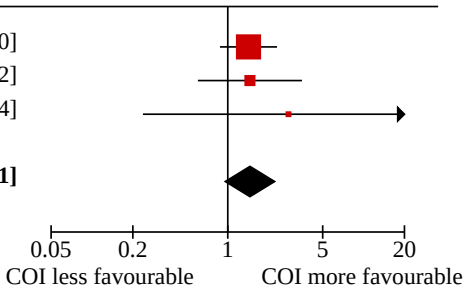
Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable



Analysis 7.6. Comparison 7: Sensitivity analyses for clinical guidelines, Outcome 6: Re-categorising financial conflicts of interest into financial conflicts of interest related to any for-profit company

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
Aakre 2012	0.3514	0.2466	74.7%	1.42 [0.88 , 2.30]
Tibau 2015	0.3756	0.45	22.4%	1.46 [0.60 , 3.52]
Wang 2010	1.0296	1.2593	2.9%	2.80 [0.24 , 33.04]
Total (95% CI)			**100.0%**	**1.46 [0.96 , 2.21]**

Heterogeneity: Tau² = 0.00; Chi² = 0.28, df = 2 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.77 (P = 0.08)
Test for subgroup differences: Not applicable



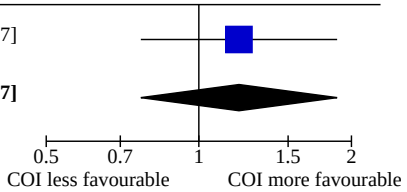
Comparison 8. Sensitivity analyses for advisory committee reports

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.1 Excluding advisory committee reports with unclear or undisclosed conflicts of interest	1	91	Risk Ratio (IV, Random, 95% CI)	1.20 [0.77, 1.87]
8.2 Excluding advisory committee reports with neutral recom-mendations	2	172	Risk Ratio (IV, Random, 95% CI)	1.28 [0.96, 1.70]
8.3 Excluding all studies of advisory committee reports which disclose a relevant conflict of interest of study authors	3	253	Risk Ratio (IV, Random, 95% CI)	1.39 [1.08, 1.80]
8.4 Re-analysing our primary analyses using fixed-effect meta-analyses	4	629	Risk Ratio (IV, Fixed, 95% CI)	1.15 [1.00, 1.32]
8.5 Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer	3	410	Risk Ratio (IV, Random, 95% CI)	1.24 [0.99, 1.54]

Analysis 8.1. Comparison 8: Sensitivity analyses for advisory committee reports, Outcome 1: Excluding advisory committee reports with unclear or undisclosed conflicts of interest

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Ackerley 2009	44	70	11	21	100.0%	1.20 [0.77 , 1.87]
Total (95% CI)		**70**		**21**	**100.0%**	**1.20 [0.77 , 1.87]**
Total events:	44		11			

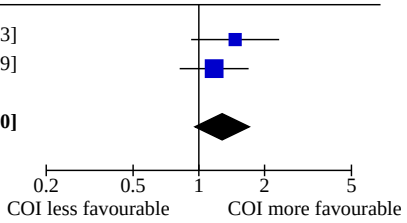
Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Sensitivity analyses for advisory committee reports, Outcome 2: Excluding advisory committee reports with neutral recommendations

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Ackerley 2009	44	70	12	28	38.0%	1.47 [0.92 , 2.33]
Lurie 2006	31	45	17	29	62.0%	1.18 [0.82 , 1.69]
Total (95% CI)		**115**		**57**	**100.0%**	**1.28 [0.96 , 1.70]**
Total events:	75		29			

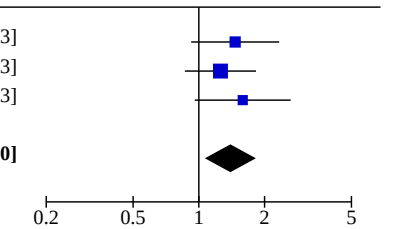
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 8.3. Comparison 8: Sensitivity analyses for advisory committee reports, Outcome 3: Excluding all studies of advisory committee reports which disclose a relevant conflict of interest of study authors

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Ackerley 2009	44	70	12	28	29.6%	1.47 [0.92 , 2.33]
Lurie 2006	31	45	17	31	45.4%	1.26 [0.86 , 1.83]
Tibau 2016	28	47	12	32	25.0%	1.59 [0.96 , 2.63]
Total (95% CI)		**162**		**91**	**100.0%**	**1.39 [1.08 , 1.80]**
Total events:	103		41			

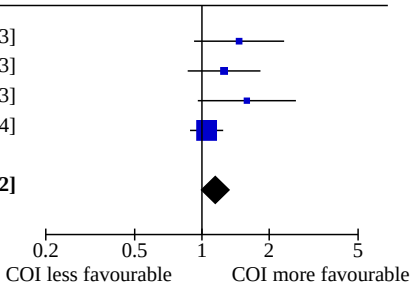
Heterogeneity: Tau² = 0.00; Chi² = 0.60, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 2.58 (P = 0.010)
Test for subgroup differences: Not applicable



Analysis 8.4. Comparison 8: Sensitivity analyses for advisory committee reports, Outcome 4: Re-analysing our primary analyses using fixed-effect meta-analyses

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Fixed, 95% CI
Ackerley 2009	44	70	12	28	9.3%	1.47 [0.92 , 2.33]
Lurie 2006	31	45	17	31	14.2%	1.26 [0.86 , 1.83]
Tibau 2016	28	47	12	32	7.8%	1.59 [0.96 , 2.63]
Zhang 2019	42	57	224	319	68.6%	1.05 [0.88 , 1.24]
Total (95% CI)		**219**		**410**	**100.0%**	**1.15 [1.00 , 1.32]**
Total events:	145		265			

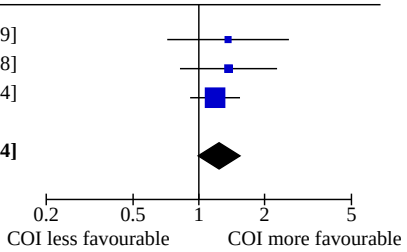
Heterogeneity: Chi² = 3.94, df = 3 (P = 0.27); I² = 24%
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 8.5. Comparison 8: Sensitivity analyses for advisory committee reports, Outcome 5: Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Ackerley 2009	7	12	12	28	11.7%	1.36 [0.72 , 2.59]
Lurie 2006	6	8	17	31	18.4%	1.37 [0.82 , 2.28]
Zhang 2019	10	12	224	319	69.8%	1.19 [0.91 , 1.54]
Total (95% CI)		**32**		**378**	**100.0%**	**1.24 [0.99 , 1.54]**
Total events:	23		253			

Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 2 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



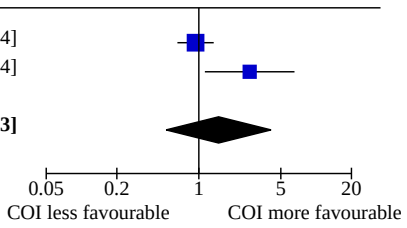
Comparison 9. Sensitivity analyses for opinion pieces

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Excluding opinion pieces with unclear or undisclosed conflicts of interest	2	160	Risk Ratio (IV, Random, 95% CI)	1.47 [0.53, 4.13]
9.2 Excluding opinion pieces with neutral recommendations	3	187	Risk Ratio (IV, Random, 95% CI)	2.00 [0.77, 5.21]
9.3 Excluding all studies of opinion pieces which disclosed a relevant conflict of interest of study authors	3	153	Risk Ratio (IV, Random, 95% CI)	3.84 [1.81, 8.13]
9.4 Re-analysing our primary analyses using fixed-effect meta-analyses	4	284	Risk Ratio (IV, Fixed, 95% CI)	1.27 [0.94, 1.72]
9.5 Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer	2	70	Risk Ratio (IV, Random, 95% CI)	14.69 [4.10, 52.68]
9.6 Re-categorising financial conflicts of interest into financial conflicts of interest related to any for-profit company	3	276	Risk Ratio (IV, Random, 95% CI)	2.45 [0.78, 7.74]

Analysis 9.1. Comparison 9: Sensitivity analyses for opinion pieces, Outcome 1: Excluding opinion pieces with unclear or undisclosed conflicts of interest

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Bariani 2013	32	63	26	48	57.5%	0.94 [0.66 , 1.34]
Lerner 2012	12	23	5	26	42.5%	2.71 [1.13 , 6.54]
Total (95% CI)		**86**		**74**	**100.0%**	**1.47 [0.53 , 4.13]**
Total events:	44		31			

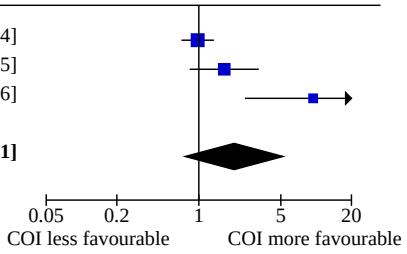
Heterogeneity: Tau² = 0.45; Chi² = 4.81, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9: Sensitivity analyses for opinion pieces, Outcome 2: Excluding opinion pieces with neutral recommendations

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Bariani 2013	32	58	35	62	41.1%	0.98 [0.71 , 1.34]
Lerner 2012	12	17	6	14	35.4%	1.65 [0.84 , 3.25]
Wang 2010	12	14	2	22	23.4%	9.43 [2.47 , 35.96]
Total (95% CI)		**89**		**98**	**100.0%**	**2.00 [0.77 , 5.21]**
Total events:	56		43			

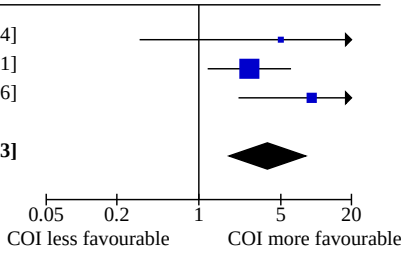
Heterogeneity: Tau² = 0.56; Chi² = 11.53, df = 2 (P = 0.003); I² = 83%
Test for overall effect: Z = 1.42 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 9.3. Comparison 9: Sensitivity analyses for opinion pieces, Outcome 3: Excluding all studies of opinion pieces which disclosed a relevant conflict of interest of study authors

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Hayes 2019	2	4	0	4	7.2%	5.00 [0.31 , 79.94]
Lerner 2012	12	23	6	31	67.6%	2.70 [1.19 , 6.11]
Wang 2010	12	36	2	55	25.3%	9.17 [2.18 , 38.56]
Total (95% CI)		**63**		**90**	**100.0%**	**3.84 [1.81 , 8.13]**
Total events:	26		8			

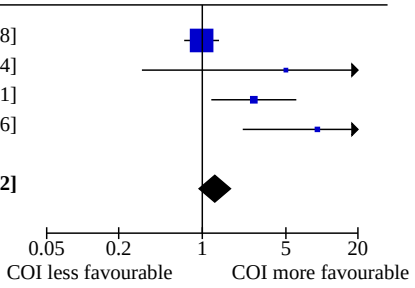
Heterogeneity: Tau² = 0.04; Chi² = 2.15, df = 2 (P = 0.34); I² = 7%
Test for overall effect: Z = 3.51 (P = 0.0004)
Test for subgroup differences: Not applicable



Analysis 9.4. Comparison 9: Sensitivity analyses for opinion pieces, Outcome 4: Re-analysing our primary analyses using fixed-effect meta-analyses

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Fixed, 95% CI
Bariani 2013	32	63	35	68	80.9%	0.99 [0.71 , 1.38]
Hayes 2019	2	4	0	4	1.2%	5.00 [0.31 , 79.94]
Lerner 2012	12	23	6	31	13.6%	2.70 [1.19 , 6.11]
Wang 2010	12	36	2	55	4.4%	9.17 [2.18 , 38.56]
Total (95% CI)		**126**		**158**	**100.0%**	**1.27 [0.94 , 1.72]**
Total events:	58		43			

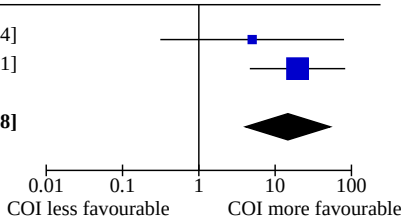
Heterogeneity: Chi² = 13.64, df = 3 (P = 0.003); I² = 78%
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 9.5. Comparison 9: Sensitivity analyses for opinion pieces, Outcome 5: Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Hayes 2019	2	4	0	4	21.2%	5.00 [0.31 , 79.94]
Wang 2010	5	7	2	55	78.8%	19.64 [4.66 , 82.81]
Total (95% CI)		**11**		**59**	**100.0%**	**14.69 [4.10 , 52.68]**
Total events:	7		2			

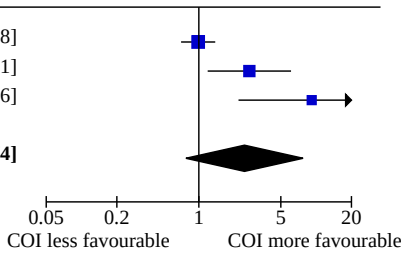
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 4.12 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 9.6. Comparison 9: Sensitivity analyses for opinion pieces, Outcome 6: Re-categorising financial conflicts of interest into financial conflicts of interest related to any for-profit company

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Bariani 2013	32	63	35	68	40.3%	0.99 [0.71 , 1.38]
Lerner 2012	12	23	6	31	34.4%	2.70 [1.19 , 6.11]
Wang 2010	12	36	2	55	25.3%	9.17 [2.18 , 38.56]
Total (95% CI)		**122**		**154**	**100.0%**	**2.45 [0.78 , 7.74]**
Total events:	56		43			

Heterogeneity: Tau² = 0.83; Chi² = 12.69, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 1.53 (P = 0.13)
Test for subgroup differences: Not applicable



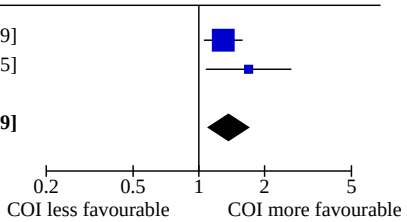
Comparison 10. Sensitivity analyses for narrative reviews

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Excluding narrative reviews with unclear or undisclosed conflicts of interest	2	201	Risk Ratio (IV, Random, 95% CI)	1.37 [1.11, 1.69]
10.2 Excluding narrative reviews with neutral recommendations	3	336	Risk Ratio (IV, Random, 95% CI)	1.17 [0.97, 1.42]
10.3 Excluding all studies of narrative reviews which disclosed a relevant conflict of interest of study authors	3	304	Risk Ratio (IV, Random, 95% CI)	1.39 [0.68, 2.86]
10.4 Re-analysing our primary analyses using fixed-effect meta-analyses	4	457	Risk Ratio (IV, Fixed, 95% CI)	1.19 [1.05, 1.36]
10.5 Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer	3	268	Risk Ratio (IV, Random, 95% CI)	1.16 [0.95, 1.40]
10.6 Re-categorising financial conflicts of interest into financial conflicts of interest related to any for-profit company	2	237	Risk Ratio (IV, Random, 95% CI)	2.86 [0.35, 23.30]

Analysis 10.1. Comparison 10: Sensitivity analyses for narrative reviews, Outcome 1: Excluding narrative reviews with unclear or undisclosed conflicts of interest

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Dunn 2016	55	72	62	105	79.5%	1.29 [1.05 , 1.59]
Hartog 2012	8	8	9	16	20.5%	1.69 [1.08 , 2.65]
Total (95% CI)		**80**		**121**	**100.0%**	**1.37 [1.11 , 1.69]**
Total events:	63		71			

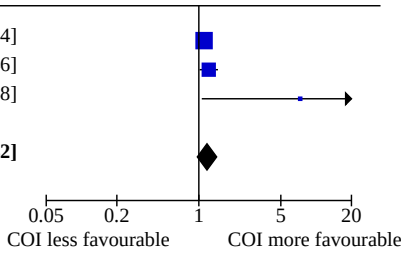
Heterogeneity: Tau² = 0.00; Chi² = 1.12, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 2.89 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 10.2. Comparison 10: Sensitivity analyses for narrative reviews, Outcome 2: Excluding narrative reviews with neutral recommendations

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Dunn 2016	77	82	61	72	56.3%	1.11 [0.99 , 1.24]
Hartog 2012	8	8	113	145	42.8%	1.21 [1.01 , 1.46]
Wang 2010	9	16	1	13	0.9%	7.31 [1.06 , 50.48]
Total (95% CI)		**106**		**230**	**100.0%**	**1.17 [0.97 , 1.42]**
Total events:	94		175			

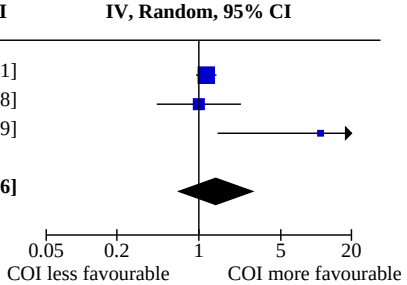
Heterogeneity: Tau² = 0.01; Chi² = 4.27, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 10.3. Comparison 10: Sensitivity analyses for narrative reviews, Outcome 3: Excluding all studies of narrative reviews which disclosed a relevant conflict of interest of study authors

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Dunn 2016	75	108	63	105	56.4%	1.16 [0.95 , 1.41]
Hayes 2019	6	6	1	1	33.2%	1.00 [0.44 , 2.28]
Wang 2010	9	38	1	46	10.4%	10.89 [1.44 , 82.19]
Total (95% CI)		**152**		**152**	**100.0%**	**1.39 [0.68 , 2.86]**
Total events:	90		65			

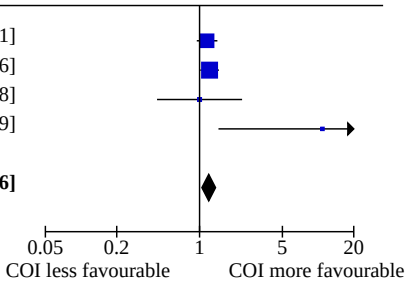
Heterogeneity: Tau² = 0.23; Chi² = 4.83, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable



Analysis 10.4. Comparison 10: Sensitivity analyses for narrative reviews, Outcome 4: Re-analysing our primary analyses using fixed-effect meta-analyses

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Fixed, 95% CI
Dunn 2016	75	108	63	105	43.6%	1.16 [0.95 , 1.41]
Hartog 2012	8	8	113	145	53.4%	1.21 [1.01 , 1.46]
Hayes 2019	6	6	1	1	2.6%	1.00 [0.44 , 2.28]
Wang 2010	9	38	1	46	0.4%	10.89 [1.44 , 82.19]
Total (95% CI)		**160**		**297**	**100.0%**	**1.19 [1.05 , 1.36]**
Total events:	98		178			

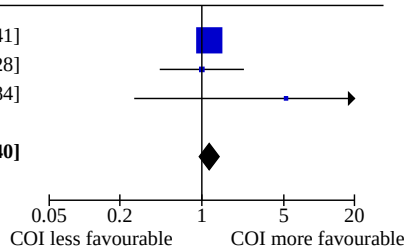
Heterogeneity: Chi² = 4.90, df = 3 (P = 0.18); I² = 39%
Test for overall effect: Z = 2.64 (P = 0.008)
Test for subgroup differences: Not applicable



Analysis 10.5. Comparison 10: Sensitivity analyses for narrative reviews, Outcome 5: Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Dunn 2016	75	108	63	105	94.1%	1.16 [0.95 , 1.41]
Hayes 2019	6	6	1	1	5.5%	1.00 [0.44 , 2.28]
Wang 2010	0	2	1	46	0.4%	5.22 [0.27 , 102.84]
Total (95% CI)		**116**		**152**	**100.0%**	**1.16 [0.95 , 1.40]**
Total events:	81		65			

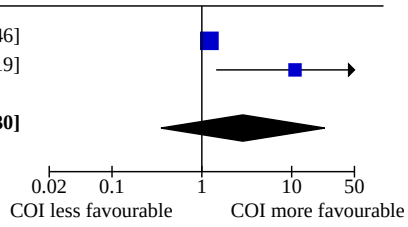
Heterogeneity: Tau² = 0.00; Chi² = 1.10, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 10.6. Comparison 10: Sensitivity analyses for narrative reviews, Outcome 6: Re-categorising financial conflicts of interest into financial conflicts of interest related to any for-profit company

Study or Subgroup	COI Events	COI Total	No COI Events	No COI Total	Weight	Risk Ratio IV, Random, 95% CI
Hartog 2012	8	8	113	145	61.0%	1.21 [1.01 , 1.46]
Wang 2010	9	38	1	46	39.0%	10.89 [1.44 , 82.19]
Total (95% CI)		**46**		**191**	**100.0%**	**2.86 [0.35 , 23.30]**
Total events:	17		114			

Heterogeneity: Tau² = 1.87; Chi² = 4.49, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 0.98 (P = 0.33)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Terminology

We use the overall term ‘conflicts of interest’ to refer to both financial and non-financial conflicts of interest as specified below.

We use the definition by the Institute of Medicine (US) and define 'conflicts of interest' as *"a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest"* (Institute of Medicine 2009). This includes both financial and non-financial conflicts of interest. By financial conflicts of interest we include authors' financial relationships, for example employment, research grants, speaker's bureau membership, stock ownership, and consultancy work and also funding of publication (e.g. a clinical guideline). We focus on financial conflicts of interest related to the drug or device industry. Financial conflicts of interest related to other industries (e.g. tobacco industry) are not included. We define 'drugs' as medications requiring approval from a regulatory authority as a prescription drug. We define 'devices' according to the Food and Drug Administration (FDA) as instruments used in diagnosis, treatment, or prevention of disease (FDA 2017).

As there is no consensus concerning the definition of non-financial conflicts of interest, we generally use the definition used by the authors of the included studies. If the authors do not use the term non-financial conflicts of interest, we use the following subcategories: personal and professional relationships (e.g. research collaboration), professional and specialty interests (e.g. belonging to a certain medial subspecialty), or intellectual and academic conflicts of interest (e.g. authorship of studies that are part of the evidence base for reaching a particular recommendation) (Akl 2014). We do not focus on studies investigating beliefs (e.g. political or religious), personal experience (e.g. abuse or trauma), or institutional conflicts of interest (Bero 2016). In some cases an interest can be considered both a financial and non-financial. For example, a surgeon who uses a particular surgical intervention which he/she then investigates in a clinical guideline. This can be viewed as a financial conflict of interest, because the surgeon might benefit financially if the intervention is recommended. It can also be viewed as a non-financial conflict of interest, because the surgeon uses the surgical procedure as part of clinical practice (i.e. specialty interest) or may have conducted some of the studies included in the guideline (i.e. academic interest). For this review, we regard such relationships as non-financial because they differ from what is typically regarded as financial conflicts of interest (i.e. direct financial relationships with the drug or device industry).

We use the term 'clinical guidelines' to refer to guidelines. We define 'clinical guidelines' as *"Systematically developed statement s to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances"* (Institute of Medicine 1990).

We use the term 'advisory committee reports' to refer to reports or transcripts from meetings held in committees, boards, councils, or similar that are established to advise an organisation and provide a recommendation concerning an intervention (e.g. the Food and Drug Administration's advisory committee on oncological drugs).

We define 'opinion pieces' as documents that are not research studies in which an author expresses a personal opinion about a specific intervention (e.g. editorials, commentaries, and letters-to-the-editors).

We define 'narrative reviews' as literature reviews without a systematic search of the literature with clear eligibility criteria.

We use the term 'documents' to refer to clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews included in the studies.

Appendix 2. PubMed search strategy

Block 1A: drug and device industry

1. Drug Industry (MeSH)

2. Manufacturing Industry (MeSH)

3. (Drug [Title/Abstract] OR drugs[Title/Abstract] OR pharmaceutical[Title/Abstract] OR pharmaceutic [Title/Abstract] OR pharmacological[Title/Abstract] OR pharma*[Title/Abstract] OR biotech*[Title/Abstract] OR bio-tech[Title/Abstract] OR biopharma*[Title/Abstract] OR bio-pharma*[Title/Abstract] OR biomed*[Title/Abstract] OR bio-med*[Title/Abstract] OR device[Title/Abstract] OR devices[Title/Abstract] OR imaging[Title/Abstract] OR for-profit[Title/Abstract] OR private[Title/Abstract]) AND (industry[Title/Abstract] OR industries[Title/Abstract] OR company[Title/Abstract] OR companies[Title/Abstract] OR manufacturer[Title/Abstract] OR manufacturers[Title/Abstract] OR organisation[Title/Abstract] OR organisations[Title/Abstract] OR organization[Title/Abstract] OR organizations[Title/Abstract] OR agency[Title/Abstract] OR agencies[Title/Abstract] OR sector[Title/Abstract] OR sectors[Title/Abstract])

4. Personal[Title] OR self-reported[Title] OR selfreported[Title] OR author[Title] OR authors[Title] OR authorship[Title] OR ((committee[Title] OR board[Title]) AND (member[Title] OR members[Title])) OR voting[Title] OR votings[Title] OR financial[Title] OR finance[Title]

5. 1 OR 2 OR 3 OR 4

Block 1B: financial conflicts of interest

6. Conflict of interest (MeSH)

7. Financial support (MeSH)

8. Research support as topic (MeSH)

9. (Conflict[Title/Abstract] OR conflicts[Title/Abstract] OR conflicting[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])

10. (Competing[Title/Abstract] OR vested[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])

11. (Industry[Title/Abstract] OR industries[Title/Abstract] OR company[Title/Abstract] OR companies[Title/Abstract] OR manufacturer[Title/Abstract] OR manufacturers[Title/Abstract] OR finance[Title/Abstract] OR financial[Title/Abstract]) AND (funded[Title/Abstract] OR funding[Title/Abstract] OR sponsor[Title/Abstract] OR sponsors[Title/Abstract] OR sponsorship[Title/Abstract] OR sponsoring[Title/Abstract] OR support[Title/Abstract] OR supported[Title/Abstract] OR finance[Title/Abstract] OR financial[Title/Abstract] OR involvement[Title/Abstract] OR involving[Title/Abstract] OR payment[Title/Abstract] OR payments[Title/Abstract] OR relationship[Title/Abstract] OR relationships[Title/Abstract] OR relation[Title/Abstract] OR relations[Title/Abstract] OR tie[Title/Abstract] OR ties[Title/Abstract] OR collaboration[Title/Abstract] OR collaborations[Title/Abstract])

12. Industry-funded[Title/Abstract] OR industry-funding[Title/Abstract] OR industry-sponsor*[Title/Abstract] OR company-funded[Title/Abstract] OR company-funding[Title/Abstract] OR company-sponsor*[Title/Abstract] OR industry-support[Title/Abstract] OR industry-supported[Title/Abstract] OR company-support[Title/Abstract] OR company-supported[Title/Abstract]

13. (Commercial-academic[Title/Abstract] OR academic-commercial[Title/Abstract] OR industry-academic[Title/Abstract] OR academic-industry[Title/Abstract] OR commercial-industry[Title/Abstract] OR industry-commercial[Title/Abstract] OR industry-physician[Title/Abstract] OR physician-industry[Title/Abstract]) AND (interaction[Title/Abstract] OR interactions[Title/Abstract] OR relationship[Title/Abstract] OR relationships[Title/Abstract] OR relation[Title/Abstract] OR relations[Title/Abstract] OR collaboration[Title/Abstract] OR collaborations[Title/Abstract])

14. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13

Block 2A: non-financial, personal, and academic

15. Non-financial[Title/Abstract] OR nonfinancial[Title/Abstract]

16. Personal[Title] OR individual[Title] OR self-reported[Title] OR selfreported[Title] OR author[Title] OR authors[Title] OR authorship[Title]

17. Specialist[Title/Abstract] OR specialists[Title/Abstract] OR specialty[Title/Abstract] OR expert[Title/Abstract] OR experts[Title/Abstract] OR intellectual[Title/Abstract] OR intellectuals[Title/Abstract] OR professional[Title/Abstract] OR professionals[Title/Abstract] OR academic[Title/Abstract] OR academics[Title/Abstract]

18. 15 OR 16 OR 17

Block 2B: non-financial conflicts of interest

19. Conflict of interest (MeSH)

20. Conflict[Title] OR conflicts[Title] OR conflicting[Title] OR competing[Title] OR vested[Title]

21. Relation[Title] OR relations[Title] OR relationship[Title] OR relationships[Title]

22. Interest[Title] OR interests[Title]

23. 19 OR 20 OR 21 OR 22

Block 3: clinical guidelines, advisory committee reports opinion pieces, and narrative reviews

24. (Opinion[Title/Abstract] OR opinions[Title/Abstract] OR policy[Title/Abstract] OR policies[Title/Abstract] OR statement[Title/Abstract] OR statements[Title/Abstract]) AND (piece[Title/Abstract] OR pieces[Title/Abstract] OR article[Title/Abstract] OR articles[Title/Abstract])

25. (Narrative[Title/Abstract] OR descriptive[Title/Abstract] OR non-systematic[Title/Abstract] OR non-systematical[Title/Abstract] OR non-systematically[Title/Abstract] OR nonsystematic[Title/Abstract] OR nonsystematical[Title/Abstract] OR nonsystematically[Title/Abstract]) AND (review[Title/Abstract] OR reviews[Title/Abstract] OR overview[Title/Abstract] OR overviews[Title/Abstract])

26. Non[Title/Abstract] AND (systematic[Title/Abstract] OR systematical[Title/Abstract] OR systematically[Title/Abstract]) AND (review[Title/Abstract] OR reviews[Title/Abstract] OR overview[Title/Abstract] OR overviews[Title/Abstract])

27. Editorial[Title] OR editorials[Title] OR essay[Title] OR essays[Title] OR commentary[Title] OR commentaries[Title] OR comment[Title] OR comments[Title] OR letter[Title] OR letters[Title]

28. (Treatment[Title/Abstract] OR treatments[Title/Abstract] OR screening[Title/Abstract] OR screen[Title/Abstract] OR testing[Title/Abstract] OR test[Title/Abstract] OR tests[Title/Abstract OR diagnostic[Title/Abstract] OR diagnosis[Title/Abstract] OR therapy[Title/Abstract] OR therapies[Title/Abstract]) AND (recommendation[Title/Abstract] OR recommendations[Title/Abstract])

29. Guidelines as Topic (MeSH)

30. Health Planning Guidelines (MeSH)

31. (Clinical[Title] OR clinic[Title] OR health[Title] OR practice[Title]) AND (guideline[Title] OR guidelines[Title] OR recommendation[Title] OR recommendations[Title])

32. (Advisory[Title/Abstract] OR advising[Title/Abstract] OR formulary[Title/Abstract] OR counselling[Title/Abstract] OR counselling[Title/Abstract] OR drug[Title/Abstract] OR drugs[Title/Abstract]) AND (board[Title/Abstract] OR boards[Title/Abstract] OR committee[Title/Abstract] OR committees[Title/Abstract] OR panel[Title/Abstract] OR panels[Title/Abstract] OR meeting[Title/Abstract] OR meetings[Title/Abstract])

33. 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32

Combined searches

34. 5 AND 14

35. 18 AND 23

36. (34 OR 35) AND 33

Appendix 3. Data extraction

Two review authors independently extracted the following information.

Study characteristics

- Title.
- Name of lead author.
- Name of journal.
- Year published.
- Primary aim of the study.
- Design of study: cohort, cross-sectional study, systematic review or meta-analysis, or other.
- Study domain - category: clinical guideline, advisory committee report, opinion pieces, narrative review, or mixed.
- Sample description: for example, clinical guidelines on treatment of hypertensionStrategy used to collect sample: for example, search of PubMed and time period coveredDefinition of clinical guidelines, advisory committee reports, opinion pieces, or narrative reviews used in the study. Verbatim extraction.
- Number of included documents (separate data for clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews).
- Types of documents included in the study. Verbatim extraction.
- Types of documents included in the study (drug, device or both).

Conflict of interest and outcome data

- Definition of financial conflicts of interest used in the study. Verbatim extraction.
- Definition of non-financial conflicts of interest used in the study. Verbatim extraction.
- Types of financial conflicts of interest investigated, potential categories are:
  - funding;
  - author grant;
  - honorarium;
  - consulting;
  - speakers bureau.
- Types of non-financial conflicts of interest investigated.
- Definition of favourable recommendations used by the authors of the study. Verbatim extraction.
- Definition of primary analysis used in the study. Verbatim extraction.

- Total number of documents with and without conflicts of interest. Stratified by type of document (i.e. clinical guideline, advisory committee reports, opinion piece, narrative review) and type of conflicts of interest (i.e. financial, non-financial).
- Number of documents with and without conflicts of interest with favourable recommendations stratified by type of documents (i.e. clinical guideline, advisory committee reports, opinion piece, narrative review) and type of conflicts of interest (i.e. financial, non-financial).
- Any data on estimates of the association between financial conflicts of interest/non-financial conflicts of interest and recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews (for example, adjusted effect estimates and confidence intervals).

Data for informing subgroup analyses or reflection on heterogeneity

- Total number of documents with conflicts of interest and number with favourable recommendations. Stratified by document type (i.e. clinical guidelines, advisory committee reports, opinion pieces, narrative reviews) and category of financial conflicts of interest (e.g. investigator, grants, honorarium, consulting, speaker's bureau, equity/stock, gifts).
- Any data on the association between each category of financial conflicts of interest and favourable recommendations.
- Total number of clinical guidelines following standardised methods with and without conflicts of interest and number with favourable recommendations. Stratified by type of conflicts of interest (i.e. financial, non-financial).
- Total number of clinical guidelines not following standardised methods with and without conflicts of interest and number with favourable recommendations. Stratified by type of conflicts of interest (i.e. financial, non-financial).
- Any data on the association between conflicts of interest and favourable recommendations for clinical guidelines following standardised methods and clinical guidelines not following standardised methods.
- Total number of documents with conflicts of interest and number with favourable recommendations. Stratified by document type (i.e. clinical guidelines, advisory committee reports, opinion pieces, narrative reviews) and degree of financial conflicts of interest (i.e. major and minor).
- Any data on the association between major and minor financial conflicts of interest and favourable recommendations.

Data for performing sensitivity analyses

- Total number of documents with and without conflicts of interest and number of documents in each group with favourable recommendations, when excluding documents with unclear or undisclosed conflicts of interest. Stratified by document type (i.e. clinical guidelines, advisory committee reports, opinion pieces, narrative reviews) and type of conflicts of interest (i.e. financial, non-financial).
- Any data on the association between conflicts of interest and favourable recommendations, when excluding documents with unclear or undisclosed conflicts of interest.
- Total number of documents with and without conflicts of interest and number of documents in each group with favourable recommendations, when excluding documents with neutral recommendations. Stratified by document type (i.e. clinical guidelines, advisory committee reports, opinion pieces, narrative reviews) and type of conflicts of interest (i.e. financial, non-financial).
- Any data on the association between conflicts of interest and favourable recommendations, when excluding documents with neutral recommendations.
- Total number of documents with and without financial conflicts of interest and number of documents in each group with favourable recommendations. Stratified by document type (i.e. clinical guidelines, advisory committee reports, opinion pieces, narrative reviews) and type of financial conflict of interest (i.e. related to the manufacturer or related to any for-profit company).
- Any data on the association between financial conflicts of interest and favourable recommendations. Stratified by type of financial conflict of interest (i.e. related to the manufacturer or related to any for-profit company).

Additional data

- Funding and conflicts of interest statement in the study. Verbatim extraction.
- Additional relevant information.

Appendix 4. Dealing with missing data

Protocols

We contacted authors in an attempt to obtain published or unpublished protocols for all the studies. All author teams but two responded (Cooper 2019; Xu 2017). Nine author teams replied that no protocol was used (Aakre 2012; Ackerley 2009; Bariani 2013; Dunn 2016; George 2014; Hartog 2012; Hayes 2019; Pham-Kanter 2014; Zhang 2019), six author teams replied that they had a protocol, but could not locate or access it (Lerner 2012; Norris 2012; Norris 2013; Stelfox 1998; Tibau 2015; Tibau 2016), and two author teams supplied us with their protocol (Downing 2014; Lurie 2006). One author team replied that they had a protocol, but it was incorporated in the study publication (Wang 2010), and one author team supplied us with a master thesis that was used as basis of the study (Schott 2013). However, in both cases these were in our views not protocols (i.e. a document that details the study rationale and proposed methods written prior to study conduct) (Chan 2013).

'Risk of bias' assessment

If the studies did not report their methods in a way that enabled us to conduct our 'Risk of bias' assessment, we contacted the authors to clarify these issues. In total, we contacted authors of all the studies and received clarifications for all but two studies (Cooper 2019; Xu 2017).

Unpublished data

We contacted the authors of the included studies in an attempt to obtain additional individual study data or summary data in the following cases.

- If the studies included a mixture of documents, but only reported combined data. For example, if a study included clinical guidelines and randomised trials, we contacted the authors to obtain separate data on clinical guidelines.
- If the studies performed unadjusted or adjusted regression analyses, but did not report the raw numbers.
- If the studies extracted information on different types of financial conflicts of interest and/or number of authors with and without financial conflicts of interest in each document, but did not report this information.
- If the studies included documents with undisclosed conflicts of interest and/or neutral recommendations, but did not report this in a separate category.

In total, we contacted authors of 17 studies (Aakre 2012; Ackerley 2009; Bariani 2013; Cooper 2019; Downing 2014; Dunn 2016; Hartog 2012; Hayes 2019; Lerner 2012; Lurie 2006; Pham-Kanter 2014; Stelfox 1998; Tibau 2015; Tibau 2016; Wang 2010; Xu 2017; Zhang 2019) and received data for 11 of these studies; eight full data sets (Ackerley 2009; Bariani 2013; Dunn 2016; Hartog 2012; Lerner 2012; Lurie 2006; Wang 2010; Zhang 2019) and in three cases additional summary data (Pham-Kanter 2014; Tibau 2015; Tibau 2016).

When we received unpublished data, we analysed the data according to the methods used in the original studies. For the study on advisory committee reports by Ackerley and colleagues (Ackerley 2009), we restricted the sample for analysis to standing or temporary committee members that participated in the meeting and the voting in line with the authors' analysis.

Appendix 5. Calculation of prediction intervals

Formula for prediction interval

We only calculated prediction intervals when at least four studies were included in the pooled analysis, because intervals will be imprecise when the effect estimates are based on only a few studies (IntHout 2016).

To calculate prediction intervals, we used the formula presented in an article by Riley and colleagues (Riley 2011):

$$\hat{u} - t_{k-2} \cdot \sqrt{(T^2 + SE(\hat{u})^2)},\ \hat{u} + t_{k-2} \cdot \sqrt{(T^2 + SE(\hat{u})^2)}$$

Where $\hat{u}$ was the estimate of the average effect measure across studies, $SE(\hat{u})$ was the standard error of $\hat{u}$, $\hat{T}$ was the estimate of between study standard deviation, and t_{k-2} was the 100(1-(α/2)) percentile of the t-distribution with k-2 degrees of freedom, where k was the number of studies in the meta-analysis and was 0.05 to give a 95% prediction interval. To meet the assumption on normal distribution, the prediction interval was derived on the natural log scale (Riley 2011). As T^2 is already a measure for the heterogeneity for ln(RR), this was used directly in the calculation (IntHout 2016).

Calculation of prediction interval for clinical guidelines

The prediction interval for the RR of favourable recommendations in clinical guidelines with financial conflicts of interest compared with clinical guidelines without financial conflicts of interest was calculated as: 0.65 to 2.43. Thus, one can expect that clinical guidelines with financial conflicts of interest more often have favourable recommendations compared with clinical guidelines without financial conflicts of interest, but for an individual study of clinical guidelines the association may be reversed.

As our analysis on non-financial conflicts of interest in clinical guidelines was based on only one study, calculation of a prediction interval was only possible for financial conflicts of interest.

Calculation of prediction interval for advisory committee reports

The prediction interval for the RR of favourable recommendations in advisory committee reports with financial conflicts of interest compared with advisory committee reports without financial conflicts of interest was calculated as: 0.66 to 2.19. Thus, one can expect that advisory committee reports with financial conflicts of interest more often have favourable recommendations compared with advisory committee reports without financial conflicts of interest, but for an individual study of advisory committee reports the association may be reversed.

Calculation of prediction interval for opinion pieces

The prediction interval for the RR of favourable recommendations in opinion pieces with financial conflicts of interest compared with opinion pieces without financial conflicts of interest was calculated as: 0.03 to 220.56. Thus, one can expect that opinion pieces with financial conflicts of interest more often have favourable recommendations compared with opinion pieces without financial conflicts of interest, but for an individual study of opinion pieces the association may be reversed.

Calculation of prediction interval for narrative reviews

The prediction interval for the RR of favourable recommendations in narrative reviews with financial conflicts of interest compared with narrative reviews without financial conflicts of interest was calculated as: 0.56 to 2.59. Thus, one can expect that narrative reviews with financial conflicts of interest more often have favourable recommendations compared with narrative reviews without financial conflicts of interest, but for an individual study of narrative reviews the association may be reversed.

Calculation of prediction interval for combined post-hoc secondary analysis

The prediction interval for the RR of favourable recommendations in documents with financial conflicts of interest compared with documents without financial conflicts of interest was calculated as: 0.88 to 1.80. Thus, one can expect that documents with financial conflicts of interest more often have favourable recommendations compared with documents without financial conflicts of interest, but for an individual study the association may be reversed.

Appendix 6. Number Needed to Read

Number Needed to Read

For each document type, we calculated a Number Needed to Read as 1/Risk Difference. We calculated the Risk Difference based on the estimates presented in the 'Summary of findings' table (Appendix 9). For each estimated Number Needed to Read, we calculated corresponding 95% confidence intervals using the methods described by Altman (Altman 1998) with Number Needed to Read Favourable (NNRF) representing the expected number of documents with conflicts of interest needed to be read rather than documents without conflicts of interest for one additional document having a favourable recommendation, and Number Needed to Read Unfavourable (NNRU) representing the expected number of documents with conflicts of interest needed to be read rather than documents without conflicts of interest for one additional document having an unfavourable recommendation.

The Number Needed to Read for clinical guidelines was 9.1. The corresponding 95% CI was NNRU 33.3 to ∞ to NNRF 3.4.

The Number Needed to Red for advisory committee reports was 7.7. The corresponding 95% CI was NNRU 100.0 to ∞ to NNRF 3.4.

The Number Needed to Read for opinion pieces was 2.3. The corresponding 95% CI was NNRU 50.0 to ∞ to NNRF 1.4.

The Number Needed to Read for narrative reviews was 8.3. The corresponding 95% CI was NNRU 50.0 to ∞ to NNRF 3.4.

The Number Needed to Read for all document types was 7.1. The corresponding 95% CI was NNRF 20 to NNRF 4.2.

The Number Needed to Read for non-financial conflicts of interest in clinical guidelines was 2.1. The corresponding 95% CI was NNRU 25.0 to ∞ to NNRF 1.8.

Appendix 7. Subgroup analyses

Findings from subgroup analyses on clinical guidelines

Different types of financial conflicts of interest

Of the four studies included in our pooled analysis on financial conflicts of interest, two studies specified subtypes of financial conflicts of interest (Aakre 2012; Wang 2010). We were able to pool data on six different types of financial conflicts of interest: advisory board membership, consultancy, grants, honoraria, industry funding of the clinical guideline, and speaker fees.

We found no difference in recommendations between guidelines with different types of financial conflicts of interest, but estimates were statistically imprecise (P value for interaction test: 0.95; Analysis 3.1).

High risk of bias versus low risk of bias studies

We planned to compare studies assessed as high risk of bias with studies assesses as low risk of bias. However, all four studies included in our pooled analysis on clinical guidelines were assessed as having high risk of bias, and it was not possible to carry out this subgroup analysis.

Clinical guidelines developed using standardised methods versus clinical guidelines not developed using standardised methods

We planned to compare clinical guidelines developed using standardised methods (e.g. through GRADE or US Preventive Services Task Force) with clinical guidelines developed without. Only one of the four studies included in our pooled analysis on financial conflicts of

interest in clinical guidelines clearly stated that included clinical guidelines had to provide documentation that a systematic literature search and review was done (Norris 2013). In the remaining three studies, methodological aspects of the included clinical guidelines were not reported and the study samples could potentially be a mixture of clinical guidelines with and without standardised methods. None of the studies had any references to either GRADE or US Preventive Services Task Force. Therefore, our data did not enable us to carry out this subgroup analysis.

Clinical guidelines with major financial conflicts of interest versus clinical guidelines with minor financial conflicts of interest

We were able to assess the number of authors with financial conflicts of interest in each clinical guideline in two studies (Norris 2013; Wang 2010). We found no difference in recommendations between guidelines with major (i.e. at least half of the authors) and minor (i.e. less than half of the authors) financial conflicts of interest, but estimates were statistically imprecise (P value for interaction test: 0.20, Analysis 3.2).

Findings from subgroup analyses on advisory committee reports

Different types of financial conflicts of interest

Of the four studies included in our primary analysis on financial conflicts of interest, one study specified different types of financial conflicts of interest (Ackerley 2009). We were able to pool data on five different types of financial conflicts of interest: consultancy, grants, investments, lecturing and honoraria, and other relationships of committee members (including e.g. patents and expert witness).

We found no difference in recommendations between advisory committee reports with different types of financial conflicts of interest, but estimates were statistically imprecise (P value for interaction test: 0.82, Analysis 4.1).

High risk of bias versus low risk of bias studies

We planned to analyse studies assessed as high risk of bias with studies assesses as low risk of bias. However, all four studies included in our pooled analysis on advisory committee reports were assessed as high risk of bias, and it was not possible to carry out this subgroup analysis.

Advisory committee reports with major financial conflicts of interest versus advisory committee reports with minor financial conflicts of interest

We were able to assess the number of committee members with financial conflicts of interest in each advisory committee report in two studies (Ackerley 2009; Lurie 2006). We found no difference in recommendations between advisory committee reports with major (i.e. at least half of the committee members) and minor (i.e. less than half of the committee members)financial conflicts of interest, but estimates were statistically imprecise (P value for interaction test: 0.92, Analysis 4.2).

Findings from subgroup analyses on opinion pieces

Different types of financial conflicts of interest

Three of the four studies included in our pooled analysis on financial conflicts of interest in opinion pieces investigated different types of financial conflicts of interest. We were able to pool data from the studies on eight types of financial conflicts of interest: advisory board membership, consultancy, employment, grants, honoraria, lecture or speaker fees, other relationships (including royalties, testimony, patents, and travel grants), and stock ownership.

We found no difference in recommendations between opinion pieces with different types of financial conflicts of interest, but estimates were statistically imprecise (P value for interaction test: 0.84, Analysis 5.1).

High risk of bias versus low risk of bias studies

We planned to compare studies assessed as high risk of bias with studies assessed as low risk of bias. However, all four studies included in our pooled analysis on opinion pieces were assessed as high risk of bias, and it was not possible to carry out this subgroup analysis.

Opinion pieces with major financial conflicts of interest versus opinion pieces with minor financial conflicts of interest

We were able to assess the number of authors with financial conflicts of interest in each opinion piece in one study (Wang 2010). We found no difference in recommendations between opinion pieces with major (i.e. at least half of the authors)and minor (i.e. less than half of the authors) financial conflicts of interest, but estimates were statistically imprecise (P value for interaction test: 0.74, Analysis 5.2).

Findings from subgroup analyses on narrative reviews

Different types of financial conflicts of interest

Three of the four studies investigating narrative reviews investigated different types of financial conflicts of interest. We were able to pool data on nine types: advisory board membership, assistance provided by industry, consultancy, employment, grants, honoraria, industry funding of the review, lecture or speaker fees, other relationships of review authors, and travel grants.

We found no difference in recommendations between reviews with different types of financial conflicts of interest, but estimates were statistically imprecise (P value for interaction test: 0.90, Analysis 6.1).

High risk of bias versus low risk of bias studies

We planned to compare studies assessed as high risk of bias with studies assessed as low risk of bias. However, all four studies included in our pooled analysis on narrative reviews were assessed as high risk of bias, and it was not possible to carry out this subgroup analysis.

Narrative reviews with major financial conflicts of interest versus narrative reviews with minor financial conflicts of interest

We were able to assess the number of authors with financial conflicts of interest in narrative review in two studies (Dunn 2016; Wang 2010). We found no difference in recommendations between reviews with major (i.e. at least half of the authors)and minor (i.e. less than half of the authors) financial conflicts of interest, but estimates were statistically imprecise (P value for interaction test: 0.42, Analysis 6.2).

Appendix 8. Sensitivity analyses

Findings from sensitivity analyses on clinical guidelines

Excluding clinical guidelines with unclear or undisclosed conflicts of interest

One of the studies included in the pooled analysis on financial conflicts of interest only included clinical guidelines with clear conflicts of interest statements (Norris 2013). In the remaining three studies it was not possible to exclude clinical guidelines with unclear or undisclosed conflicts of interest, because reporting of data did not allow it (Tibau 2015), or the authors did not code this information in their raw datasets (Aakre 2012; Wang 2010). In our analysis excluding clinical guidelines with undisclosed financial conflicts of interest, we found somewhat similar results as the primary analysis (from RR: 1.26, 95% CI: 0.93 to 1.69 in the primary analysis to RR: 1.08, 95% CI: 0.71 to 1.64, Analysis 7.1).

The one study investigating non-financial conflicts of interest included no clinical guidelines with undisclosed conflicts of interest (Norris 2012).

Excluding clinical guidelines with neutral recommendations

One of the studies included in our pooled analysis on financial conflicts of interest included no clinical guidelines with neutral recommendations (Norris 2013). In two studies, the sample did not include any clinical guidelines without favourable recommendations (Aakre 2012) or without conflicts of interest (Wang 2010), when we removed clinical guidelines with neutral recommendations. In the remaining study, it was not possible to remove clinical guidelines with neutral recommendations, because reporting of data did not allow it (Tibau 2015). Thus, our sensitivity analysis for financial conflicts of interest was based on one study (Norris 2013). We found somewhat similar results as our primary analysis (from RR: 1.26, 95% CI: 0.93 to 1.69 in the primary analysis to RR: 1.08, 95% CI: 0.71 to 1.64, Analysis 7.2).

In the one study investigating specialty interest in clinical guidelines, a neutral category was not used for categorising recommendations. Therefore, it was not possible to undertake a sensitivity analysis excluding clinical guidelines with neutral recommendations (Norris 2012).

Excluding all studies of clinical guidelines which disclosed a relevant conflict of interest of study authors

One of the studies included in our pooled analysis disclosed financial conflicts of interest of study authors (Tibau 2015). Excluding this study from our pooled analysis on financial conflicts of interest did not affect our findings (from RR: 1.26, 95% CI: 0.93 to 1.69 in the primary analysis to RR: 1.23, 95% CI: 0.90 to 1.69, Analysis 7.3).

The one study investigating non-financial conflicts of interest did not disclose any conflicts of interest of the study authors (Norris 2012).

Re-analysing our primary analyses using fixed-effect meta-analyses

Re-analysing our primary analysis using fixed-effect models did not affect our findings on financial conflicts of interest (from RR: 1.26, 95% CI: 0.93 to 1.69 in the primary analysis to RR: 1.26, 95% CI: 0.93 to 1.69, Analysis 7.4).

As only one study was included in our analysis on non-financial conflicts of interest, it was not meaningful to carry out this sensitivity analysis.

Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer and financial conflicts of interest related to any for-profit company

One of the studies included in our pooled analysis measured financial conflicts of interest related to the manufacturer of the investigated drug (Norris 2013), whereas three studies measured financial conflicts of interest related to any for-profit company (Aakre 2012; Tibau 2015), or included only clinical guidelines with financial conflicts of interest related to any for-profit company (Wang 2010). Both our sensitivity analyses showed somewhat similar results as our primary analysis (from RR: 1.26, 95% CI: 0.93 to 1.69 in the primary analysis

to RR: 1.08, 95% CI: 0.71 to 1.64 for financial conflicts of interest related to the manufacturer, Analysis 7.5; and to RR: 1.46, 95% CI: 0.96 to 2.21 for financial conflicts of interest related to any for-profit company, Analysis 7.6).

Findings from sensitivity analyses on advisory committee reports

Excluding advisory committee reports with unclear or undisclosed conflicts of interest

In the three of the four studies included in our pooled analysis on advisory committee reports, it was not possible to remove advisory committee reports with undisclosed conflicts of interest, because the authors did not code this information in their raw dataset (Lurie 2006; Zhang 2019) or reporting of data did not allow it (Tibau 2016). In the remaining study, we excluded all committee members with unclear conflicts of interest declarations. We found similar results as in our primary analysis (from RR: 1.20, 95% CI: 0.99 to 1.45 in the primary analysis to RR: 1.20, 95% CI: 0.77 to 1.87, Analysis 8.1).

Excluding advisory committee reports with neutral recommendations

Only one of the studies included in our pooled analysis reported neutral recommendations in a separate category in the primary analysis (Lurie 2006), and additionally one study coded whether the voting outcome of the meetings were unanimous (but did not include any unanimous meetings) (Ackerley 2009). For the remaining studies, the authors did not code neutral recommendations (e.g. unanimous voting outcomes) in their raw dataset (Zhang 2019) or reporting of data did not allow us to exclude advisory committee reports with neutral recommendations (Tibau 2016). We found somewhat similar results as in our primary analysis (from RR: 1.20, 95% CI: 0.99 to 1.45 in the primary analysis to RR: 1.28, 95% CI: 0.96 to 1.70, Analysis 8.2).

Excluding all studies of advisory committee reports which disclose a relevant conflict of interest of study authors

One of the studies included in our pooled analysis disclosed financial conflicts of interest of study authors (Zhang 2019). Excluding this study from our pooled analysis on financial conflicts of interest increased the effect estimate and increased statistical precision (from RR: 1.20, 95% CI: 0.99 to 1.45 in the primary analysis to RR: 1.39, 95% CI: 1.08 to 1.80, Analysis 8.3).

Re-analysing our primary analyses using fixed-effect meta-analyses

Re-analysing our primary analysis on advisory committee reports using fixed-effect models did not affect our findings (from RR: 1.20, 95% CI: 0.99 to 1.45 in the primary analysis to RR: 1.15, 95% CI: 1.00 to 1.32, Analysis 8.4).

Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer and financial conflicts of interest related to any for-profit company

The four studies included in our pooled analysis on advisory committee reports both investigated financial conflicts of interest related to the manufacturer of the investigated drug and any for-profit company. One of the studies only reported summary odds ratio for financial conflicts of interest related to the manufacturer and competitor and was not included in our pooled analysis (Tibau 2016). Thus, we were able to include data from three studies in our sensitivity analysis restricted to financial conflicts of interest related to the manufacturer (Ackerley 2009; Lurie 2006; Zhang 2019). Our analysis showed similar findings as our primary analysis (from RR: 1.20, 95% CI: 0.99 to 1.45 in the primary analysis to RR: 1.24, 95% CI: 0.99 to 1.54, Analysis 8.5). The remaining study had different effect estimates for financial conflicts of interest related to the manufacturer (OR: 1.79, 95% CI: 0.75 to 4.26) and any for-profit company (OR: 1.06, 95% CI: 0.78 to 1.44), though with statistical imprecision (Tibau 2016).

In our primary analysis, all studies included advisory committee reports with financial conflicts of interest related to any for-profit company (e.g. the manufacturer, competitor, or both) in the financial conflicts of interest group. Thus, we did not perform the sensitivity analysis restricted to any for-profit company as the results would be identical with the primary analysis.

Findings from sensitivity analyses on opinion pieces

Excluding opinion pieces with unclear or undisclosed conflicts of interest

Two studies coded opinion pieces with unclear or undisclosed financial conflicts of interest (Bariani 2013; Lerner 2012). In the remaining studies, it was not possible to separate opinion pieces with unclear or undisclosed financial conflicts of interest, because the authors did not code this information (Hayes 2019; Wang 2010). Our sensitivity analysis showed somewhat similar results compared with our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 1.47, 95% CI: 0.53 to 4.13, Analysis 9.1).

Excluding opinion pieces with neutral recommendations

We were able to exclude opinion pieces with neutral recommendations for three studies investigating opinion pieces (Bariani 2013; Lerner 2012; Wang 2010). The remaining study did not distinguish between neutral and unfavourable opinion pieces (Hayes 2019). An analysis based on these three studies showed somewhat similar results as our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 2.00, 95% CI: 0.77 to 5.21, Analysis 9.2).

Excluding all studies of opinion pieces which disclose a relevant conflict of interest of study authors

From the four studies included in our primary analysis, one study disclosed financial conflicts of interest of study authors (Bariani 2013). An analysis excluding this study had somewhat different results than our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 3.84, 95% CI: 1.81 to 8.13, Analysis 9.3), though the estimate was statistically imprecise.

Re-analysing our primary analyses using fixed-effect meta-analyses

Our re-analysis of our primary analysis using a fixed-effect model showed somewhat similar results as our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 1.27, 95% CI: 0.94 to 1.72, Analysis 9.4).

Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer and financial conflicts of interest related to any for-profit company

Two of the studies included in our pooled analysis investigated financial conflicts of interest related to the manufacturer of the studied drug or device (Hayes 2019; Lerner 2012). Our sensitivity analysis restricted to financial conflicts of interest related to the manufacturer showed a stronger association than our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 14.69, 95% CI: 4.10 to 52.68, Analysis 9.5).

One study solely investigated financial conflicts of interest related to the manufacturer (Hayes 2019). When we excluded this study from the analysis to include only studies on financial conflicts of interest related to any for-profit companies, we found similar results as our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 2.45, 95% CI: 0.78 to 7.74, Analysis 9.6).

Findings from sensitivity analyses on narrative reviews

Excluding narrative reviews with unclear or undisclosed conflicts of interest

We were able to exclude narrative reviews with unclear of undisclosed conflicts of interest from two studies (Dunn 2016; Hartog 2012). An analysis based on these two studies had somewhat similar results as our primary analysis (from RR: 1.20, 95% CI: 0.97 to 1.49 in the primary analysis to RR: 1.37, 95% CI: 1.11 to 1.69, Analysis 10.1).

Excluding narrative reviews with neutral recommendations

We were able to exclude narrative reviews with neutral recommendations from two studies (Dunn 2016; Wang 2010). Additionally, one study investigating narrative reviews did not include any narrative reviews with neutral recommendations (Hartog 2012). The remaining study did not code unfavourable and neutral recommendations separately (Hayes 2019). Our sensitivity analysis had somewhat similar results as our primary analysis (from RR: 1.20, 95% CI: 0.97 to 1.49 in the primary analysis to RR: 1.17, 95% CI: 0.97 to 1.42, Analysis 10.2).

Excluding all studies of narrative reviews which disclose a relevant conflict of interest of study authors

From the studies included in the pooled analysis, one study disclosed conflicts of interest of study authors (Hartog 2012). Our analysis excluding this study showed somewhat similar results as our primary analysis (from RR: 1.20, 95% CI: 0.97 to 1.49 in the primary analysis to RR: 1.39, 95% CI: 0.68 to 2.86, Analysis 10.3).

Re-analysing our primary analyses using fixed-effect meta-analyses

Our re-analysis of our primary analysis on narrative reviews using a fixed-effect model had somewhat similar results compared to our primary analysis (from RR: 1.20, 95% CI: 0.97 to 1.49 in the primary analysis to RR: 1.19, 95% CI: 1.05 to 1.36, Analysis 10.4).

Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer and financial conflicts of interest related to any for-profit company

Two of the studies on narrative reviews investigated financial conflicts of interest related to the manufacturer of the drug or device of interest (Dunn 2016; Hayes 2019), one study investigated financial conflicts of interest related to both the manufacturer and any for-profit company (Wang 2010), and the remaining study investigated financial conflicts of interest related to any for-profit company (Hartog 2012).

Both our sensitivity analyses showed somewhat similar results as our primary analysis (from RR: 1.20, 95% CI: 0.97 to 1.49 in the primary analysis to RR: 1.16, 95% CI: 0.95 to 1.40 for financial conflicts of interest related to the manufacturer, Analysis 10.5; and to: RR: 2.86, 95% CI: 0.35 to 23.30 for financial conflicts of interest related to any for-profit company, Analysis 10.6).

Appendix 9. 'Summary of findings' table

We assessed the certainty of the evidence for our primary outcome using both the GRADE approach for intervention studies (Guyatt 2008) (observational studies preliminary graded as providing low certainty evidence) and prognostic studies (Foroutan 2020) (observational studies preliminary graded as providing high certainty evidence).

Summary of findings table

Document type	Absolute effect (95% CI)*		Relative effect	Number of studies	Certainty of the evidence using the GRADE approach for intervention studies**	Certainty of the evidence using the GRADE approach for prognostic studies***
	Event rate in documents with conflicts of interest	Event rate in documents without conflicts of interest	RR (95% CI)			
Financial conflicts of interest						
Clinical guidelines	54 (40 to 72) clinical guidelines with favourable recommendations per 100 clinical guidelines with financial conflicts of interest****	43 clinical guidelines with favourable recommendations per 100 clinical guidelines without financial conflicts of interest	**1.26** (0.93 to 1.69)	4 studies including 86 clinical guidelines	**Very low** Downgraded due to study limitations (four studies with high risk of bias) and imprecision (wide CI*****)	**Low**
Advisory committee reports	78 (64 to 94) advisory committee reports with favourable recommendations per 100 advisory committee reports with financial conflicts of interest	65 advisory committee reports with favourable recommendations per 100 advisory committee reports without financial conflicts of interest	**1.20** (0.99 to 1.45)	4 studies including 629 advisory committee reports	**Very low** Downgraded due to study limitations (two studies with high risk of bias) and imprecision (wide CI*****)	**Low**
Opinion pieces	71 (25 to 100******) opinion pieces with favourable recommendations per 1000 opinion pieces with financial conflicts of interest	27 opinion pieces with favourable recommendations per 100 opinion pieces without financial conflicts of interest	**2.62** (0.91 to 7.55)	4 studies including 284 opinion pieces	**Very low** Downgraded due to study limitations (three studies with high risk of bias), imprecision (wide CI*****), and inconsistency (substantial statistical heterogeneity)	**Very low**
Narrative reviews	72 (58-89) narrative reviews with favourable recommendations per 100 narrative reviews with financial conflicts of interest	60 narrative reviews with favourable recommendations per 100 narrative reviews without financial conflicts of interest	**1.20** (0.97 to 1.49)	4 studies including 457 narrative reviews	**Very low** Downgraded due to study limitations (three studies with high risk of bias) and imprecision (wide CI*****)	**Low**
Non-financial conflicts of interest						
Clinical guidelines	90 (39-100*****) clinical guidelines with favourable recommendations per 100 clinical guidelines with one or more radiology authors	43 clinical guidelines with favourable recommendations per 100 clinical guidelines without radiology authors	**2.10** (0.92-4.77)	1 study including 12 clinical guidelines	**Very low** Downgraded due to study limitations (one study with high risk of bias) and imprecision (wide CI*****)	**Low**

CI: *confidence interval;* ***RR:*** *risk ratio;* ***GRADE:*** *Grading of Recommendations Assessment, Development and Evaluation*
**The event rate of the control group (i.e. no conflicts of interest group) was calculated as the mean risk (i.e. number of documents with favourable recommendations divided by total number of documents). The event rate (and its 95% CI) in the intervention group (i.e. conflicts of interest group) is based on the assumed risk in the control group and the relative effect of the intervention (and its 95% CI).*

***The procedure for assessing the certainty of the evidence followed the GRADE approach for intervention studies (observational studies preliminary graded as providing low certainty evidence).*
****The procedure for assessing the certainty of the evidence followed the GRADE approach for prognostic studies (observational studies preliminary graded as providing high certainty evidence).*
*****Numbers on clinical guidelines do not account for panel data in the Norris 2013 study (i.e. 13 clinical guidelines with 24 recommendations each).*
******We used an effect size of 0.05 on a relative scale (i.e. RR < 0.95 or RR >1.05) as a methodologically important difference (Guyatt 2011). This cut-off was based on effect sizes of important study design biases in trials (Page 2016).*
*******Upper event rate truncated at 100.*

HISTORY

Protocol first published: Issue 6, 2013
Review first published: Issue 12, 2020

Date	Event	Description
3 October 2019	New citation required but conclusions have not changed	This protocol was re-published in October 2019 to generate a new citation, reflecting the change in title and authorship from the original version (Lundh A, Jørgensen AW, Bero L. Association between personal conflicts of interest and recommendations on medical interventions. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: MR000040).
25 April 2018	Amended	The text has been updated to align it with other Cochrane Methodology reviews on conflicts of interest.

CONTRIBUTIONS OF AUTHORS

AL conceived the idea for the study. The protocol was developed primarily by CHN, AH, and AL with contribution from LB, KJJ, and AWJ. The protocol was based on a previous protocol developed by AL, AWJ, and LB (Lundh 2013). CHN and either AWJ or AL assessed studies for inclusion; CHN and either ML, AWJ, or AL extracted data and assessed risk of bias. CHN performed the data analysis, and all authors participated in data interpretation. CHN wrote the draft review and all authors contributed in revising the review. CHN is guarantor of the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DECLARATIONS OF INTEREST

We declare that we have no conflicts of interest. LB is co-author of one of the included studies. LB was not involved in the study inclusion, data extraction, and 'Risk of bias' assessment of any studies.

SOURCES OF SUPPORT

Internal sources

- Centre for Evidence-Based Medicine Odense (CEBMO), Odense University Hospital and University of Southern Denmark, Denmark

  CHN, AH, and AL were personally salaried by this institution during the period of the review
- The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark

  CHN and KJJ were personally salaried by this institution during the period of the review
- Charles Perkins Centre and Faculty of Medicine and Health, The University of Sydney, Sydney, Australia

  LB was personally salaried by this institution during periods of the review
- Center for Bioethics and Humanities, University of Colorado, USA

  LB was personally salaried by this institution during periods of the review
- Otorhinolaryngology and Head & Neck Surgery, Aarhus, Denmark

  AWJ was personally salaried by this institution during periods of the review

- ENT Clinic Hobro, Denmark

  AWJ was personally salaried by this institution during periods of the review
- Department of Infectious Diseases, Hvidovre Hospital, Copenhagen, Denmark

  AL was personally salaried by this institution during periods of the review

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We decided to analyse clinical guidelines and advisory committee reports separately, partly because we had more data than we anticipated for these specific categories, and partly because we wanted to minimise heterogeneity. This decision was taken prior to data analysis.

We included one post hoc secondary analysis analysing advisory committee reports on individual level.

We included one post hoc secondary analysis combining all document types in one analysis.

We decided only to calculate prediction intervals for pooled analyses that included at least five studies, as prediction intervals based on limited data are highly uncertain.

We estimated Number Needed to Read for each document type and the combined analysis of all document types.

We included one new subgroup analysis (referred to as post hoc subgroup analysis). This compared documents by authors with major financial conflicts of interest (defined as at least half of the authors/committee members having financial conflicts of interest) with documents by authors with minor financial conflicts of interest (defined as less than half of the authors/committee members with financial conflicts of interest).

We included one new sensitivity analysis (referred to as post hoc sensitivity analysis). We differentiated between financial conflicts of interest related to the manufacturer and to any for-profit company in two separate analyses.

We decided only to conduct subgroup and sensitivity analyses when we had sufficient data (i.e. at least five documents in each group).

Appendix 5. Publication for sub-study II – BMJ

Sub-study II is reported in two co-publications. The second is published in:

Nejstgaard CH, Bero L, Hróbjartsson A, et al. Association between conflicts of interest and recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: systematic review. *BMJ* 2020;371:m4234.

Association between conflicts of interest and favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews: systematic review

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Additional material is published online only. To view please visit the journal online.

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ABSTRACT

OBJECTIVE

To investigate the association between conflicts of interest and favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews.

DESIGN

Systematic review.

ELIGIBILITY CRITERIA

Studies that compared the association between conflicts of interest and favourable recommendations of drugs or devices (eg, recommending a drug) in clinical guidelines, advisory committee reports, opinion pieces (eg, editorials), or narrative reviews.

DATA SOURCES

PubMed, Embase, Cochrane Methodology Register (from inception to February 2020), reference lists, Web of Science, and grey literature.

DATA EXTRACTION AND ANALYSIS

Two authors independently extracted data and assessed the methodological quality of the studies. Pooled relative risks and 95% confidence intervals were estimated using random effects models (relative risk >1 indicates that documents with conflicts of interest more often had favourable recommendations than documents with no conflicts of interest). Financial and non-financial conflicts of interest were analysed separately, and the four types of documents were analysed separately (preplanned) and combined (post hoc).

RESULTS

21 studies that analysed 106 clinical guidelines, 1809 advisory committee reports, 340 opinion pieces, and 497 narrative reviews were included. Unpublished data were received for 11 studies (eight full datasets and three summary datasets). 15 studies showed risk of confounding because the compared documents could differ in factors other than conflicts of interest (eg, different drugs used for different populations). The relative risk for associations between financial conflicts of interest and favourable recommendations for clinical guidelines was 1.26 (95% confidence interval 0.93 to 1.69; four studies of 86 clinical guidelines), for advisory committee reports was 1.20 (0.99 to 1.45; four studies of 629 advisory committee reports), for opinion pieces was 2.62 (0.91 to 7.55; four studies of 284 opinion pieces), and for narrative reviews was 1.20 (0.97 to 1.49; four studies of 457 narrative reviews). An analysis of all four types of documents combined supported these findings (1.26, 1.09 to 1.44). In one study that investigated specialty interests, the association between including radiologists as authors of guidelines and recommending routine breast cancer was: relative risk 2.10, 95% confidence interval 0.92 to 4.77; 12 clinical guidelines).

CONCLUSIONS

We interpret our findings to indicate that financial conflicts of interest are associated with favourable recommendations of drugs and devices in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. Limitations of this review were risk of confounding in the included studies and the statistical imprecision of individual analyses of each document type. It is not certain whether non-financial conflicts of interest influence recommendations.

SYSTEMATIC REVIEW REGISTRATION

Cochrane Methodology Review Protocol MR000040.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Clinical guidelines, opinion pieces, and narrative reviews are often written by authors with conflicts of interest related to the drug or device industry; similarly, members of advisory committees, such as regulatory drug advisory committees, often have conflicts of interest

Previous studies found that financial conflicts of interest are associated with favourable conclusions in primary research studies and systematic reviews

It is not known to what degree conflicts of interest affect recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews

WHAT THIS STUDY ADDS

The findings of this review indicate an association between financial conflicts of interest and favourable recommendations of drugs and devices in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews

The included studies were, however, at risk of confounding, and some degrees of statistical imprecision was found in individual analyses by document type

It is uncertain whether non-financial conflicts of interest influence recommendations

Introduction

Diagnostic and treatment recommendations in clinical guidelines or advisory committee reports have an important impact on patient care. Similarly, recommendations in opinion pieces, such as editorials, and narrative reviews written by key opinion leaders could influence clinical practice. But making recommendations requires judgment, and a concern is whether conflicts of interest might influence such recommendations.

Recommendations are often written by authors with financial conflicts of interest related to the drug or

device industry.[1 2] For example, in a study of 45 clinical guidelines, 53% of authors had financial conflicts of interest.[3] Researchers have also studied non-financial conflicts of interest such as specialty and academic interests, although which interests and relationships constitute a non-financial conflict of interest and whether the term is appropriate is debatable.[4]

Numerous studies have investigated the impact of financial conflicts of interest on the interpretation of study results. One Cochrane methodology review reported an association between industry funding and favourable conclusions in primary research studies, mainly clinical trials,[5] and similar results were reported in another Cochrane methodology review on financial conflicts of interest in systematic reviews.[6]

In the current systematic review we investigated to what degree financial and non-financial conflicts of interest are associated with favourable recommendations (eg, recommending a drug) in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews.

Methods

The details of the methods have been published in a Cochrane methodology review protocol.[7] Here we describe the core methods.

Eligibility criteria

Studies considered eligible for review were published and unpublished studies in any language and of any design that assessed the association between conflicts of interest and favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, or narrative reviews of drug or device interventions. We defined advisory committee reports as transcripts or reports from meetings held in committees to advise an organisation on a drug or device intervention, such as records from the Food and Drug Administration advisory committee on oncological drugs. Opinion pieces were defined as commentaries, editorials, and letters. Narrative reviews (non-systematic reviews) were defined as literature reviews without a systematic search of the literature and without clear eligibility criteria (see supplementary appendix 1).

For financial conflicts of interest, we included studies regardless of the type of financial conflict—that is, financial conflicts of interest related to both industry funding of documents and authors' company ties. For non-financial conflicts of interest, we included studies on intellectual, academic, professional, or specialty interests, and on personal or professional relationships.[8]

Studies were excluded if they concerned: financial conflicts of interest not related to the drug or device industry (eg, tobacco or nutrition industry) as the impact from conflicts of interest might differ between industries; beliefs (eg, religious), personal experiences (eg, experiencing the medical condition), or membership of certain groups (sex or ethnicity), even if the original authors defined this as non-financial conflicts of interest; both financial and non-financial conflicts of interest at the level of an institution (eg, employment at a university that collaborates with industry); and conflicts of interest related to reports from scientific grant committees.

Search strategy and study inclusion

PubMed, Embase, and the Cochrane Methodology Register (from inception to February 2020) were searched for studies and protocols. The search strategy we developed for PubMed was adapted for the other databases (see supplementary appendix 2). To identify additional studies and protocols, we searched reference lists of the included studies, Web of Science (from inception to March 2020) for studies that cited any of the included studies, and PubMed (from inception to March 2020) for publications by the first and last author of the included studies.

We also searched proceedings from peer review congresses,[9] Cochrane colloquiums,[10] and Evidence Live[11] for conference abstracts published up to February 2020. PROSPERO (from inception to February 2020) was searched for registered systematic reviews, and the ProQuest database (from inception to February 2020) for dissertations and theses. Finally, we searched Google Scholar (from inception to March 2020).

One review author (CHN) screened titles and abstracts for obvious exclusions. Two review authors (CHN and AWJ or AL) independently assessed potentially eligible studies based on the full text. Disagreements were resolved by discussion, with arbitration by a third review author (AL or AH) when needed.

Outcomes and data extraction

Our primary outcome was favourable recommendations, defined as such by the authors of the included studies.

Two review authors (CHN and either AWJ, ML, or AL) independently extracted data from included studies. Disagreements were resolved by discussion, with arbitration by a third review author (AH or AL) when needed.

We extracted data on basic study characteristics and on the association between conflicts of interest and favourable recommendations. Extracted data on conflicts of interest were based on the definitions used by the authors of the included studies. Information was also extracted on funding and authors' conflicts of interest for the included studies. Supplementary appendix 3 provides details of our data extraction.

Unpublished data

We contacted the authors of the included studies to obtain unpublished data, clarify problems in our assessment of methodological quality, or receive copies of unpublished protocols (supplementary appendix 4).

Assessment of methodological quality in included studies

As tools for assessing methodological quality in these types of studies have not been published, we developed our own criteria based on those used in

previous Cochrane methodology reviews on financial conflicts of interest in primary research studies and systematic reviews.[5 6]

Two review authors (CHN and either AWJ, ML, or AL) independently assessed methodological quality in included studies. Disagreements were resolved by discussion, with arbitration by a third review author (AL or AH) when needed. We used the following criteria:

- Whether the methods for including documents were adequate (adequate methodological quality might, for example, include reporting of clear inclusion criteria, with two or more assessors independently selecting documents).
- Whether the methods for coding conflicts of interest were adequate (adequate methodological quality might, for example, include coding by two or more assessors based on multiple information sources).
- Whether the methods for coding recommendations were adequate (adequate methodological quality might, for example, include coding by two or more assessors blinded to conflicts of interest information).
- Whether the methods for dealing with confounding were adequate. The documents included in a study might differ on key aspects—for example, in a sample of clinical guidelines, the guidelines might differ in types of patients and conditions, interventions, the quality of the underlying evidence, and the quality of the guidelines, which could potentially confound the association between conflicts of interest and favourable recommendations. Therefore, adequate methodological quality could, for example, include documents with and without conflicts of interest discussing the same treatment used in similar groups of patients.

We coded a study as having overall adequate methodological quality if all criteria were assessed as adequate; otherwise, we coded it as having inadequate methodological quality.

Data synthesis

Data management of individual studies

In our primary analyses, we used similar coding of conflicts of interest and recommendations to the included studies. If an ordinal scale was used to grade recommendations, for example highly positive, positive, neutral, negative, and highly negative, we recoded recommendations into two categories: favourable versus neutral or unfavourable.

If a study included different types of documents (such as both clinical guidelines and research papers), we included the study in our pooled analyses only if we had separate data for the types of documents relevant for our review.

In our analyses on clinical guidelines, we included one study that investigated 13 guidelines that each included recommendations on 24 different drugs.[12] To allow for this type of panel data, we used Poisson generalised estimating equations to calculate effect estimates, which we could include in our pooled analyses.[13]

In our analyses on advisory committee reports, we included studies with two types of analysis units: committee members and their individual votes (individual level) and advisory committee reports and the overall voting outcome (meeting level). In our primary analysis, we analysed data at meeting level, as this level of analysis was most comparable with recommendations in the other types of documents (eg, clinical guidelines).

In some cases, the same document was included in two separate studies. When we had access to unpublished data, it was possible to remove the duplicate documents, and we chose to remove it from the study with the latest publication date. We included two studies that investigated the same FDA advisory committee reports[14 15] and removed duplicates from one of the studies.[15] In our analyses on opinion pieces, we included two studies that investigated editorials published in some of the same oncology journals in overlapping periods[16 17] and removed duplicates from one of the studies.[16]

Primary analyses

Owing to expected clinical and methodological heterogeneity between the included studies, we used inverse variance random effects models to estimate relative risks with 95% confidence intervals. We compared recommendations between documents with and without conflicts of interest and ensured uniform directionality, so a relative risk value of more than 1 indicated that documents with conflicts of interest more often had favourable recommendations than documents without conflicts of interest. We analysed financial and non-financial conflicts of interests separately, and clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews separately. We dealt with statistical heterogeneity using the I^2 statistic and prediction intervals (supplementary appendix 5).

Using the methods for calculating a number needed to treat, we calculated a number needed to read for each document type (supplementary appendix 6).[18] The number needed to read was defined as the expected number of documents with conflicts of interest needed to be read rather than documents without conflicts of interest for one additional document having a favourable recommendation. As it is difficult to describe the 95% confidence interval for number needed to read when the confidence interval of the relative risk crosses the boundary of no effect,[19] we report the 95% confidence interval of the number needed to read in supplementary appendix 6.

Secondary analyses

We analysed advisory committee reports at individual level (ie, individual votes).

In a post hoc analysis, we combined all four types of documents (clinical guidelines, advisory committee

reports, opinion pieces, and narrative reviews) in one analysis of financial conflicts of interest.

Subgroup and sensitivity analyses

Various subgroup analyses were undertaken, including stratification by different types of financial conflicts of interest, such as funding, honorariums, and gifts, and stratification by different degrees of financial conflicts of interest (≥50% vs <50% of the authors or committee members with financial conflicts of interest). In addition, we undertook various sensitivity analyses in relation to how information on conflicts of interest and recommendations were coded, using fixed effect models, and by excluding studies with authors who had conflicts of interest (supplementary appendices 7 and 8).

Analyses were conducted in either RevMan 5.4 or Stata 15.

Assessment of certainty of the evidence

Based on experience, using formal systems such as GRADE (Grading of Recommendations Assessment, Development and Evaluation) for assessing the certainty of evidence from methodological studies is challenging. We therefore focused on interpreting our results in the context of the statistical precision of our estimates (width of confidence intervals) and risk of confounding. Supplementary appendix 9 shows the GRADE assessments using a similar approach to both observational intervention studies and prognostic studies.[20 21]

Patient and public involvement

We decided to undertake our study without patient or public involvement. Although our protocol was available in the public domain,[7] we received no comments on it.

Results

Of 9973 records identified in the searches, 21 studies that analysed 106 clinical guidelines, 1809 advisory committee reports, 340 opinion pieces, and 497 narrative reviews were included in the review (fig 1).[2 12 14-17 22-36] No unpublished studies or protocols for planned studies were identified.

Table 1 presents the characteristics of the included studies. The 21 studies were published between 1998 and 2019. Eight studies analysed clinical guidelines (median 9 (range 2-50) guidelines), seven analysed advisory committee reports (376 (79-416) reports), six analysed opinion pieces (44 (8-131) opinion pieces), and five analysed narrative reviews (84 (7-213) narrative reviews). Sixteen studies investigated drugs, three investigated devices, and two investigated both drugs and devices.

Twenty studies investigated financial conflicts of interest only and one study investigated both financial conflicts of interest and specialty affiliations among guideline authors (non-financial conflicts of interest). None of the included studies reported industry funding, but six did not report funding information. Seven of the included studies that investigated documents with and without financial conflicts of interest were conducted by authors who themselves had financial conflicts of interest.

Unpublished data were received for 11 studies; full datasets (n=8)[14-17 29-31 35] and additional summary data (n=3).[25 27 28] No published protocols were found, and only two studies provided unpublished protocols.[14 32] No discrepancies were found between outcomes in these protocols and study publications. Nine of 21 author teams replied that no protocol existed for their study, and two author teams supplied reports that we did not consider to be protocols (supplementary appendix 4).

Methodological quality in included studies

In total, 20 studies were assessed as having overall inadequate methodological quality and one study as having adequate methodological quality (fig 2). Around half of the included studies had adequate methodological quality in the document inclusion process (n=10), and most had adequate methodological quality in the coding of conflicts of interest (n=15) and recommendations (n=17). Six studies were assessed as adequate for dealing with confounding and 15 as inadequate for dealing with confounding, because they included documents of different topics, such as various cancer drugs for different indications, or included documents on the same drug used for different populations, such as diabetes drugs used in adults, children, or pregnant women.

Financial conflicts of interest: differences in recommendations

Clinical guidelines

Eight studies investigated a total of 106 clinical guidelines.[12 22-25 32 35 36] Data from four of these studies (86 clinical guidelines) could be included in the pooled primary analysis.[12 22 25 35] The relative risk for the association between financial conflicts of interest and favourable recommendations in clinical guidelines was 1.26 (95% confidence interval 0.93 to 1.69, I^2=0%; fig 3). The number needed to read for clinical guidelines was 9.1 (supplementary appendix 6). The remaining four studies had similar results to those of the pooled analysis (supplementary appendix 6).[23 24 32 36]

Advisory committee reports

Seven studies investigated a total of 1809 advisory committee reports.[2 14 15 26-29] Data from five studies could be included in our primary or secondary pooled analyses.[14 15 27-29] In the primary analysis, including four studies of 629 advisory committee reports, the relative risk for the association between advisory committee reports with any member who had financial conflicts of interest and voting in favour of approving a drug or device was 1.20 (0.99 to 1.45, I^2=24%; fig 3). The number needed to read for advisory committee reports was 7.7 (supplementary appendix 6). In the secondary analysis, including three studies of 17 816 votes, the relative risk for the association between financial conflicts of interest of individual advisory committee members and voting in favour of approving

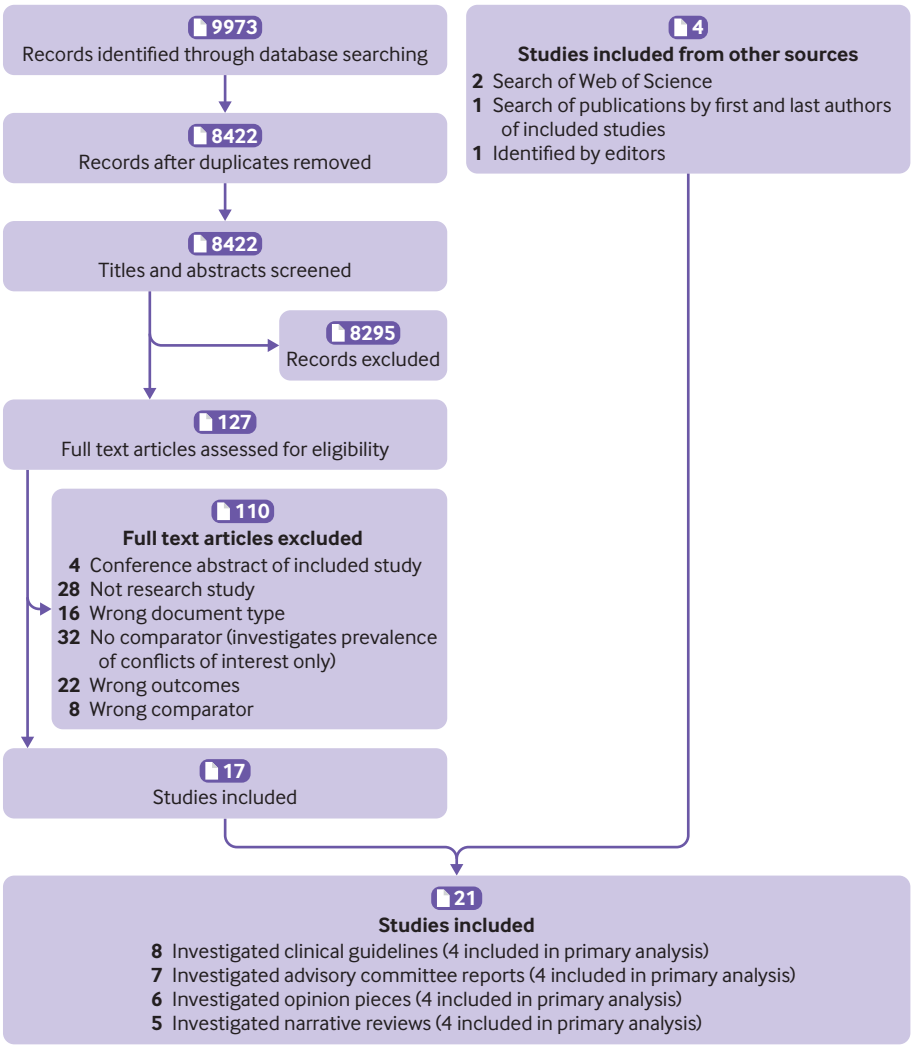

Fig 1 | Flow chart of study inclusion

a drug or device was 1.14 (1.07 to 1.21, I^2=35%; fig 4). The remaining two studies investigated voting behaviour among advisory committee members; one of these studies had similar results to our pooled analysis (supplementary appendix 6).[2]

Opinion pieces

Six studies investigated a total of 340 opinion pieces.[16 17 32-35] Data from four of these studies (284 opinion pieces) could be included in our pooled primary analysis.[16 17 33 35] The relative risk for the association between financial conflicts of interest and favourable recommendations in opinion pieces was 2.62 (0.91 to 7.55, I^2=78%; fig 3). The number needed to read for opinion pieces was 2.3 (supplementary appendix 6). The remaining two studies had similar results to our pooled analysis (supplementary appendix 6).[32 34]

Narrative reviews

Five studies investigated a total of 497 narrative reviews.[30-33 35] Data from four of these studies (457 narrative reviews) could be included in our pooled primary analysis.[30 31 33 35] The relative risk for the association between financial conflicts of interest and favourable recommendations in narrative reviews was 1.20 (0.97 to 1.49, I^2=39%; fig 3). The number needed to read for narrative reviews was 8.3 (supplementary appendix 6). The remaining study had similar results to our pooled analysis (supplementary appendix 6).[32]

All document types

In a post hoc analysis, when all types of documents were combined, the relative risk for an association between financial conflicts of interest and favourable recommendations was 1.26 (1.09 to 1.44, I^2=38%; fig 3). The number needed to read was 7.1 (supplementary appendix 6).

Non-financial conflicts of interest: differences in recommendations

One study investigated specialty interests and included 12 clinical guidelines on mammography screening.[36] The focus was on whether the guideline author team included a radiologist. The relative risk for an association between having radiologists on the guideline panel and recommending routine screening for breast cancer was 2.10 (0.92 to 4.77). The number needed to read was 2.1 (supplementary appendix 6).

Table 1 | Characteristics of included studies

Studies	Type and No of included documents	Definition of conflicts of interest	Definition or classification of favourable recommendations
Studies investigating financial conflicts of interest			
Aakra 2012[22]	18 clinical guidelines on self-monitoring of blood glucose	Guideline funded by industry	Weakly or strongly in favour of self-monitoring (using 4 point scale)
George 2014[23]	2 clinical guidelines on treatment of primary immune thrombocytopenia	Guideline funded by or author financial ties to companies that manufacture products in guideline	Strong recommendation for thrombopoietin receptor agonists
Norris 2013[12]	13 clinical guidelines on glycaemic control in type 2 diabetes	At least one author with financial ties to companies that manufacture drugs included in guideline	Drug recommended in guidance portion of guideline
Schott 2013[24]	2 clinical guidelines on efalizumab for treatment of psoriasis	At least one author with financial ties to drug companies	Efalizumab judged more favourable
Tibau 2015[25]	50 clinical guidelines on anticancer drugs*	At least one author with financial ties to companies with economic, commercial, or competing interest in guideline recommendation	Specific drugs recommended in guideline abstract
Ackerley 2009[15]	98 committee reports and 1191 committee members from FDA drug, radiology, device, and biologic advisory committees†	At least one committee member with financial ties to the product manufacturer or competitor	Voted in favour of product
Cooper 2019[26]	416 committee reports and 1483 committee members from FDA drug advisory committees	Committee member with financial ties to any drug company	Voted in favour of drug
Lurie 2006[14]	76 committee reports and 886 committee members from FDA drug advisory committees‡	At least one committee member with financial ties to drug manufacturer or competitor	Voted in favour of drug
Pham-Kanter 2014[27]	379 committee reports and 15 739 committee members from FDA drug advisory committees	Committee member with financial ties to drug manufacturer or competitor	Voted in favour of drug
Tibau 2016[28]	79 committee reports from FDA oncological drug advisory committees§	At least one committee member with financial ties to drug manufacturer or competitor	Voted in favour of drug
Xu 2017[2]	385 committee reports from FDA drug advisory committees	At least one committee member with financial ties to drug manufacturer or competitor	Voted in favour of drug
Zhang 2019[29]	376 committee reports from FDA drug advisory committees	At least one committee members with financial ties to drug manufacturer or competitor	Voted in favour of drug
Bariani 2013[16]	131 editorials commenting on phase III oncology clinical trials¶	At least one author with financial ties to drug company	Positive or highly positive interpretation of trial (using 5 point scale)
Lerner 2012[17]	54 editorials commenting on phase III oncology clinical trials	At least one author with financial ties to for profit organisation	Favourable interpretation of trial (using 3 point scale)
Dunn 2016[30]	213 narrative reviews of neuraminidase inhibitors for influenza	At least one author with financial ties to manufacturer of neuraminidase inhibitor of interest	Concluded safety and efficacy of ≥1 neuraminidase inhibitors
Hartog 2012[31]	153 narrative reviews on hydroxyethyl starch for various conditions	At least one author with financial ties to manufacturer of any commercially available intravenous fluid	Recommended hydroxyethyl starch over other fluids
Downing 2014[32]	4 clinical guidelines; 23 editorials and commentaries; 40 reviews (mainly narrative) commenting on randomised trial of fenofibrate (ACCORD-Lipid trial)**	At least one author with financial ties to manufacturer of fenofibrate or any other drug company with commercial interests in fenofibrate	Recommended fibrates
Hayes 2019[33]	8 opinion pieces; 7 narrative reviews commenting on randomised trial on tumour treating fields	At least one author with financial ties to manufacturer of tumour treating fields	Supported tumour treating fields without caveats
Stelfox 1998[34]	33 letters; 32 reviews (mainly systematic); 5 original research studies on safety of calcium channel antagonists	Individual authors with financial ties to drug companies	Supported calcium channel antagonists (using 3 point scale)
Wang 2010[35]	5 clinical guidelines; 91 letters, editorials, and commentaries; 84 narrative reviews on cardiovascular risk of rosiglitazone	Industry funding of document or at least one author with financial ties to manufacturers of antihyperglycaemic drugs	Recommended rosiglitazone
Studies investigating both financial and non-financial conflicts of interest			
Norris 2012[36]	12 clinical guidelines on screening mammography	Percentages of authors disclosing any financial conflicts of interest. At least one radiologist in author team	Recommended routine screening

FDA=Food and Drug Administration.
*91 clinical guidelines included in study (not all had data available in a format for inclusion in analysis).
†611 advisory committee reports included in study and 221 duplicates also included in Lurie 2006[14] removed (not all had data available in a format for inclusion in analysis).
‡221 advisory committee reports included in study (not all had data available in a format for inclusion in analysis).
§82 advisory committee reports included in study (not all had data available in a format for inclusion in analysis).
¶131 opinion pieces included in analysis after removing 19 duplicates also included in Lerner 2012.[17]
**5 clinical guidelines, 24 editorials and commentaries, and 70 reviews included in study (not all had data available in a format for inclusion in analysis.

Subgroup and sensitivity analyses

No differences were found in effect estimates by the type of financial conflicts of interest or the degree of financial conflicts of interest for any document type (supplementary appendix 7).

Sensitivity analyses were robust in 20 of 23 analyses of financial conflicts of interest. In three analyses the association between financial conflicts of interest and favourable recommendations became stronger (supplementary appendix 8).

Assessment of certainty of the evidence

The evidence on financial conflicts of interest in all four types of documents and non-financial conflicts

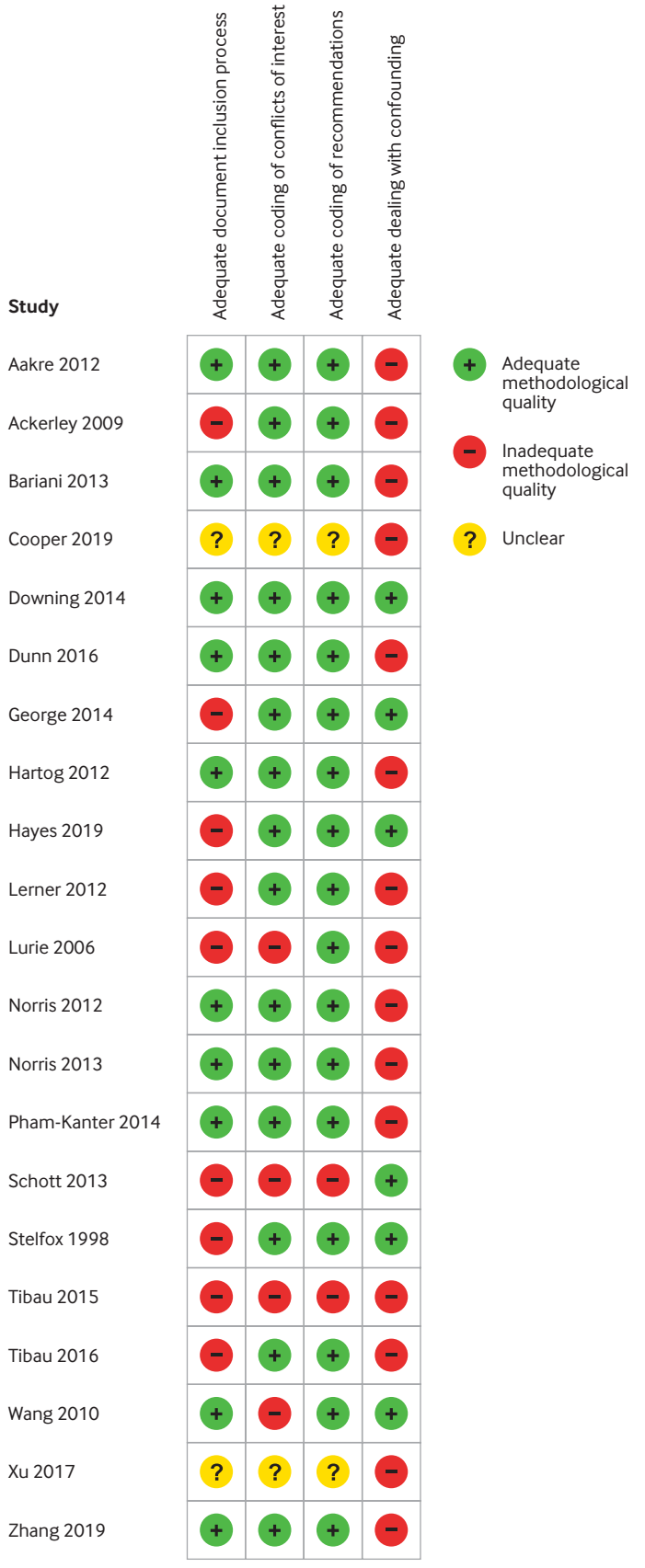

Fig 2 | Methodological quality in included studies

of interest in clinical guidelines should be interpreted with caution as most of the studies (15 out of 21) dealt inadequately with confounding and all effect estimates in our primary analyses lacked statistical precision. Using the GRADE approaches for intervention and prognostic studies resulted in low to very low certainty of the evidence depending on the type of document and the GRADE system used (supplementary appendix 9).

Discussion

In this systematic review we found an association between financial conflicts of interest and favourable recommendations of drugs and devices in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. The four primary analyses resulted in effect estimates of a fairly similar magnitude and consistent direction, but each with varying degrees of statistical precision. The post hoc analysis in which all document types were combined confirmed these findings, and statistical precision was increased. Our findings on the impact of non-financial conflicts of interest on recommendations were limited to evidence from a single study of breast cancer screening guidelines and the involvement of radiologist authors, with statistically imprecise results. It is therefore uncertain whether specialty interests or other types of non-financial conflicts of interest have an effect on recommendations.

Strengths and limitations of this study

A major strength of our study is the inclusion of unpublished data from 11 of 21 studies. We retrieved eight full datasets and unpublished summary data for three additional studies, which ensured high data quality and comprehensive analyses thereby increasing statistical precision and minimising reporting bias. Furthermore, we searched grey literature for published and unpublished protocols. We only obtained two protocols,[14 32] and a comparison of outcomes in the protocols with outcomes in the study publications showed no evidence of selective outcome reporting.

Six of 21 included studies were, however, reported in a format that did not allow inclusion in meta-analysis. Four of these studies reported similar results to our meta-analysis. Two of the four studies combined different types of documents without stratifying results, with estimates (relative risk 1.69, 95% confidence interval 1.07 to 2.67, and 13.91, 1.99 to 96.97) in line with our primary analysis.[32 34] The other two of the four studies sampled a single pair of clinical guidelines with and without financial conflicts of interest, and in both cases only guidelines with conflicts were favourable.[23 24] The last two of the six studies (29% of all documents)[2 26] sampled FDA committee reports from the same period as the studies included in our meta-analysis, implying a considerable risk of documents overlapping between the studies. The two studies reported no results for our primary analysis; if we had had access to the raw data we would likely have excluded a considerable proportion of the documents to avoid double counting. Thus, we find it

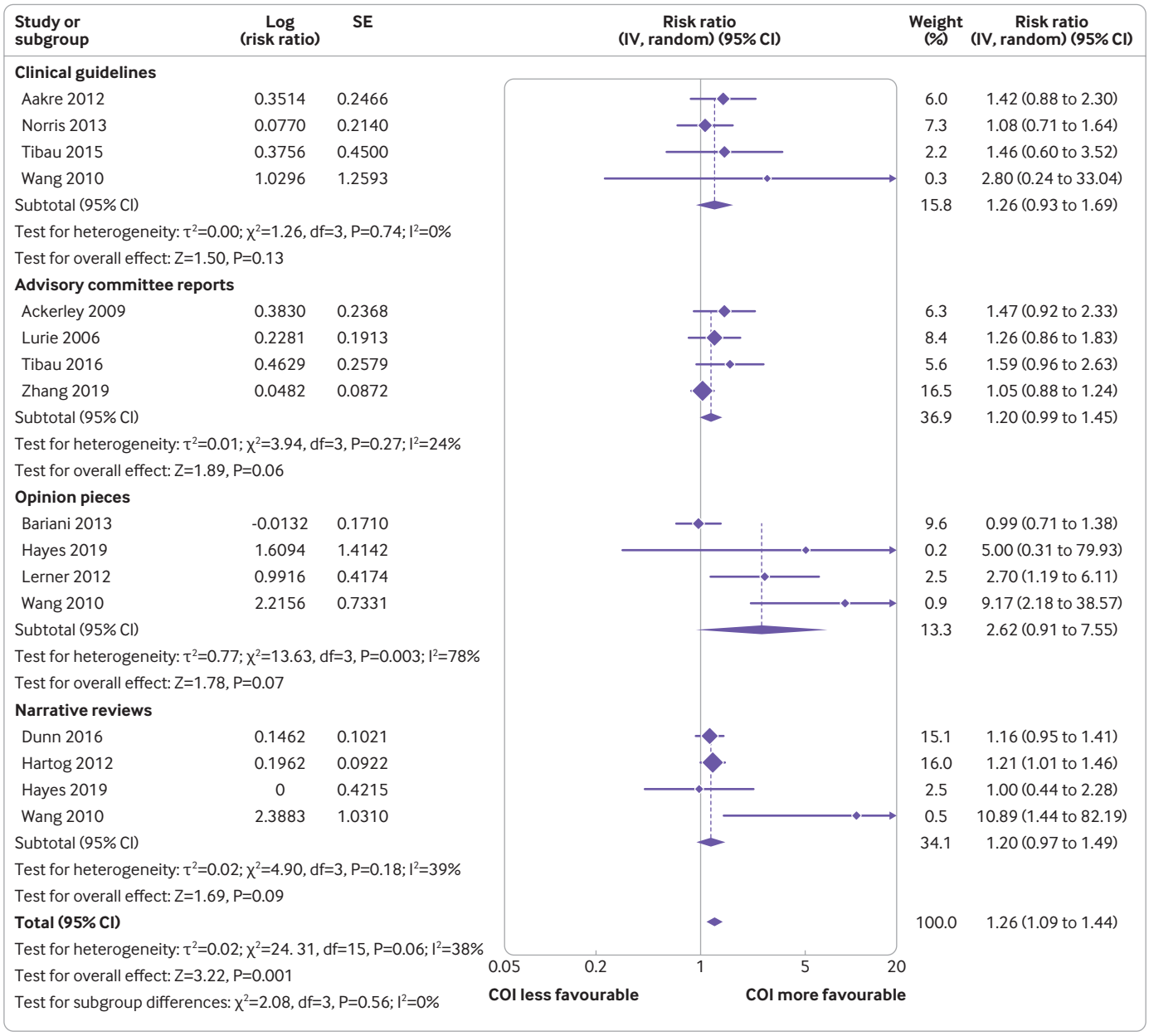

Fig 3 | Meta-analysis of association between financial conflicts of interest and favourable recommendations for each type of document and documents combined. IV=inverse variance; COI=conflicts of interest

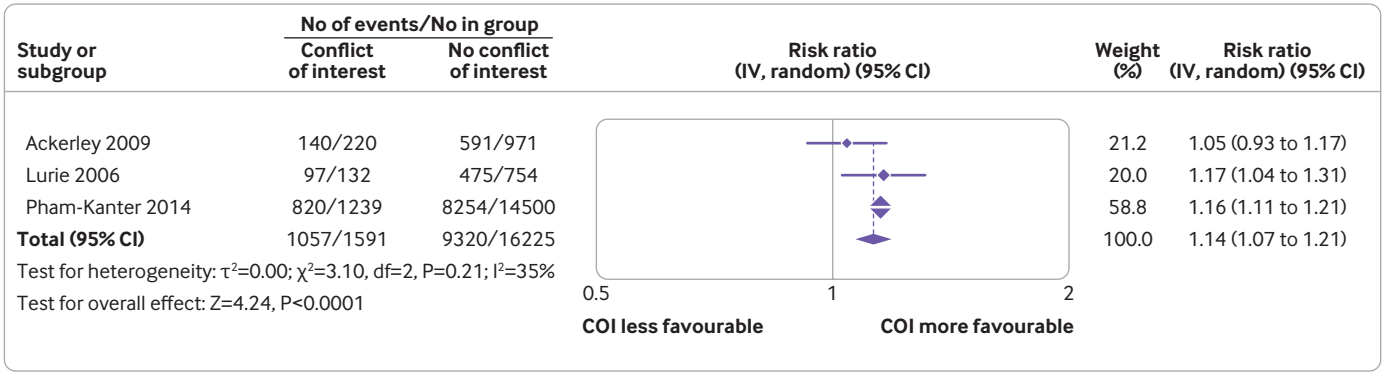

Fig 4 | Meta-analysis of association between financial conflicts of interest and favourable votes of committee members. IV=inverse variance; COI=conflicts of interest

unlikely that our result would have been qualitatively different had the six studies reported results in a format suitable for meta-analysis.[37]

Nevertheless, this review has some limitations. Firstly, the different types of documents were described using various terms in the included studies, and, despite using a comprehensive search strategy, we might have missed relevant studies. Furthermore, only four studies were included in each of our four primary analyses. Therefore, our effect estimates have some degree of statistical imprecision and none of our primary analyses were statistically significant at the conventional 5% level. The sizes of the effect estimates were, however, similar for clinical guidelines, advisory committee reports, and narrative reviews, and slightly higher for opinion pieces, and when we combined all document types in a post hoc analysis, including 13 studies, the statistical precision was increased and we found a statistically significant association with moderate heterogeneity.

Secondly, our criteria for assessment of the methodological quality of the studies for adequately dealing with confounding might be viewed as strict, and others might interpret the methodological quality of studies differently. Nevertheless, most of the studies were at risk of confounding because compared documents might differ in other factors than conflicts of interest (eg, documents on different drugs used for different patient groups). Although confounding could have influenced our estimates, the association between conflicts of interest and recommendations was fairly consistent across document types, despite some studies including comparable documents, such as clinical guidelines on efalizumab for the treatment of psoriasis,[24] and others including different documents, such as advisory committee reports on a wide range of different drugs.[27] Moreover, recommendations in guidelines and narrative reviews could have been influenced by conflicts of interest in the underlying evidence. For example, in certain clinical specialties such as oncology,[38] conflicts of interest are common, which could have impacted the conclusions of clinical trials and systematic reviews[5 6] and thereby indirectly affected guideline recommendations and potentially resulted in effect modification. Furthermore, how conflicts of interest in the primary clinical trials and systematic reviews underpinning a guideline are interpreted could be associated with the guideline authors' conflicts of interest.

Thirdly, the number of authors with financial conflicts of interest might influence recommendations in a document. Our subgroup analyses of documents where a majority of the authors had financial conflicts of interest compared with those with a minority of authors found no difference in effect. However, the analyses were simplistic and based on few data, resulting in statistically imprecise results. Another important factor is the role of authors with financial conflicts of interest. For example, the chair of a guideline committee or the lead author of a narrative review could have a greater influence on recommendations than an author with a less prominent role. However, none of the included studies reported data that allowed such a comparison.

Fourthly, 11 of the 21 included studies relied solely on disclosed information in the included documents for coding conflicts of interest. This could have led to an underestimation of our effect estimates, as conflicts of interest are often underreported in various publication types, including clinical guidelines.[3]

Finally, the interpretation of our results can be debated. No published guidance is specifically tailored for summarising and interpreting evidence from methodological studies. One approach could be to use the GRADE system,[20] but it is questionable whether using GRADE for observational intervention studies or prognostic studies is best suited for methodological studies, since the methodology of studies or the presence of conflicts of interest cannot be randomised. In our supplementary appendix 9, we reported assessments using both strategies and obtained low to very low certainty of evidence depending on the type of document and approach. Using the GRADE approach for intervention studies resulted in a more conservative interpretation of the certainty of the evidence.

Comparison with other studies or reviews

Other systematic reviews of financial conflicts of interest in different types of studies produced similar findings to those of our review. A recent Cochrane methodology review focusing on primary research studies, mainly trials, reported that industry funded studies more often had favourable conclusions than non-industry funded studies (relative risk 1.34, 95% confidence interval 1.19 to 1.51).[5] Similarly, another recent Cochrane methodology review reported that systematic reviews with industry funding or by authors with financial conflicts of interest more often had favourable conclusions than systematic reviews without financial conflicts of interest (relative risk 1.98, 95% confidence interval 1.26 to 3.11).[6]

Financial conflicts of interest have also been investigated in relation to other industries than the drug and device industry. A systematic review reported that industry funded nutrition studies and reviews more often had favourable conclusions than non-industry funded nutrition studies and reviews (relative risk 1.31, 95% confidence interval 0.99 to 1.72).[39]

Meaning of the study

For our analyses, we included studies of four types of documents that are common and involved the authors' interpretation of external evidence (involving methods less stringent than in a systematic review). Although we had anticipated potential differences between the document types, we found a fairly consistent association between financial conflicts of interest and favourable recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. One reason could be that authors with conflicts of interest are more prone to confirm prior beliefs by selectively citing and interpreting the literature.[40] This could also explain

the somewhat stronger association found in opinion pieces, which to some degree allow authors more room for interpretation than narrative reviews, which undergo peer review, and clinical guidelines, which are increasingly done using standardised methods. On an absolute scale, the association between conflicts of interest and recommendations was particularly strong for opinion pieces and specialty interest in clinical guidelines with numbers needed to read of only 2.3 and 2.1, respectively, although the estimates had considerable statistical imprecision.

Our findings support conflicts of interest policies from major organisations that issue guidelines, such as the US Preventive Services Task Force, World Health Organization, and National Institute for Health and Care Excellence.[41-43] These policies aim to minimise the number and role of guideline authors with conflicts of interest. Similarly, some high impact journals manage conflicts of interest beyond disclosure—for example, *The New England Journal of Medicine* prohibits narrative reviews and editorials by authors with major financial conflicts of interest (>$10 000; >£7715; >€8540), and *The Lancet* prohibits commentaries, seminars, reviews, and series by authors with relevant stock ownership, employment, or company board membership.[44 45] Other journals should consider introducing such polices to minimise the influence of conflicts of interest on journal content.

In line with this, in 2008 the FDA introduced more stringent criteria on the types of conflicts of interest allowed by committee members.[15] This might explain why a study[29] that exclusively sampled committee reports from 2008 and onwards, found a weaker association between financial conflicts of interest and recommendations in advisory committee reports than the three other studies included in the pooled analysis.[14 15 28]

Unanswered questions and future research

Ideally, future studies should try to minimise the risk of confounding by, for example, using a matched study design.[46] However, identifying editorials commenting on the same study, or guidelines addressing the same question and developed using similar methods, might be a challenge. Furthermore, future research could focus on investigating whether specific types of financial conflicts of interest (eg, advisory board membership) or conflicts of interest related to specific companies (eg, drug manufacturer) have a greater impact than others. The included studies used various definitions of financial conflicts of interest and recommendations, and therefore use of a standardised terminology would be helpful.

Investigating the impact of non-financial conflicts of interest is challenging as no uniform definition exists. Nonetheless, a multitude of factors can be viewed as non-financial conflicts of interest, such as specialty interests, intellectual interests, personal beliefs, and personal relationships.[47 48] Labelling personal beliefs and theoretical schools of thoughts as conflicts of interest is problematic as no researcher is completely free from interest or from intellectual preconceptions.[4 49 50] Furthermore, the distinction between financial and non-financial conflicts of interest is not always clear. For example, in the included study on mammography screening guidelines[36] it can be debated whether being a radiologist should be considered a purely non-financial conflicts of interest, as radiologists often have direct financial income (in the form of salary) from breast cancer screening. Future studies could focus on investigating the impact of the various types of non-financial conflicts of interest on favourable recommendations and on the impact of managing such interests using guideline panels with a broad range of skill sets, rather than mainly content area experts.

Conclusions

We interpret our findings to indicate that financial conflicts of interest are associated with favourable recommendations of drugs and devices in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews. Although the magnitude of effect is fairly consistent across document types, most studies had a risk of confounding and our individual analyses of each document type had some degrees of statistical imprecision. It is uncertain whether non-financial conflicts of interest influence recommendations.

This article is based on a Cochrane methodology review. The protocol is published in the Cochrane Database of Systematic Reviews 2019;10:14651858.MR000040.pub2. The review is expected to be published in the Cochrane Database of Systematic Reviews 2020;12:14651858.MR000040.pub3 (see www.cochranelibrary.com for information). Cochrane reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the review.

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Contributors: AL conceived the study. CHN, AH, and AL primarily developed the protocol, with contributions from LB, KJJ, and AWJ. The protocol was based on a previous protocol developed by AL, AWJ, and LB.[51] CHN and either AWJ or AL assessed studies for inclusion. CHN and either ML, AWJ, or AL extracted data and assessed studies for methodological quality. CHN analysed the data. All authors interpreted the data. CHN wrote the draft review of the manuscript and all authors revised the manuscript. CHN is guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not required.

Data sharing: No additional data available.

The lead author (CHN) affirms that the 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.

Dissemination to participants and related patient and public communities: No specific plan beyond dissemination through journal publication and news media.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Supplementary information: additional material

ONLINE SUPPLEMENTARY APPENDICES

Supplementary appendix 1. Terminology

Conflicts of interest: any financial or non-financial conflicts of interest as specified below.

Financial conflicts of interest: any funding of clinical guidelines, opinion pieces, or narrative reviews by drug or device companies, or any authors or advisory committee members with ties to such companies (e.g. advisory board membership).

Non-financial conflicts of interest: any relationships that differ from what is typically regarded as financial conflicts of interest (i.e. relationships with the drug or device industry), regardless of the definitions used by the authors of the included studies. However, we did not include studies investigating beliefs (e.g. political or religious), personal experience (e.g. abuse or trauma), or institutional conflicts of interest.[1]

Drugs: medications that require approval from a regulatory authority.

Devices: instruments used in diagnosis, treatment, or prevention of disease.[2] This term also includes medical imaging technologies.

Clinical guidelines: *"Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances".*[3]

Advisory committee reports: reports from meetings held in committees, boards, councils, or similar formalised groups that are established to advise an organisation and provide a recommendation concerning a drug or device intervention (e.g. records from the Food and Drug Administration (FDA) advisory committee on oncological drugs).

Opinion pieces: publications that are not research studies in which an author expresses a personal opinion about a specific intervention (e.g. editorials, commentaries, and letters).

Narrative reviews: literature reviews without a systematic search of the literature and without clear eligibility criteria.

Documents: clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews.

Supplementary appendix 2. PubMed Search Strategy

Block 1A: drug and device industry

1. Drug Industry (MeSH)

2. Manufacturing Industry (MeSH)

3. (Drug [Title/Abstract] OR drugs[Title/Abstract] OR pharmaceutical[Title/Abstract] OR pharmaceutic [Title/Abstract] OR pharmacological[Title/Abstract] OR pharma*[Title/Abstract] OR biotech*[Title/Abstract] OR bio-tech[Title/Abstract] OR biopharma*[Title/Abstract] OR bio-pharma*[Title/Abstract] OR biomed*[Title/Abstract] OR bio-med*[Title/Abstract] OR device[Title/Abstract] OR devices[Title/Abstract] OR imaging[Title/Abstract] OR for-profit[Title/Abstract] OR private[Title/Abstract]) AND (industry[Title/Abstract] OR industries[Title/Abstract] OR company[Title/Abstract] OR companies[Title/Abstract] OR manufacturer[Title/Abstract] OR manufacturers[Title/Abstract] OR organisation[Title/Abstract] OR organisations[Title/Abstract] OR organization[Title/Abstract] OR organizations[Title/Abstract] OR agency[Title/Abstract] OR agencies[Title/Abstract] OR sector[Title/Abstract] OR sectors[Title/Abstract])

4. Personal[Title] OR self-reported[Title] OR selfreported[Title] OR author[Title] OR authors[Title] OR authorship[Title] OR ((committee[Title] OR board[Title]) AND (member[Title] OR members[Title])) OR voting[Title] OR votings[Title] OR financial[Title] OR finance[Title]

5. 1 OR 2 OR 3 OR 4

Block 1B: financial conflicts of interest

6. Conflict of interest (MeSH)

7. Financial support (MeSH)

8. Research support as topic (MeSH)

9. (Conflict[Title/Abstract] OR conflicts[Title/Abstract] OR conflicting[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])

10. (Competing[Title/Abstract] OR vested[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])

11. (Industry[Title/Abstract] OR industries[Title/Abstract] OR company[Title/Abstract] OR companies[Title/Abstract] OR manufacturer[Title/Abstract] OR manufacturers[Title/Abstract] OR finance[Title/Abstract] OR financial[Title/Abstract]) AND (funded[Title/Abstract] OR funding[Title/Abstract] OR sponsor[Title/Abstract] OR sponsors[Title/Abstract] OR sponsorship[Title/Abstract] OR sponsoring[Title/Abstract] OR support[Title/Abstract] OR supported[Title/Abstract] OR finance[Title/Abstract] OR financial[Title/Abstract] OR involvement[Title/Abstract] OR involving[Title/Abstract] OR payment[Title/Abstract] OR payments[Title/Abstract] OR relationship[Title/Abstract] OR relationships[Title/Abstract] OR relation[Title/Abstract] OR

relations[Title/Abstract] OR tie[Title/Abstract] OR ties[Title/Abstract] OR collaboration[Title/Abstract] OR collaborations[Title/Abstract])

12. Industry-funded[Title/Abstract] OR industry-funding[Title/Abstract] OR industry-sponsor*[Title/Abstract] OR company-funded[Title/Abstract] OR company-funding[Title/Abstract] OR company-sponsor*[Title/Abstract] OR industry-support[Title/Abstract] OR industry-supported[Title/Abstract] OR company-support[Title/Abstract] OR company-supported[Title/Abstract]

13. (Commercial-academic[Title/Abstract] OR academic-commercial[Title/Abstract] OR industry-academic[Title/Abstract] OR academic-industry[Title/Abstract] OR commercial-industry[Title/Abstract] OR industry-commercial[Title/Abstract] OR industry-physician[Title/Abstract] OR physician-industry[Title/Abstract]) AND (interaction[Title/Abstract] OR interactions[Title/Abstract] OR relationship[Title/Abstract] OR relationships[Title/Abstract] OR relation[Title/Abstract] OR relations[Title/Abstract] OR collaboration[Title/Abstract] OR collaborations[Title/Abstract])

14. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13

Block 2A: non-financial, personal, and academic

15. Non-financial[Title/Abstract] OR nonfinancial[Title/Abstract]

16. Personal[Title] OR individual[Title] OR self-reported[Title] OR selfreported[Title] OR author[Title] OR authors[Title] OR authorship[Title]

17. Specialist[Title/Abstract] OR specialists[Title/Abstract] OR specialty[Title/Abstract] OR expert[Title/Abstract] OR experts[Title/Abstract] OR intellectual[Title/Abstract] OR intellectuals[Title/Abstract] OR professional[Title/Abstract] OR professionals[Title/Abstract] OR academic[Title/Abstract] OR academics[Title/Abstract]

18. 15 OR 16 OR 17

Block 2B: non-financial conflicts of interest

19. Conflict of interest (MeSH)

20. Conflict[Title] OR conflicts[Title] OR conflicting[Title] OR competing[Title] OR vested[Title]

21. Relation[Title] OR relations[Title] OR relationship[Title] OR relationships[Title]

22. Interest[Title] OR interests[Title]

23. 19 OR 20 OR 21 OR 22

Block 3: clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews

24. (Opinion[Title/Abstract] OR opinions[Title/Abstract] OR policy[Title/Abstract] OR policies[Title/Abstract] OR statement[Title/Abstract] OR statements[Title/Abstract]) AND (piece[Title/Abstract] OR pieces[Title/Abstract] OR article[Title/Abstract] OR articles[Title/Abstract])

25. (Narrative[Title/Abstract] OR descriptive[Title/Abstract] OR non-systematic[Title/Abstract] OR non-systematical[Title/Abstract] OR non-systematically[Title/Abstract] OR nonsystematic[Title/Abstract] OR nonsystematical[Title/Abstract] OR nonsystematically[Title/Abstract]) AND (review[Title/Abstract] OR reviews[Title/Abstract] OR overview[Title/Abstract] OR overviews[Title/Abstract])

26. Non[Title/Abstract] AND (systematic[Title/Abstract] OR systematical[Title/Abstract] OR systematically[Title/Abstract]) AND (review[Title/Abstract] OR reviews[Title/Abstract] OR overview[Title/Abstract] OR overviews[Title/Abstract])

27. Editorial[Title] OR editorials[Title] OR essay[Title] OR essays[Title] OR commentary[Title] OR commentaries[Title] OR comment[Title] OR comments[Title] OR letter[Title] OR letters[Title]

28. (Treatment[Title/Abstract] OR treatments[Title/Abstract] OR screening[Title/Abstract] OR screen[Title/Abstract] OR testing[Title/Abstract] OR test[Title/Abstract] OR tests[Title/Abstract OR diagnostic[Title/Abstract] OR diagnosis[Title/Abstract] OR therapy[Title/Abstract] OR therapies[Title/Abstract]) AND (recommendation[Title/Abstract] OR recommendations[Title/Abstract])

29. Guidelines as Topic (MeSH)

30. Health Planning Guidelines (MeSH)

31. (Clinical[Title] OR clinic[Title] OR health[Title] OR practice[Title]) AND (guideline[Title] OR guidelines[Title] OR recommendation[Title] OR recommendations[Title])

32. (Advisory[Title/Abstract] OR advising[Title/Abstract] OR formulary[Title/Abstract] OR counselling[Title/Abstract] OR counselling[Title/Abstract] OR drug[Title/Abstract] OR drugs[Title/Abstract]) AND (board[Title/Abstract] OR boards[Title/Abstract] OR committee[Title/Abstract] OR committees[Title/Abstract] OR panel[Title/Abstract] OR panels[Title/Abstract] OR meeting[Title/Abstract] OR meetings[Title/Abstract])

33. 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32

Combined searches

34. 5 AND 14

35. 18 AND 23

36. (34 OR 35) AND 33

Supplementary appendix 3. Data Extraction

Two review authors independently extracted the following information:

Study characteristics

- Title
- Name of lead author
- Name of journal
- Year published
- Primary aim of the study
- Design of study: cohort, cross-sectional study, systematic review or meta-analysis, or other
- Study domain - category: clinical guideline, advisory committee report, opinion pieces, narrative review, or mixed
- Sample description: for example, clinical guidelines on treatment of hypertension
- Strategy used to collect sample: for example, search of PubMed and time period covered
- Definition of clinical guidelines, advisory committee reports, opinion pieces, or narrative reviews used in the study. Verbatim extraction
- Number of included documents (separate data for clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews)
- Types of documents included in the study. Verbatim extraction
- Types of documents included in the study (drug, device or both)

Conflict of interest and outcome data

- Definition of financial conflicts of interest used in the study. Verbatim extraction
- Definition of non-financial conflicts of interest used in the study. Verbatim extraction
- Types of financial conflicts of interest investigated, potential categories are:
    - Funding;
    - Author grant;
    - Honorarium;
    - Consulting;
    - Speakers bureau;
- Types of non-financial conflicts of interest investigated
- Definition of favourable recommendations used by the authors of the study. Verbatim extraction
- Definition of primary analysis used in the study. Verbatim extraction
- Total number of documents with and without conflicts of interest. Stratified by type of document (i.e. clinical guideline, advisory committee reports, opinion piece, narrative review) and type of conflicts of interest (i.e. financial, non-financial)
- Number of documents with and without conflicts of interest with favourable recommendations stratified by type of documents (i.e. clinical guideline, advisory committee reports, opinion piece, narrative review) and type of conflicts of interest (i.e. financial, non-financial)
- Any data on estimates of the association between financial conflicts of interest/non-financial conflicts of interest and recommendations in clinical guidelines, advisory committee reports, opinion pieces, and narrative reviews (for example, adjusted effect estimates and confidence intervals).

Data for informing subgroup analyses or reflection on heterogeneity

- Total number of documents with conflicts of interest and number with favourable recommendations. Stratified by document type (i.e. clinical guidelines, advisory committee

reports, opinion pieces, narrative reviews) and category of financial conflicts of interest (e.g. investigator, grants, honorarium, consulting, speaker's bureau, equity/stock, gifts)
- Any data on the association between each category of financial conflicts of interest and favourable recommendations
- Total number of clinical guidelines following standardised methods with and without conflicts of interest and number with favourable recommendations. Stratified by type of conflicts of interest (i.e. financial, non-financial)
- Total number of clinical guidelines not following standardised methods with and without conflicts of interest and number with favourable recommendations. Stratified by type of conflicts of interest (i.e. financial, non-financial)
- Any data on the association between conflicts of interest and favourable recommendations for clinical guidelines following standardised methods and clinical guidelines not following standardised methods
- Total number of documents with conflicts of interest and number with favourable recommendations. Stratified by document type (i.e. clinical guidelines, advisory committee reports, opinion pieces, narrative reviews) and degree of financial conflicts of interest (i.e. major and minor)
- Any data on the association between major and minor financial conflicts of interest and favourable recommendations

Data for performing sensitivity analyses

- Total number of documents with and without conflicts of interest and number of documents in each group with favourable recommendations, when excluding documents with unclear or undisclosed conflicts of interest. Stratified by document type (i.e. clinical guidelines, advisory committee reports, opinion pieces, narrative reviews) and type of conflicts of interest (i.e. financial, non-financial)
- Any data on the association between conflicts of interest and favourable recommendations, when excluding documents with unclear or undisclosed conflicts of interest
- Total number of documents with and without conflicts of interest and number of documents in each group with favourable recommendations, when excluding documents with neutral recommendations. Stratified by document type (i.e. clinical guidelines, advisory committee reports, opinion pieces, narrative reviews) and type of conflicts of interest (i.e. financial, non-financial)
- Any data on the association between conflicts of interest and favourable recommendations, when excluding documents with neutral recommendations
- Total number of documents with and without financial conflicts of interest and number of documents in each group with favourable recommendations. Stratified by document type (i.e. clinical guidelines, advisory committee reports, opinion pieces, narrative reviews) and type of financial conflict of interest (i.e. related to the manufacturer or related to any for-profit company)
- Any data on the association between financial conflicts of interest and favourable recommendations. Stratified by type of financial conflict of interest (i.e. related to the manufacturer or related to any for-profit company)

Additional data

- Funding and conflicts of interest statement in the study. Verbatim extraction
- Additional relevant information

Supplementary appendix 4. Dealing with unpublished data

Protocols

We contacted authors in an attempt to obtain published or unpublished protocols for all the studies. All author teams but two responded.[4,5] Nine author teams replied that no protocol was used,[6-14] six author teams replied that they had a protocol, but could not locate or access it,[15-20] and two author teams supplied us with their protocol.[21,22] One author team replied that they had a protocol, but it was incorporated in the study publication,[23] and one author team supplied us with a master thesis that was used as basis of the study.[24] However, in both cases these were in our views not protocols (i.e. a document that details the study rationale and proposed methods written prior to study conduct).[25]

Methodological quality assessment

If the studies did not report their methods in a way that enabled us to conduct our methodological quality assessment, we contacted the authors to clarify these issues. In total, we contacted authors of all the studies and received clarifications for all but two studies.[4,5]

Unpublished data

We contacted the authors of the included studies in an attempt to obtain additional individual study data or summary data in the following cases:

- If the studies included a mixture of documents, but only reported combined data. For example, if a study included clinical guidelines and randomised trials, we contacted the authors to obtain separate data on clinical guidelines.
- If the studies performed unadjusted or adjusted regression analyses, but did not report the raw numbers.
- If the studies extracted information on different types of financial conflicts of interest and/or number of authors with and without financial conflicts of interest in each document, but did not report this information.
- If the studies included documents with undisclosed conflicts of interest and/or neutral recommendations, but did not report this in a separate category.

In total, we contacted authors of 17 studies[4-7,9-15,18-23] and received data for 11 of these studies; eight full data sets[6,7,10,12,13,15,21,23] and in three cases additional summary data.[11,19,20]

When we received unpublished data, we analysed the data according to the methods used in the original studies. For the study on advisory committee reports by Ackerley and colleagues,[13] we restricted the sample for analysis to standing or temporary committee members that participated in the meeting and the voting in line with the authors' analysis.

We included one study that investigated a mixture of opinion pieces and narrative reviews and reported the coding of financial conflicts of interest and recommendations separately for each document, but without specifying the type of document.[14] To enable inclusion in our meta-analyses, two authors (CHN and AL) independently coded the type of documents in the study.

Supplementary appendix 5. Prediction Interval

Formula for prediction interval

We only calculated prediction intervals when at least four studies were included in the pooled analysis, because intervals will be imprecise when the effect estimates are based on only a few studies.[26]

To calculate prediction intervals, we used the formula presented in an article by Riley and colleagues:[27]

$$\hat{u} - t_{k-2} \cdot \sqrt{(\hat{T}^2 + SE(\hat{u})^2)},\ \hat{u} + t_{k-2} \cdot \sqrt{(\hat{T}^2 + SE(\hat{u})^2)}$$

Where $\hat{u}$ was the estimate of the average effect measure across studies, $SE(\hat{u})$ was the standard error of $\hat{u}$, $\hat{T}$ was the estimate of between study standard deviation, and t_{k-2} was the $100(1-(\alpha/2))$ percentile of the t-distribution with k-2 degrees of freedom, where k was the number of studies in the meta-analysis and α was 0.05 to give a 95% prediction interval. To meet the assumption on normal distribution, the prediction interval was derived on the natural log scale.[27] As T^2 is already a measure for the heterogeneity for ln(RR), this was used directly in the calculation.[26]

Calculation of prediction interval for clinical guidelines

The prediction interval for the risk ratio (RR) of favourable recommendations in clinical guidelines with financial conflicts of interest compared with clinical guidelines without financial conflicts of interest was calculated as: 0.65 to 2.43. Thus, one can expect that clinical guidelines with financial conflicts of interest more often have favourable recommendations compared with clinical guidelines without financial conflicts of interest, but for an individual study of clinical guidelines the association may be reversed.

As our analysis on non-financial conflicts of interest in clinical guidelines was based on only one study, calculation of a prediction interval was only possible for financial conflicts of interest.

Calculation of prediction interval for advisory committee reports

The prediction interval for the RR of favourable recommendations in advisory committee reports with financial conflicts of interest compared with advisory committee reports without financial conflicts of interest was calculated as: 0.66 to 2.19. Thus, one can expect that advisory committee reports with financial conflicts of interest more often have favourable recommendations compared with advisory committee reports without financial conflicts of interest, but for an individual study of advisory committee reports the association may be reversed.

Calculation of prediction interval for opinion pieces

The prediction interval for the RR of favourable recommendations in opinion pieces with financial conflicts of interest compared with opinion pieces without financial conflicts of interest was calculated as: 0.03 to 220.56. Thus, one can expect that opinion pieces with financial conflicts of interest more often have favourable recommendations compared with opinion pieces without financial conflicts of interest, but for an individual study of opinion pieces the association may be reversed.

Calculation of prediction interval for narrative reviews

The prediction interval for the RR of favourable recommendations in narrative reviews with financial conflicts of interest compared with narrative reviews without financial conflicts of interest was calculated as: 0.56 to 2.59. Thus, one can expect that narrative reviews with financial conflicts of interest more often

have favourable recommendations compared with narrative reviews without financial conflicts of interest, but for an individual study of narrative reviews the association may be reversed.

Calculation of prediction interval for combined post-hoc secondary analysis

The prediction interval for the RR of favourable recommendations in documents with financial conflicts of interest compared with documents without financial conflicts of interest was calculated as: 0.88 to 1.80. Thus, one can expect that documents with financial conflicts of interest more often have favourable recommendations compared with documents without financial conflicts of interest, but for an individual study the association may be reversed.

Supplementary appendix 6. Number Needed to Read and additional findings for each document type

Number Needed to Read

For each document type, we calculated a Number Needed to Read as 1/Risk Difference. We calculate the Risk Difference based on the estimates presented in the Summary of Findings table (eAppendix 9). For each estimated Number Needed to Read, we calculated corresponding 95% confidence intervals using the methods described by Altman[28] with Number Needed to Read Favourable (NNRF) representing the expected number of documents with conflicts of interest needed to be read rather than documents without conflicts of interest for one additional document having a favourable recommendation, and Number Needed to Read Unfavourable (NNRU) representing the expected number of documents with conflicts of interest needed to be read rather than documents without conflicts of interest for one additional document having an unfavourable recommendation.

The Number Needed to Read for clinical guidelines was 9.1. The corresponding 95% CI was NNRU 33.3 to ∞ to NNRF 3.4.

The Number Needed to Red for advisory committee reports was 7.7. The corresponding 95% CI was NNRU 100.0 to ∞ to NNRF 3.4.

The Number Needed to Read for opinion pieces was 2.3. The corresponding 95% CI was NNRU 50.0 to ∞ to NNRF 1.4.

The Number Needed to Read for narrative reviews was 8.3. The corresponding 95% CI was NNRU 50.0 to ∞ to NNRF 3.4.

The Number Needed to Read for all document types was 7.1. The corresponding 95% CI was NNRF 20 to NNRF 4.2.

The Number Needed to Read for non-financial conflicts of interest in clinical guidelines was 2.1. The corresponding 95% CI was NNRU 25.0 to ∞ to NNRF 1.75.

Additional findings on financial conflicts of interest in clinical guidelines

Four included studies did not report data in a way that enabled us to include them in our pooled analysis. Two studies each investigated one clinical guideline with financial conflicts of interest and one without. In both of these studies the clinical guidelines with financial conflicts of interest had favourable recommendations, whereas the clinical guidelines without had unfavourable recommendations.[8,24] One study investigated 12 clinical guidelines, but only reported the percentage of authors with financial conflicts of interest in each guideline. Three out of eight clinical guidelines with favourable recommendations included authors with financial conflicts of interest (prevalence from 12% to 53%), and two out of four clinical guidelines with unfavourable recommendations included authors with financial conflicts of interest (prevalence 9% and 11%).[16] The remaining study investigated a mixture of four clinical guidelines, 23 opinion pieces, and 40 reviews (mainly narrative) commenting on a randomised trial on fenofibrate use. The authors found that documents written by authors with conflicts of interest more often recommended fibrate use (RR: 1.69, 95% CI: 1.07 to 2.67).[22]

One of the studies included in our pooled analysis adjusted for the specific drug that was evaluated in the guideline (thereby reducing the risk of confounding). The authors found no association between financial conflicts of interest and recommendations of a drug, but did not report any effect estimates in the study publication.[17]

Additional findings on financial conflicts of interest in advisory committee reports

Two included studies did not report data in a way that enabled us to include them in our pooled analysis. One of the studies investigated the association between conflicts of interest and voting behaviour of 1482 members from 385 advisory committee reports. The authors reported that they found no association between conflicts of interest and voting outcome among members, but did not report any effect estimates on the association between financial conflicts of interest and favourable recommendations.[4] The remaining study investigated 1483 members from 416 advisory committee reports. The authors found that committee members with financial conflicts of interest had 14.3 percent greater odds of voting for approval compared with committee members without financial conflicts of interest. However, the estimate was not statistically significant (p-value: 0.12).[5]

One of the studies included in the pooled analysis adjusted for medical product and advisory committee meeting characteristics (thereby reducing the risk of confounding) and the association between financial conflicts of interest related to the manufacturing company and favourable recommendations was OR: 4.66, 95% CI: 0.64 to 33.6.[12]

Additional findings on financial conflicts of interest in opinion pieces

Two included studies did not report data in a way that enabled us to include them in our pooled analysis. One study investigated a mixture of 69 authors of original research papers, reviews (mainly systematic), and letters. The study found that authors with financial conflicts of interest related to the drug manufacturer more often had favourable recommendations than authors without financial conflicts of interest (RR: 13.91, 95% CI: 1.99 to 96.97).[18] The remaining study investigated a mixture of four clinical guidelines, 23 opinion pieces, and 40 reviews (mainly narrative) commenting on a randomised trial on fenofibrate use. The authors found that documents written by authors with conflicts of interest more often supported continued fibrate use (RR: 1.69, 95% CI: 1.07 to 2.67).[22]

One of the studies included in the pooled analysis adjusted for characteristics of the trial (e.g. type of intervention and trial conclusion) the editorial commented on (thereby reducing the risk of confounding) and the association between financial conflicts of interest and favourable recommendations was OR: 1.39, 95% CI: 0.52 to 3.70.[6]

Additional findings on financial conflicts of interest in narrative reviews

One included study did not report data in a way that enabled us to include it in our pooled analysis. The study investigated a mixture of four clinical guidelines, 23 opinion pieces, and 40 reviews (mainly narrative) commenting on a randomised trial on fenofibrate use. The authors found that documents written by authors with conflicts of interest more often recommended fibrate use (RR: 1.69, 95% CI: 1.07 to 2.67).[22]

Supplementary appendix 7. Subgroup Analyses

Planning of subgroup analyses

We planned to conduct the following pre-planned subgroup analyses for our primary analyses for all document types:

- Documents stratified by different types of financial conflicts of interest (e.g. funding, investigator, author grants, honorarium, consulting, speaker's bureau, equity/stock, or gifts)
- Studies assessed as having adequate methodological quality versus studies assessed as having inadequate methodological quality

We planned to conduct the following pre-planned subgroup analysis for our primary analysis on clinical guidelines only:

- Clinical guidelines developed using standardised methods (e.g. GRADE[29] or US Preventive Services Task Force[30]) versus clinical guidelines not developed using standardised methods. For the stratification of documents, we relied of the coding done by the authors of the included studies

In addition, we planned to conduct the following post-hoc subgroup analysis for our primary analyses:

- Documents stratified by degree of financial conflicts of interest. We compared major financial conflicts of interest (defined as at least half of the authors/committee members having financial conflicts of interest) with minor financial conflicts of interest (defined as less than half of the authors/committee members with financial conflicts of interest). The purpose of this subgroup analysis was to investigate a potential dose-response relationship between financial conflicts of interest and recommendations

We only carried out the subgroup analyses when we had sufficient data (i.e. at least five documents in the group with and without conflicts of interest in the included studies combined).

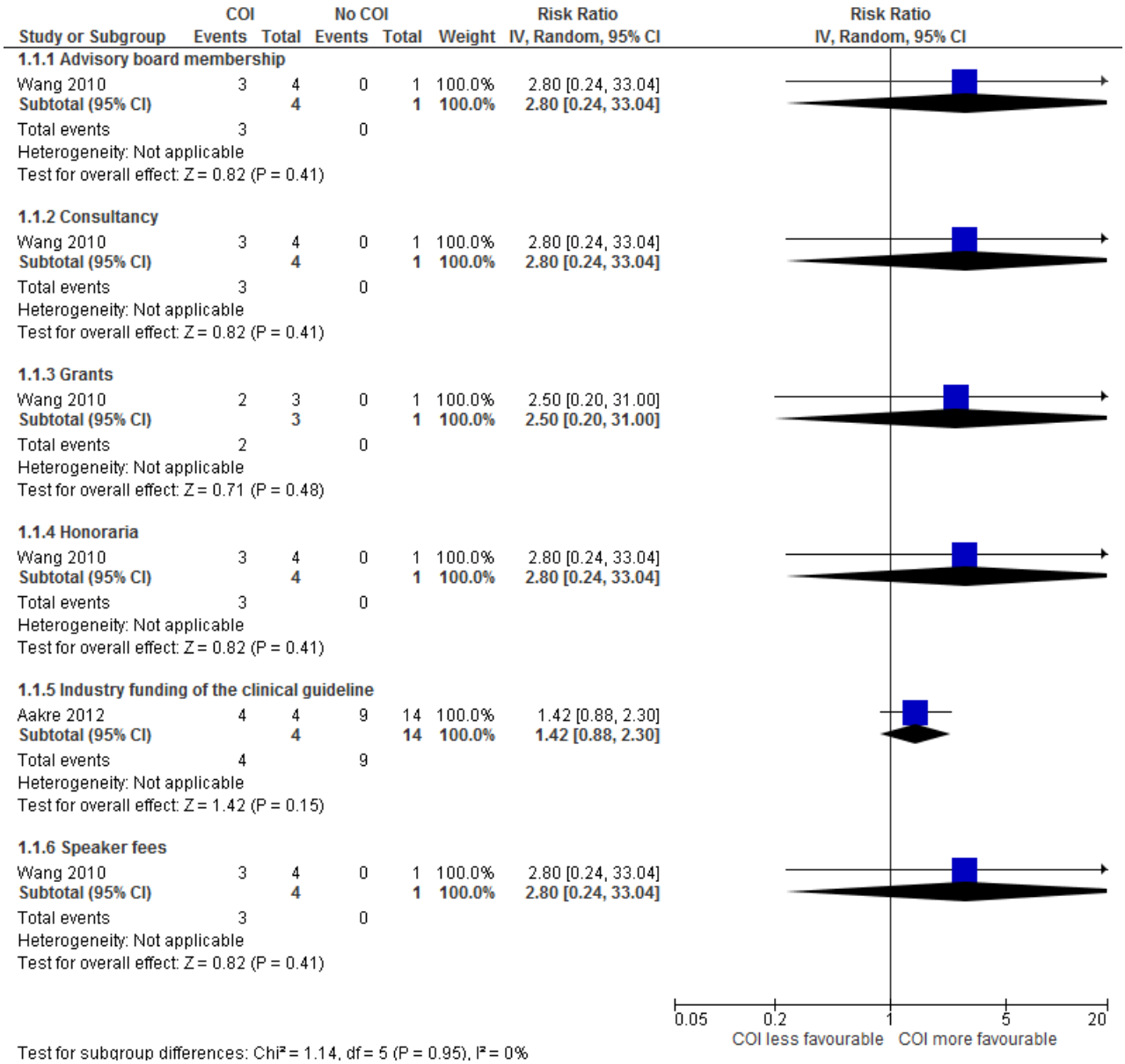
Findings from subgroup analyses on clinical guidelines

Different types of financial conflicts of interest

Of the four studies included in our pooled analysis on financial conflicts of interest, two studies specified subtypes of financial conflicts of interest.[9,23] We were able to pool data on six different types of financial conflicts of interest: advisory board membership, consultancy, grants, honoraria, industry funding of the clinical guideline, and speaker fees.

We found no difference in recommendations between guidelines with different types of financial conflicts of interest, but estimates were statistically imprecise (p-value for interaction test: 0.95, eFigure 1).

eFigure 1. Subgroup analysis of the association between different types of financial conflicts of interest and favourable recommendations in clinical guidelines



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Adequate methodological quality versus inadequate methodological quality

We planned to compare studies having adequate with studies having inadequate methodological quality. However, all four studies included in our pooled analysis on clinical guidelines were assessed as having inadequate methodological quality, and it was not possible to carry out this subgroup analysis.

Clinical guidelines developed using standardised methods versus clinical guidelines not developed using standardised methods

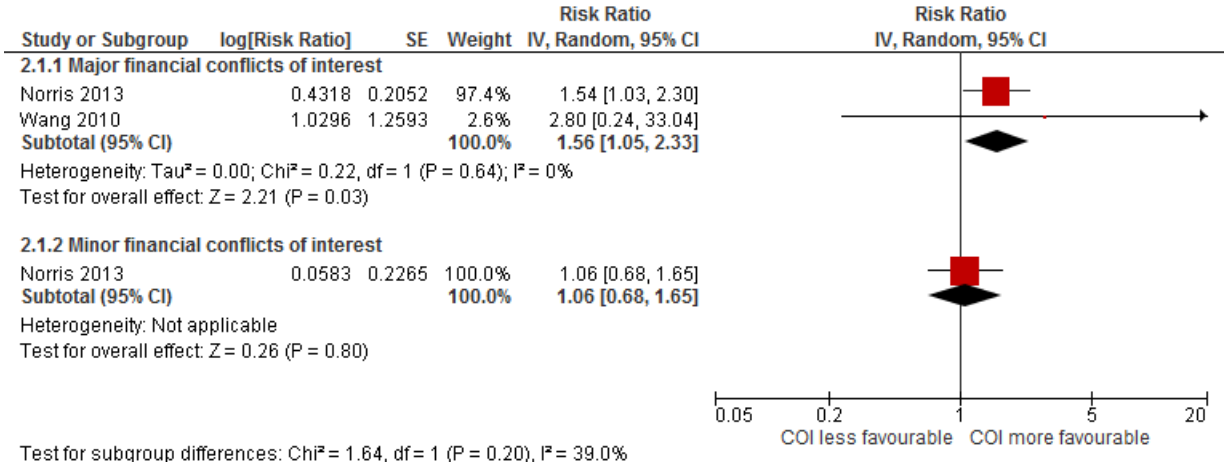
We planned to compare clinical guidelines developed using standardised methods (e.g. through GRADE or US Preventive Services Task Force) with clinical guidelines developed without. Only one of the four studies included in our pooled analysis on financial conflicts of interest in clinical guidelines clearly stated that

included clinical guidelines had to provide documentation that a systematic literature search and review was done.[17] In the remaining three studies, methodological aspects of the included clinical guidelines were not reported and the study samples could potentially be a mixture of clinical guidelines with and without standardised methods. None of the studies had any references to either GRADE or US Preventive Services Task Force. Therefore, our data did not enable us to carry out this subgroup analysis.

Clinical guidelines with major financial conflicts of interest versus clinical guidelines with minor financial conflicts of interest

We were able to assess the number of authors with financial conflicts of interest in each clinical guideline in two studies.[17,23] We found no difference in recommendations between guidelines with major (i.e. at least half of the authors) and minor (i.e. less than half of the authors) financial conflicts of interest, but estimates were statistically imprecise (p-value for interaction test: 0.20, eFigure 2).

eFigure 2. Subgroup analysis of the association between major and minor financial conflicts of interest and favourable recommendations in clinical guidelines



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval; SE: standard error

The estimate of heterogeneity should be interpreted with caution as the estimate using a random-effects model is not reliable when only two studies are included in the analysis

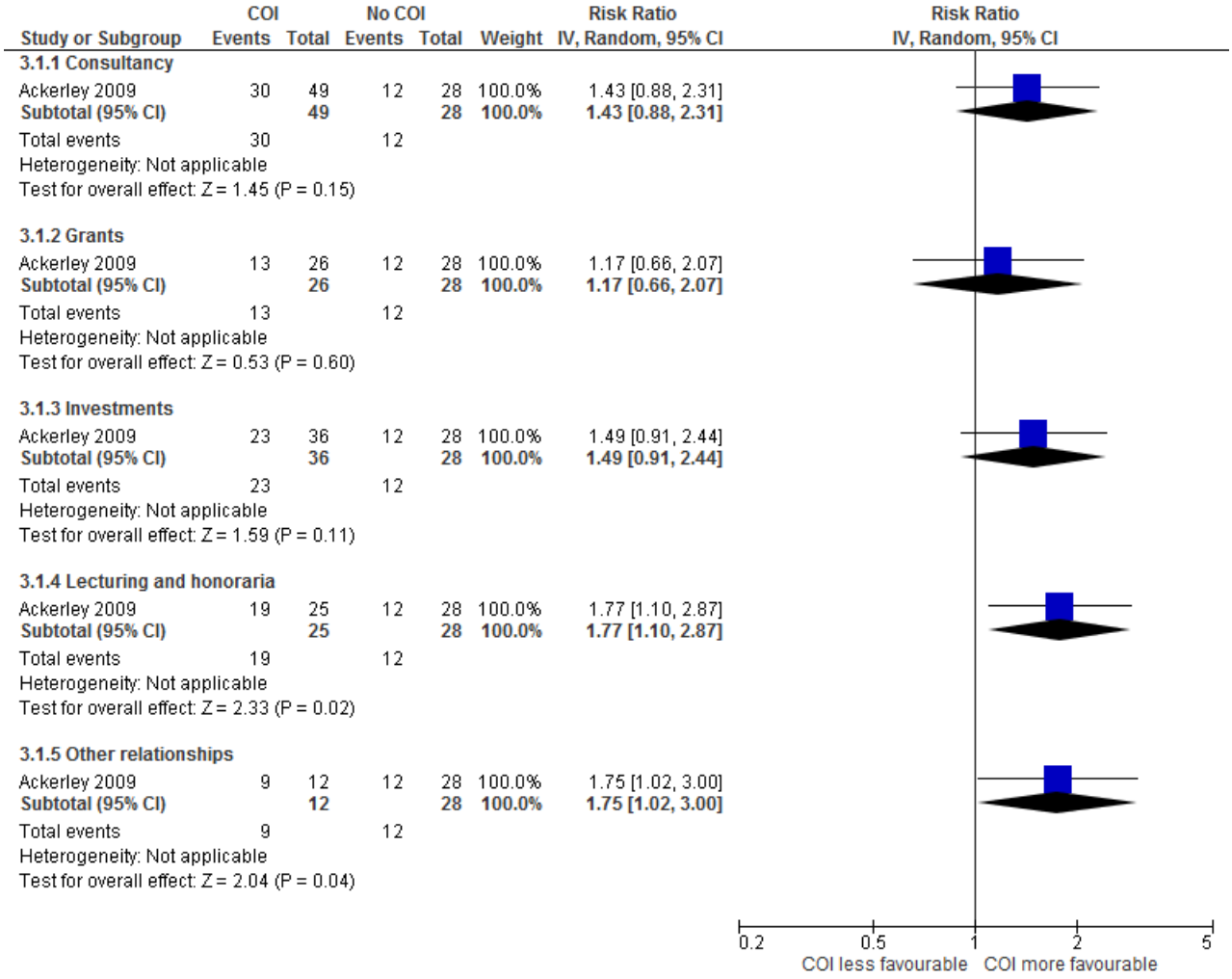
Findings from subgroup analyses on advisory committee reports

Different types of financial conflicts of interest

Of the four studies included in our primary analysis on financial conflicts of interest, one study specified different types of financial conflicts of interest.[13] We were able to pool data on five different types of financial conflicts of interest: consultancy, grants, investments, lecturing and honoraria, and other relationships of committee members (including e.g. patents and expert witness).

We found no difference in recommendations between advisory committee reports with different types of financial conflicts of interest, but estimates were statistically imprecise (p-value for interaction test: 0.82, eFigure 3).

eFigure 3. Subgroup analysis of the association between different types of financial conflicts of interest and favourable recommendations in advisory committee reports



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

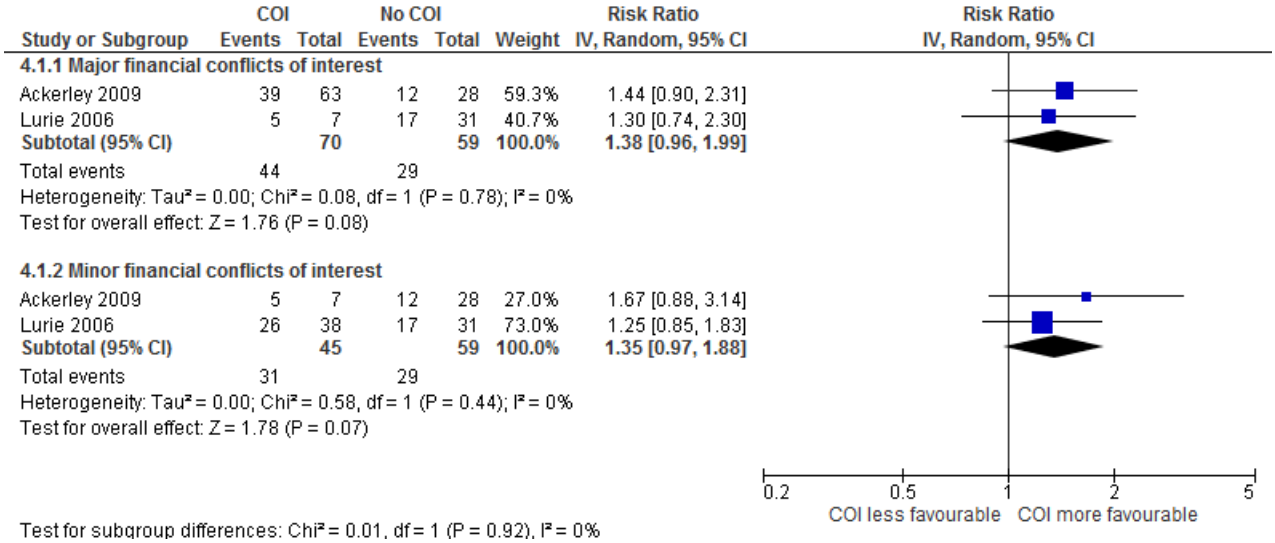
Adequate methodological quality versus inadequate methodological quality

We planned to compare studies having adequate with studies having inadequate methodological quality. However, all four studies included in our pooled analysis on advisory committee reports were assessed as having inadequate methodological quality, and it was not possible to carry out this subgroup analysis.

Advisory committee reports with major financial conflicts of interest versus advisory committee reports with minor financial conflicts of interest

We were able to assess the number of committee members with financial conflicts of interest in each advisory committee report in two studies.[13,21] We found no difference in recommendations between advisory committee reports with major (i.e. at least half of the committee members) and minor (i.e. less than half of the committee members) financial conflicts of interest, but estimates were statistically imprecise (p-value for interaction test: 0.92, eFigure 4).

eFigure 4. Subgroup analysis of the association between major and minor financial conflicts of interest and favourable recommendations in advisory committee reports



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

The estimate of heterogeneity should be interpreted with caution as the estimate using a random-effects model is not reliable when only two studies are included in the analysis

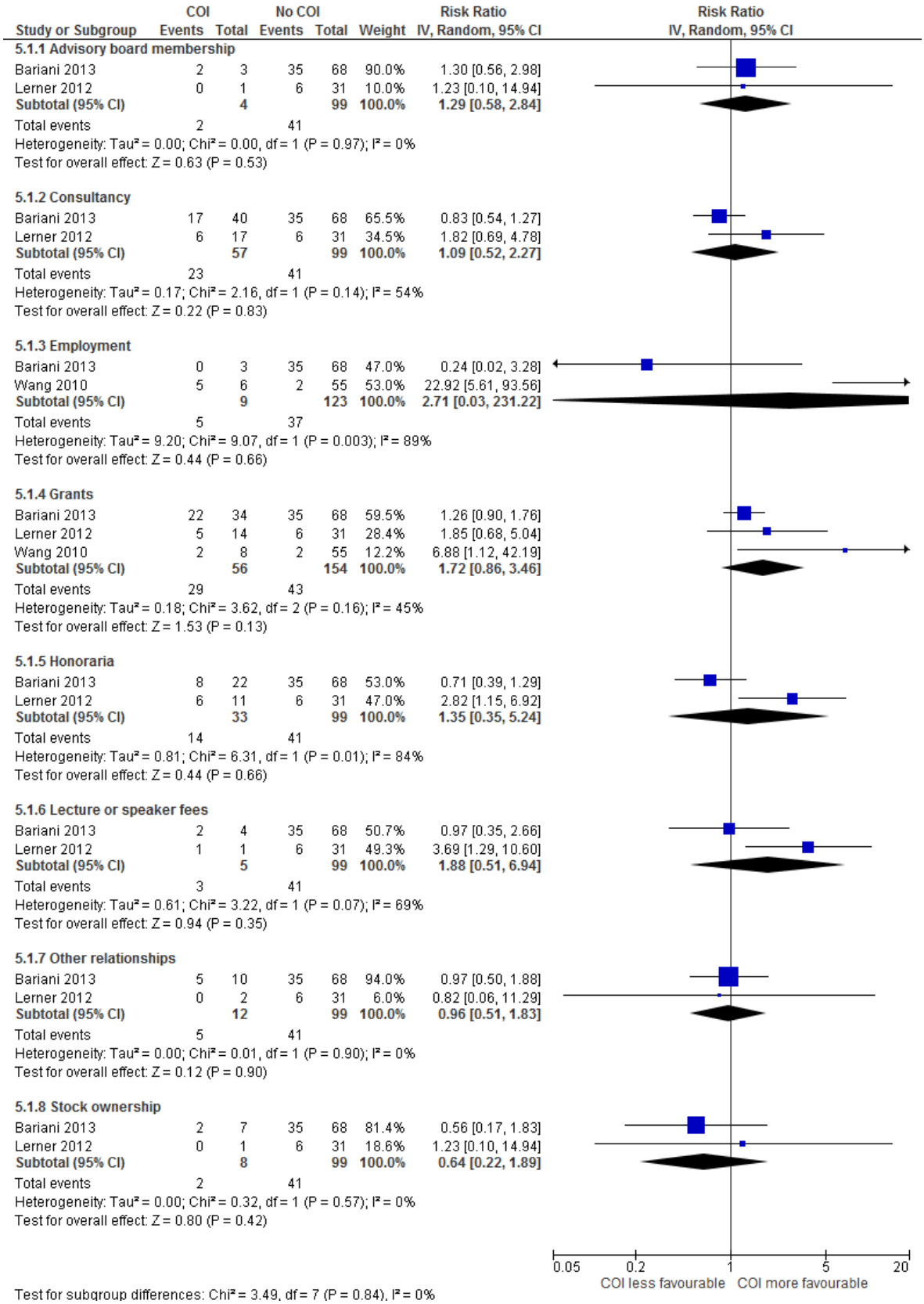
Findings from subgroup analyses on opinion pieces

Different types of financial conflicts of interest

Three of the four studies included in our pooled analysis on financial conflicts of interest in opinion pieces investigated different types of financial conflicts of interest. We were able to pool data from the studies on eight types of financial conflicts of interest: advisory board membership, consultancy, employment, grants, honoraria, lecture or speaker fees, other relationships (including royalties, testimony, patents, and travel grants), and stock ownership.

We found no difference in recommendations between opinion pieces with different types of financial conflicts of interest, but estimates were statistically imprecise (p-value for interaction test: 0.84, eFigure 5).

eFigure 5. Subgroup analysis of the association between different types of financial conflicts of interest and favourable recommendations in opinion pieces



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

The estimate of heterogeneity should be interpreted with caution as the estimate using a random-effects model is not reliable when only two studies are included in the analysis

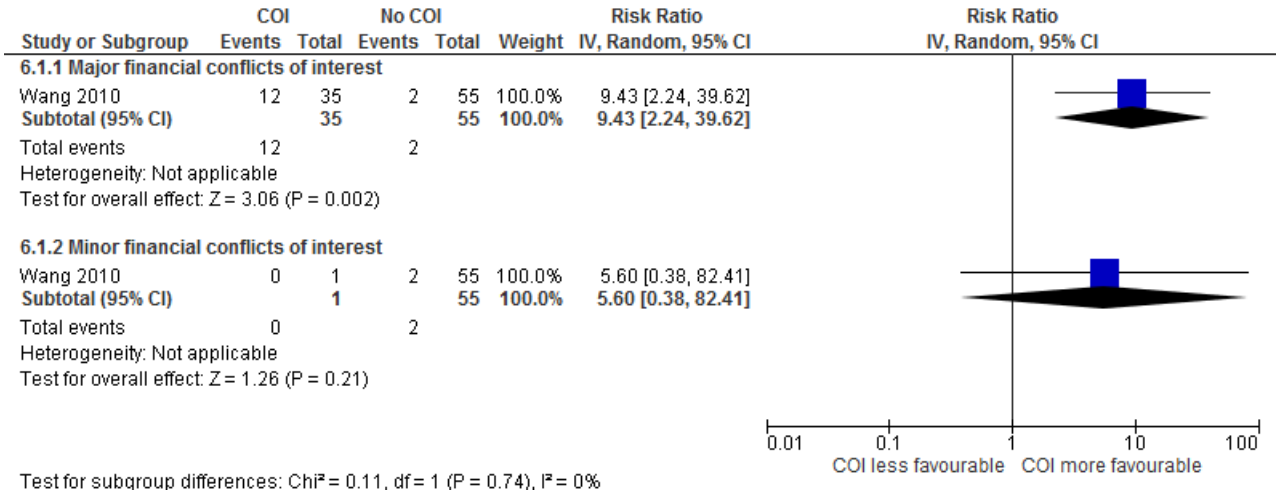
Adequate methodological quality versus inadequate methodological quality

We planned to compare studies having adequate with studies having inadequate methodological quality. However, all four studies included in our pooled analysis on opinion pieces were assessed as having inadequate methodological quality, and it was not possible to carry out this subgroup analysis.

Opinion pieces with major financial conflicts of interest versus opinion pieces with minor financial conflicts of interest

We were able to assess the number of authors with financial conflicts of interest in each opinion piece in one study.[23] We found no difference in recommendations between opinion pieces with major (i.e. at least half of the authors) and minor (i.e. less than half of the authors) financial conflicts of interest, but estimates were statistically imprecise (p-value for interaction test: 0.74, eFigure 6).

eFigure 6. Subgroup analysis of the association between major and minor financial conflicts of interest and favourable recommendations in opinion pieces



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

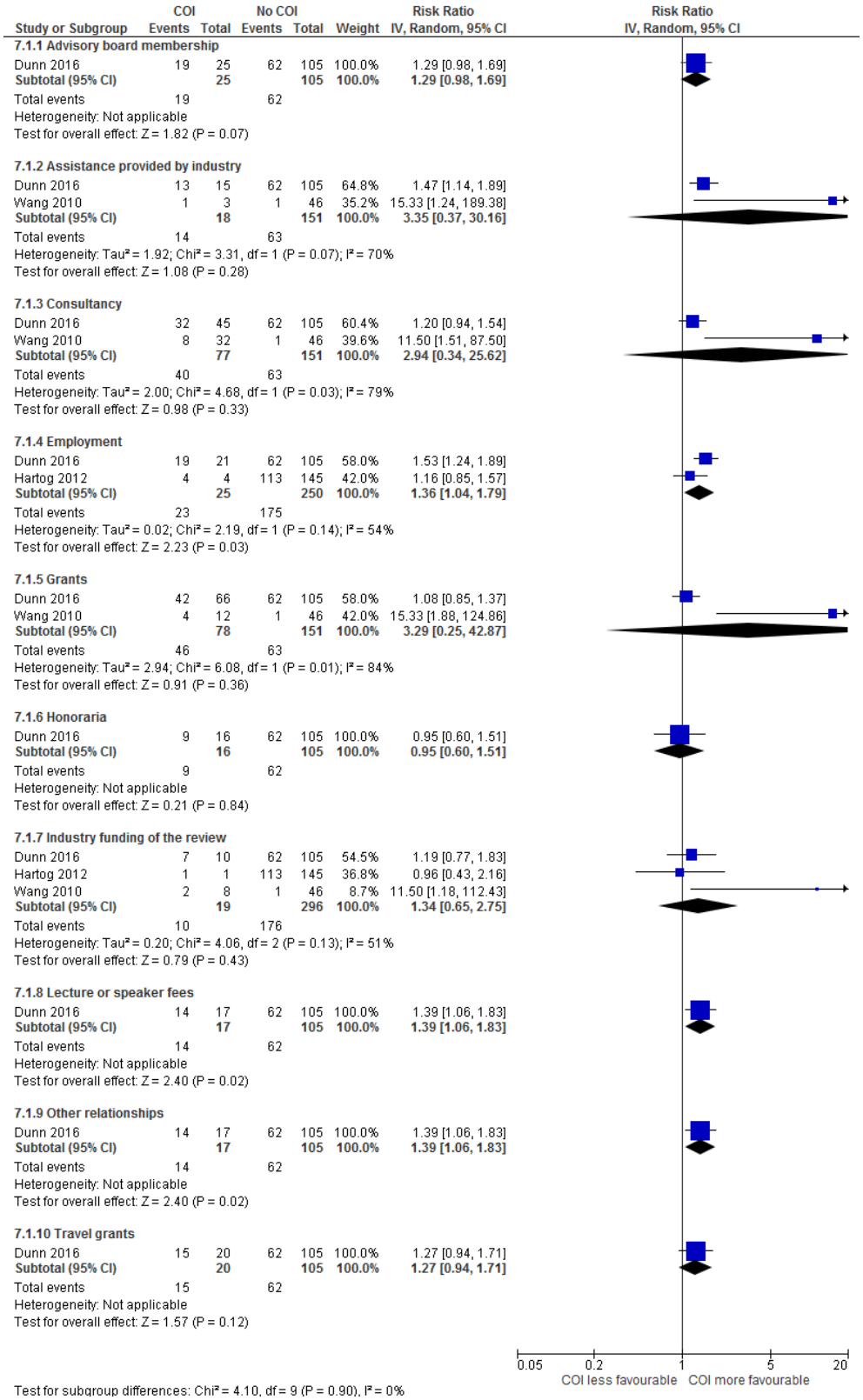
Findings from subgroup analyses on narrative reviews

Different types of financial conflicts of interest

Three of the four studies investigating narrative reviews investigated different types of financial conflicts of interest. We were able to pool data on nine types: advisory board membership, assistance provided by industry, consultancy, employment, grants, honoraria, industry funding of the review, lecture or speaker fees, other relationships of review authors, and travel grants.

We found no difference in recommendations between reviews with different types of financial conflicts of interest, but estimates were statistically imprecise (p-value for interaction test: 0.90, eFigure 7).

eFigure 7. Subgroup analysis of the association between different types of financial conflicts of interest and favourable recommendations in narrative reviews



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

The estimate of heterogeneity should be interpreted with caution as the estimate using a random-effects model is not reliable when only two studies are included in the analysis

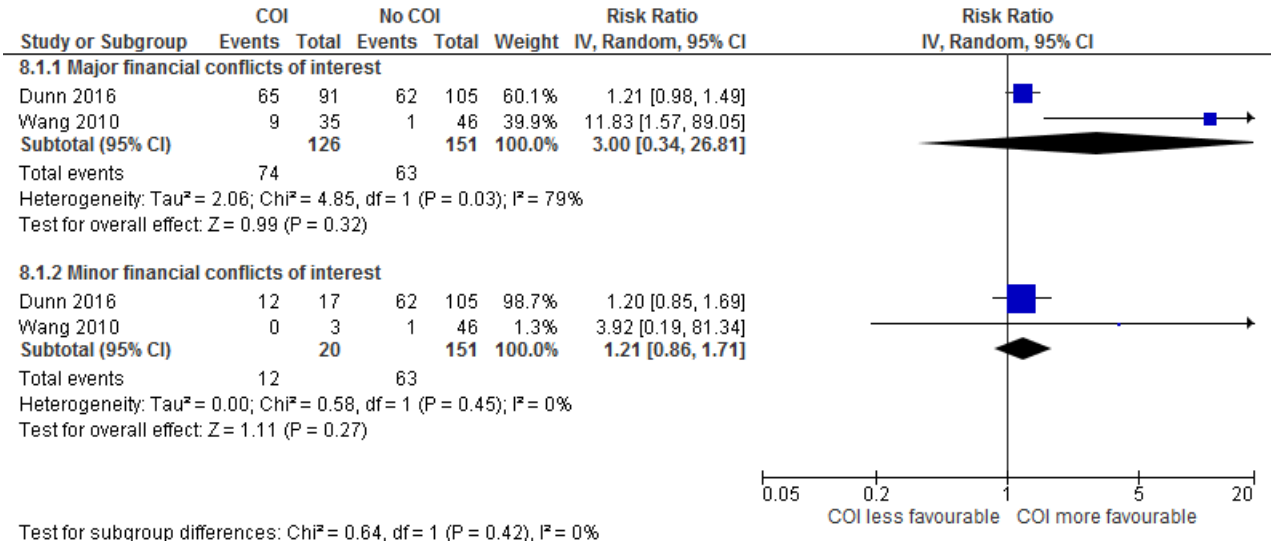
Adequate methodological quality versus inadequate methodological quality

We planned to compare studies having adequate with studies having inadequate methodological quality. However, all four studies included in our pooled analysis on narrative reviews were assessed as having inadequate methodological quality, and it was not possible to carry out this subgroup analysis.

Narrative reviews with major financial conflicts of interest versus narrative reviews with minor financial conflicts of interest

We were able to assess the number of authors with financial conflicts of interest in narrative review in two studies.[7,23] We found no difference in recommendations between reviews with major (i.e. at least half of the authors) and minor (i.e. less than half of the authors) financial conflicts of interest, but estimates were statistically imprecise (p-value for interaction test: 0.42, eFigure 8).

eFigure 8. Subgroup analysis of the association between major and minor financial conflicts of interest and favourable recommendations in narrative reviews



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

The estimate of heterogeneity should be interpreted with caution as the estimate using a random-effects model is not reliable when only two studies are included in the analysis

Supplementary appendix 8. Sensitivity Analyses

Planning of sensitivity analyses

We planned to conduct the following pre-planned sensitivity analyses for our primary analyses:

- Excluding documents with unclear or undisclosed conflicts of interest
- Excluding documents with neutral recommendations
- Excluding all studies which disclosed a relevant conflict of interest. For example, if one of the included studies was funded by a drug company, we excluded the study and re-analysed our data
- Re-analysing our primary analyses using a fixed-effect model

In addition, we planned to conduct the following post-hoc sensitivity analysis for our primary analyses:

- Re-categorising documents with financial conflicts of interest into documents with financial conflicts of interest related to the manufacturer of the drug or device of interest or to any for-profit company in two separate analyses

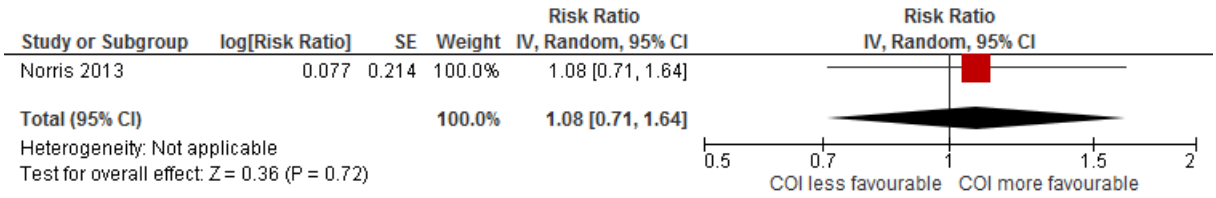
We only carried out the sensitivity analyses, when we had sufficient data (i.e. at least five documents in the group with and without conflicts of interest in the included studies combined).

Findings from sensitivity analyses on clinical guidelines

Excluding clinical guidelines with unclear or undisclosed conflicts of interest

One of the studies included in the pooled analysis on financial conflicts of interest only included clinical guidelines with clear conflicts of interest statements.[17] In the remaining three studies it was not possible to exclude clinical guidelines with unclear or undisclosed conflicts of interest, because reporting of data did not allow it,[19] or the authors did not code this information in their raw datasets.[9,23] In our analysis excluding clinical guidelines with undisclosed financial conflicts of interest, we found somewhat similar results as the primary analysis (from RR: 1.26, 95% CI: 0.93 to 1.69 in the primary analysis to RR: 1.08, 95% CI: 0.71 to 1.64, eFigure 9).

eFigure 9. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in clinical guidelines, when excluding clinical guidelines with unclear or undisclosed financial conflicts of interest



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval; SE: standard error

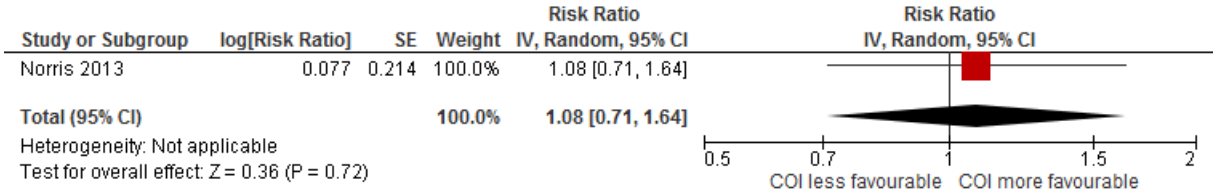
The one study investigating specialist interest included no clinical guidelines with undisclosed speciality of authors.[16]

Excluding clinical guidelines with neutral recommendations

One of the studies included in our pooled analysis on financial conflicts of interest included no clinical guidelines with neutral recommendations.[17] In two studies, the sample did not include any clinical guidelines without favourable recommendations[9] or without conflicts of interest,[23] when we removed

clinical guidelines with neutral recommendations. In the remaining study, it was not possible to remove clinical guidelines with neutral recommendations, because reporting of data did not allow it.[19] Thus, our sensitivity analysis for financial conflicts of interest was based on one study.[17] We found somewhat similar results as our primary analysis (from RR: 1.26, 95% CI: 0.93 to 1.69 in the primary analysis to RR: 1.08, 95% CI: 0.71 to 1.64, eFigure 10).

eFigure 10. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in clinical guidelines, when excluding clinical guidelines with neutral recommendations

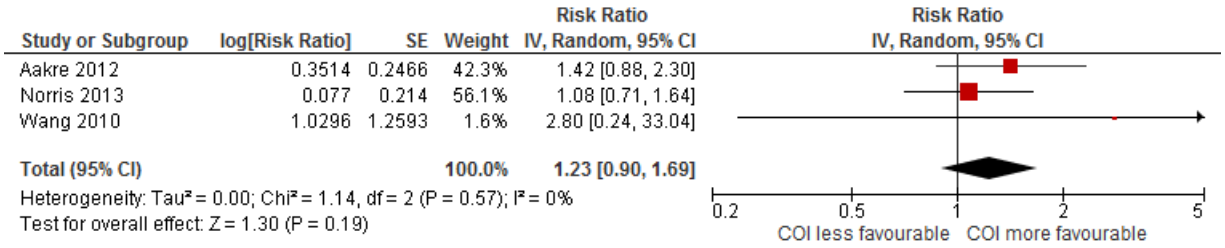


COI: conflicts of interest; IV: inverse-variance; CI: confidence interval; SE: standard error

In the one study investigating specialist interest in clinical guidelines, a neutral category was not used for categorising recommendations. Therefore, it was not possible to undertake a sensitivity analysis excluding clinical guidelines with neutral recommendations.[16]

Excluding all studies of clinical guidelines which disclosed a relevant conflict of interest of study authors
One of the studies included in our pooled analysis disclosed financial conflicts of interest of study authors.[19] Excluding this study from our pooled analysis on financial conflicts of interest did not affect our findings (from RR: 1.26, 95% CI: 0.93 to 1.69 in the primary analysis to RR: 1.23, 95% CI: 0.90 to 1.69, eFigure 11).

eFigure 11. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in clinical guidelines, when excluding all studies which disclosed a relevant conflict of interest

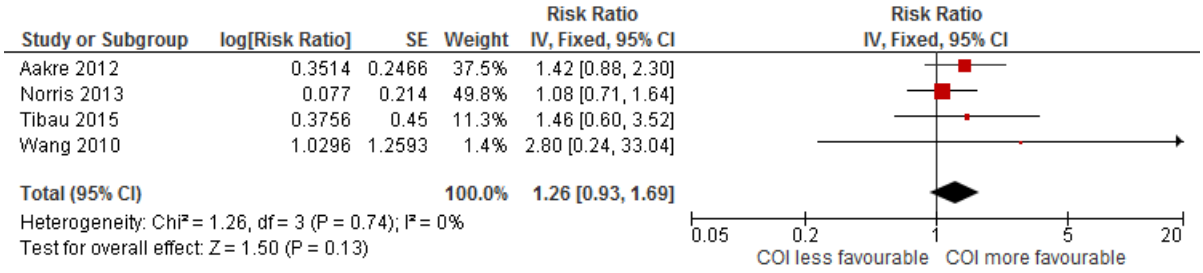


COI: conflicts of interest; IV: inverse-variance; CI: confidence interval; SE: standard error

The one study investigating specialist interest did not disclose any conflicts of interest of the study authors.[16]

Re-analysing our primary analyses using fixed-effect meta-analyses
Re-analysing our primary analysis using fixed-effect models did not affect our findings on financial conflicts of interest (from RR: 1.26, 95% CI: 0.93 to 1.69 in the primary analysis to RR: 1.26, 95% CI: 0.93 to 1.69, eFigure 12).

eFigure 12. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in clinical guidelines using fixed-effect model



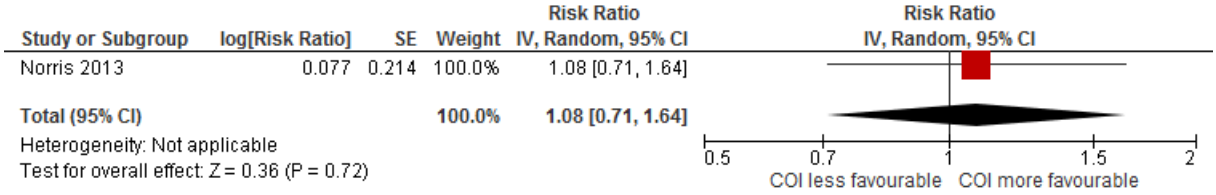
COI: conflicts of interest; IV: inverse-variance; CI: confidence interval; SE: standard error

As only one study was included in our analysis on specialist interest, it was not meaningful to carry out this sensitivity analysis.

Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer and financial conflicts of interest related to any for-profit company

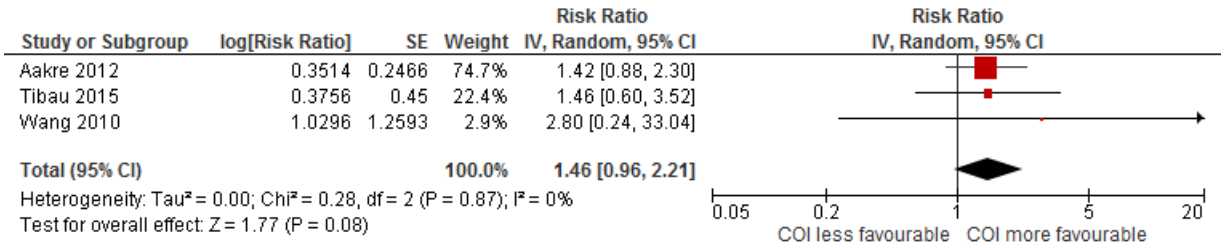
One of the studies included in our pooled analysis measured financial conflicts of interest related to the manufacturer of the investigated drug,[17] whereas three studies measured financial conflicts of interest related to any for-profit company,[9,19] or included only clinical guidelines with financial conflicts of interest related to any for-profit company.[23] Both our sensitivity analyses showed somewhat similar results as our primary analysis (from RR: 1.26, 95% CI: 0.93 to 1.69 in the primary analysis to RR: 1.08, 95% CI: 0.71 to 1.64 for financial conflicts of interest related to the manufacturer, eFigure 13; and to RR: 1.46, 95% CI: 0.96 to 2.21 for financial conflicts of interest related to any for-profit company, eFigure 14).

eFigure 13. Sensitivity analysis of the association between financial conflicts of interest related to the manufacturer and favourable recommendations in clinical guidelines



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval; SE: standard error

eFigure 14. Sensitivity analysis of the association between financial conflicts of interest related to any for-profit company and favourable recommendations in clinical guidelines



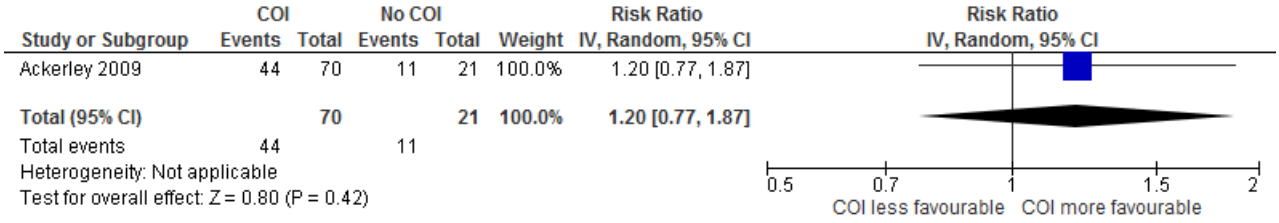
COI: conflicts of interest; IV: inverse-variance; CI: confidence interval; SE: standard error

Findings from sensitivity analyses on advisory committee reports

Excluding advisory committee reports with unclear or undisclosed conflicts of interest

In the three of the four studies included in our pooled analysis on advisory committee reports, it was not possible to remove advisory committee reports with undisclosed conflicts of interest, because the authors did not code this information in their raw dataset[12,21] or reporting of data did not allow it.[20] In the remaining study, we excluded all committee members with unclear conflicts of interest declarations. We found similar results as in our primary analysis (from RR: 1.20, 95% CI: 0.99 to 1.45 in the primary analysis to RR: 1.20, 95% CI: 0.77 to 1.87, eFigure 15)

eFigure 15. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in advisory committee reports, when excluding advisory committee reports with unclear or undisclosed financial conflicts of interest

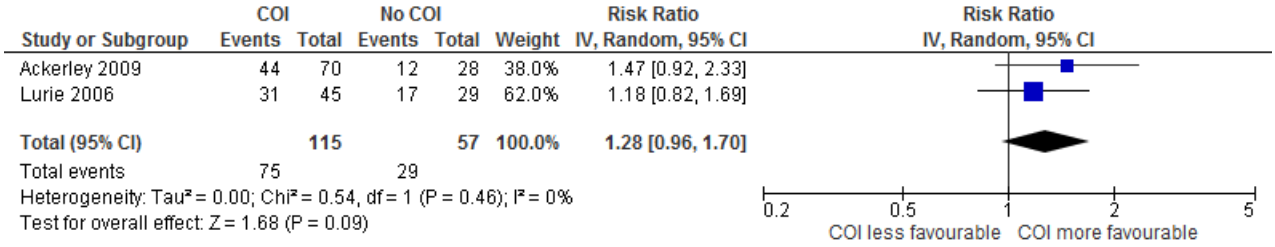


COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Excluding advisory committee reports with neutral recommendations

Only one of the studies included in our pooled analysis reported neutral recommendations in a separate category in the primary analysis,[21] and additionally one study coded whether the voting outcome of the meetings were unanimous (but did not include any unanimous meetings).[13] For the remaining studies, the authors did not code neutral recommendations (e.g. unanimous voting outcomes) in their raw dataset[12] or reporting of data did not allow us to exclude advisory committee reports with neutral recommendations.[20] We found somewhat similar results as in our primary analysis (from RR: 1.20, 95% CI: 0.99 to 1.45 in the primary analysis to RR: 1.28, 95% CI: 0.96 to 1.70, eFigure 16).

eFigure 16. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in advisory committee reports, when excluding advisory committee reports with neutral recommendations



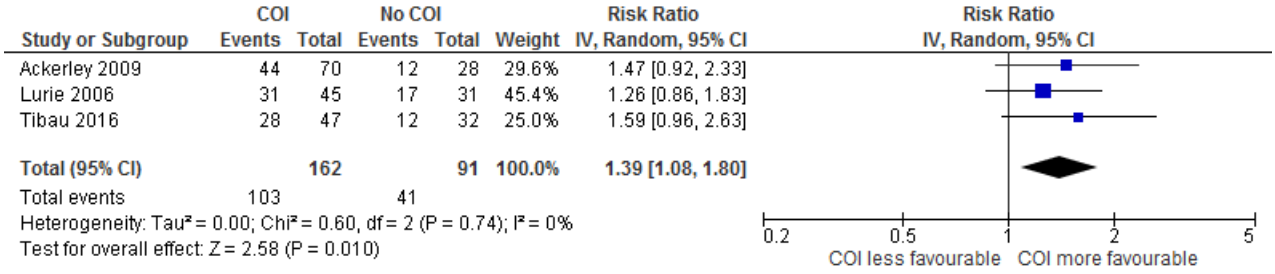
COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

The estimate of heterogeneity should be interpreted with caution as the estimate using a random-effects model is not reliable when only two studies are included in the analysis.

Excluding all studies of advisory committee reports which disclose a relevant conflict of interest of study authors

One of the studies included in our pooled analysis disclosed financial conflicts of interest of study authors.[12] Excluding this study from our pooled analysis on financial conflicts of interest increased the effect estimate and increased statistical precision (from RR: 1.20, 95% CI: 0.99 to 1.45 in the primary analysis to RR: 1.39, 95% CI: 1.08 to 1.80, eFigure 17).

eFigure 17. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in advisory committee reports, when excluding all studies which disclose a relevant conflict of interest

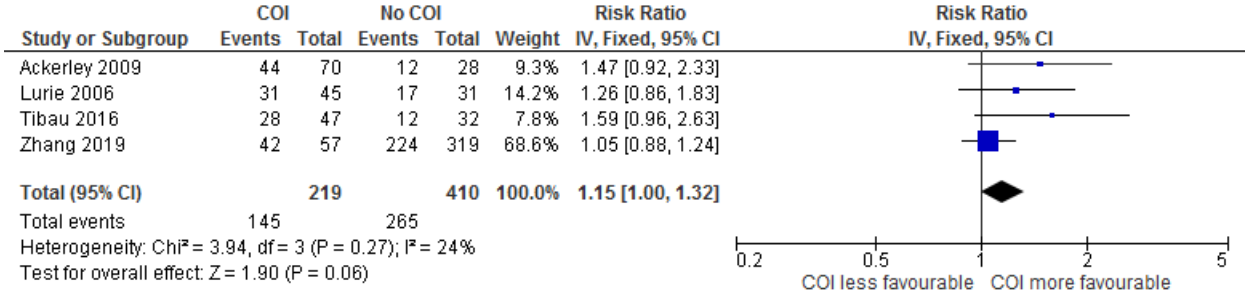


COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Re-analysing our primary analyses using fixed-effect meta-analyses

Re-analysing our primary analysis on advisory committee reports using fixed-effect models did not affect our findings (from RR: 1.20, 95% CI: 0.99 to 1.45 in the primary analysis to RR: 1.15, 95% CI: 1.00 to 1.32, eFigure 18).

eFigure 18. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in advisory committee reports using fixed-effect model



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

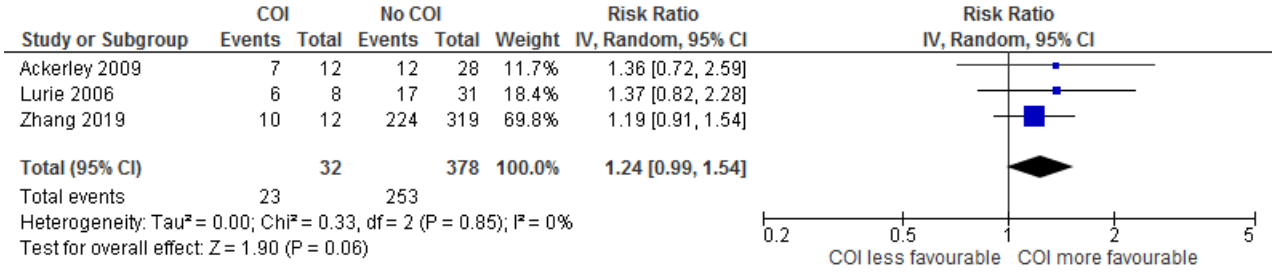
Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer and financial conflicts of interest related to any for-profit company

The four studies included in our pooled analysis on advisory committee reports both investigated financial conflicts of interest related to the manufacturer of the investigated drug and any for-profit company. One of the studies only reported summary odds ratio (OR) for financial conflicts of interest related to the manufacturer and competitor and was not included in our pooled analysis.[20] Thus, we were able to include data from three studies in our sensitivity analysis restricted to financial conflicts of interest related to the manufacturer.[12,13,21] Our analysis showed similar findings as our primary analysis (from RR: 1.20, 95% CI: 0.99 to 1.45 in the primary analysis to RR: 1.24, 95% CI: 0.99 to 1.54, eFigure 19). The remaining study had

different effect estimates for financial conflicts of interest related to the manufacturer (OR: 1.79, 95% CI: 0.75 to 4.26) and any for-profit company (OR: 1.06, 95% CI: 0.78 to 1.44), though with statistical imprecision.[20]

In our primary analysis, all studies included advisory committee reports with financial conflicts of interest related to any for-profit company (e.g. the manufacturer, competitor, or both) in the financial conflicts of interest group. Thus, we did not perform the sensitivity analysis restricted to any for-profit company as the results would be identical with the primary analysis.

eFigure 19. Sensitivity analysis of the association between financial conflicts of interest related to the manufacturer and favourable recommendations in advisory committee reports



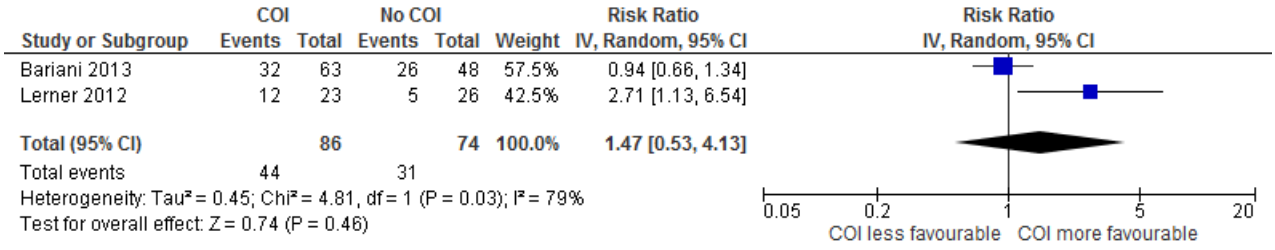
COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Findings from sensitivity analyses on opinion pieces

Excluding opinion pieces with unclear or undisclosed conflicts of interest

Two studies coded opinion pieces with unclear or undisclosed financial conflicts of interest.[6,15] In the remaining studies, it was not possible to separate opinion pieces with unclear or undisclosed financial conflicts of interest, because the authors did not code this information.[14,23] Our sensitivity analysis showed somewhat similar results compared with our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 1.47, 95% CI: 0.53 to 4.13, eFigure 20).

eFigure 20. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in opinion pieces, when excluding opinion pieces with unclear or undisclosed financial conflicts of interest



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

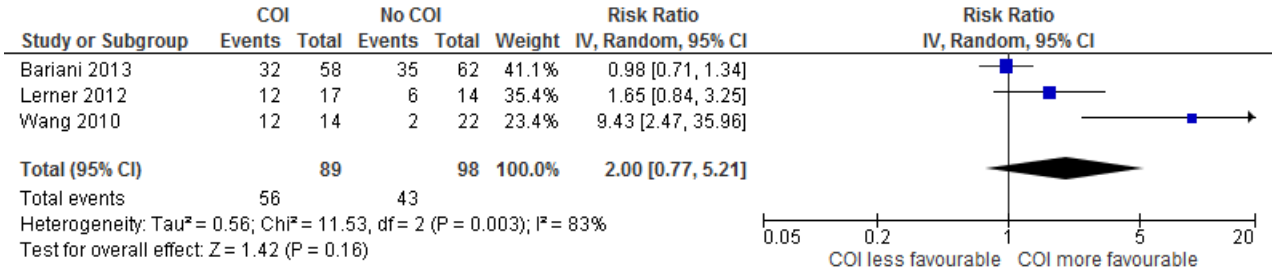
The estimate of heterogeneity should be interpreted with caution as the estimate using a random-effects model is not reliable when only two studies are included in the analysis

Excluding opinion pieces with neutral recommendations

We were able to exclude opinion pieces with neutral recommendations for three studies investigating opinion pieces.[6,15,23] The remaining study did not distinguish between neutral and unfavourable opinion

pieces.[14] An analysis based on these three studies showed somewhat similar results as our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 2.00, 95% CI: 0.77 to 5.21, eFigure 21).

eFigure 21. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in opinion pieces, when excluding opinion pieces with neutral recommendations

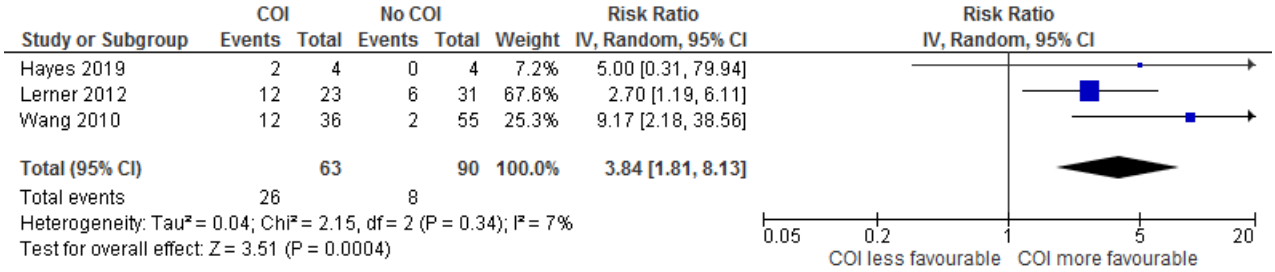


COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Excluding all studies of opinion pieces which disclose a relevant conflict of interest of study authors

From the four studies included in our primary analysis, one study disclosed financial conflicts of interest of study authors.[6] An analysis excluding this study had somewhat different results than our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 3.84, 95% CI: 1.81 to 8.13, eFigure 22), though the estimate was statistically imprecise.

eFigure 22: Forest plot showing the association between financial conflicts of interest and favourable recommendations in opinion pieces, when excluding all studies which disclosed a relevant conflict of interest

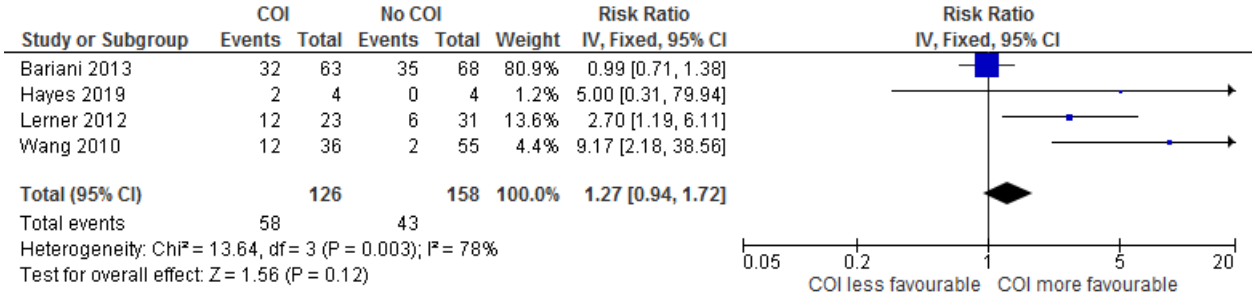


COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Re-analysing our primary analyses using fixed-effect meta-analyses

Our re-analysis of our primary analysis using a fixed-effect model showed somewhat similar results as our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 1.27, 95% CI: 0.94 to 1.72, eFigure 23).

eFigure 23. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in opinion pieces using fixed-effect model



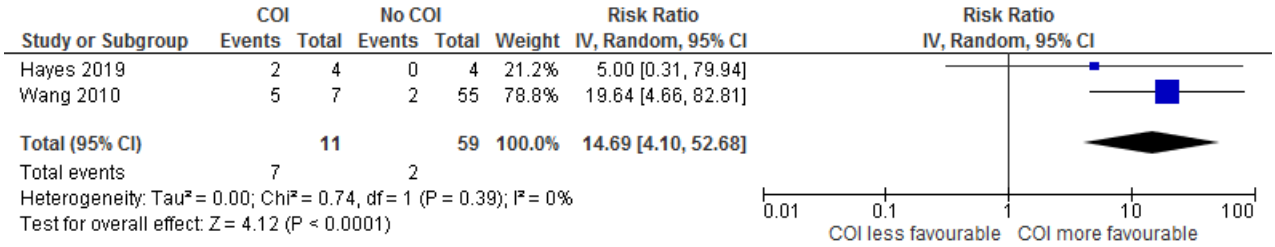
COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer and financial conflicts of interest related to any for-profit company

Two of the studies included in our pooled analysis investigated financial conflicts of interest related to the manufacturer of the studied drug or device,[14,15] Our sensitivity analysis restricted to financial conflicts of interest related to the manufacturer showed a stronger association than our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 14.69, 95% CI: 4.10 to 52.68, eFigure 24).

One study solely investigated financial conflicts of interest related to the manufacturer.[14] When we excluded this study from the analysis to include only studies on financial conflicts of interest related to any for-profit companies, we found similar results as our primary analysis (from RR: 2.62, 95% CI: 0.91 to 7.55 in the primary analysis to RR: 2.45, 95% CI: 0.78 to 7.74, eFigure 25)

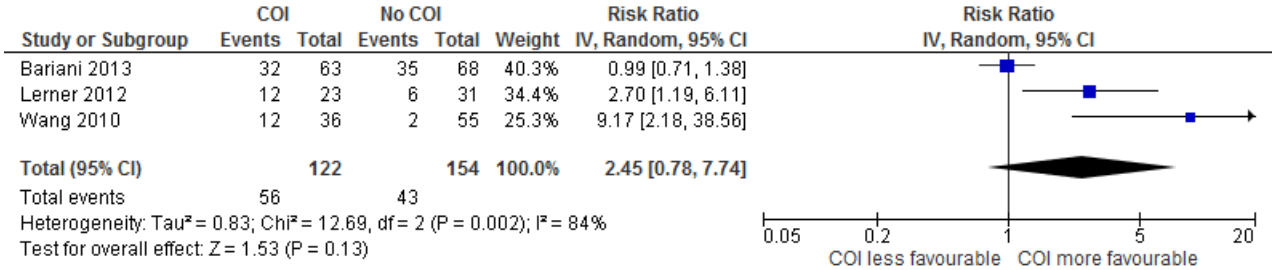
eFigure 24. Sensitivity analysis of the association between financial conflicts of interest related to the manufacturer and favourable recommendations in opinion pieces



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

The estimate of heterogeneity should be interpreted with caution as the estimate using a random-effects model is not reliable when only two studies are included in the analysis

eFigure 25. Sensitivity analysis of the association between financial conflicts of interest related to any for profit company and favourable recommendations in opinion pieces



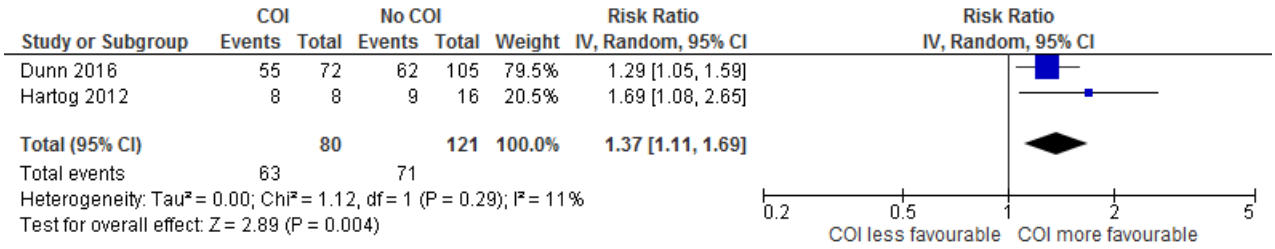
COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Findings from sensitivity analyses on narrative reviews

Excluding narrative reviews with unclear or undisclosed conflicts of interest

We were able to exclude narrative reviews with unclear of undisclosed conflicts of interest from two studies.[7,10] An analysis based on these two studies had somewhat similar results as our primary analysis (from RR: 1.20, 95% CI: 0.97 to 1.49 in the primary analysis to RR: 1.37, 95% CI: 1.11 to 1.69, eFigure 26).

eFigure 26. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in narrative reviews, when excluding narrative reviews with unclear or undisclosed financial conflicts of interest



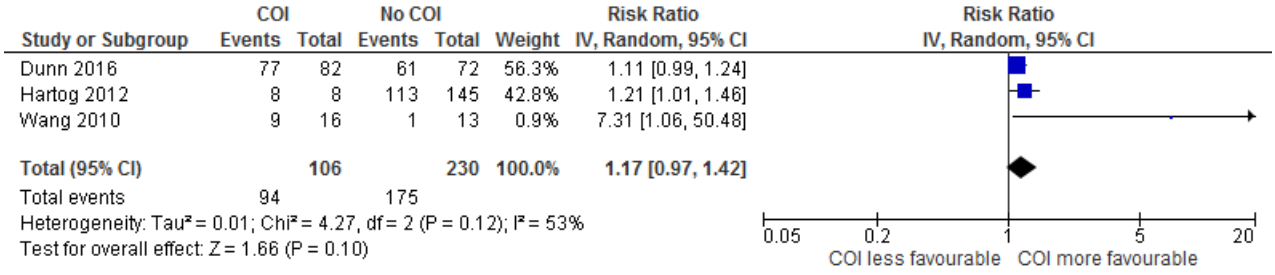
COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

The estimate of heterogeneity should be interpreted with caution as the estimate using a random-effects model is not reliable when only two studies are included in the analysis

Excluding narrative reviews with neutral recommendations

We were able to exclude narrative reviews with neutral recommendations from two studies.[7,23] Additionally, one study investigating narrative reviews did not include any narrative reviews with neutral recommendations.[10] The remaining study did not code unfavourable and neutral recommendations separately.[14] Our sensitivity analysis had somewhat similar results as our primary analysis (from RR: 1.20, 95% CI: 0.97 to 1.49 in the primary analysis to RR: 1.17, 95% CI: 0.97 to 1.42, eFigure 27).

eFigure 27. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in narrative reviews, when excluding narrative reviews with neutral recommendations

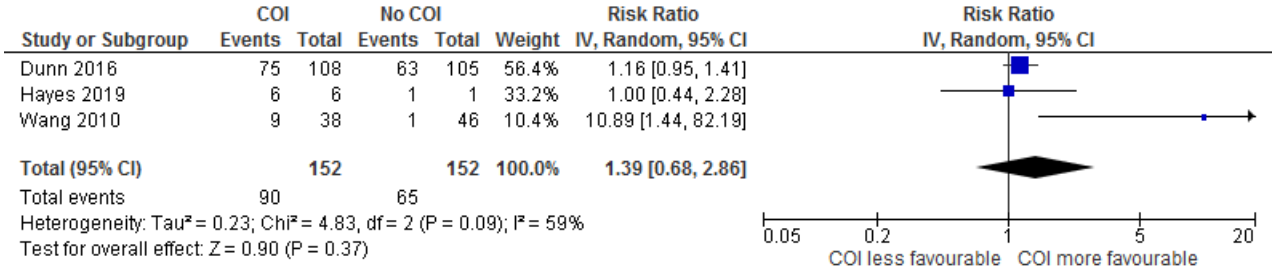


COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Excluding all studies of narrative reviews which disclose a relevant conflict of interest of study authors

From the studies included in the pooled analysis, one study disclosed conflicts of interest of study authors.[10] Our analysis excluding this study showed somewhat similar results as our primary analysis (from RR: 1.20, 95% CI: 0.97 to 1.49 in the primary analysis to RR: 1.39, 95% CI: 0.68 to 2.86, eFigure 28).

eFigure 28. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in narrative reviews, when excluding all studies which disclosed a relevant conflict of interest

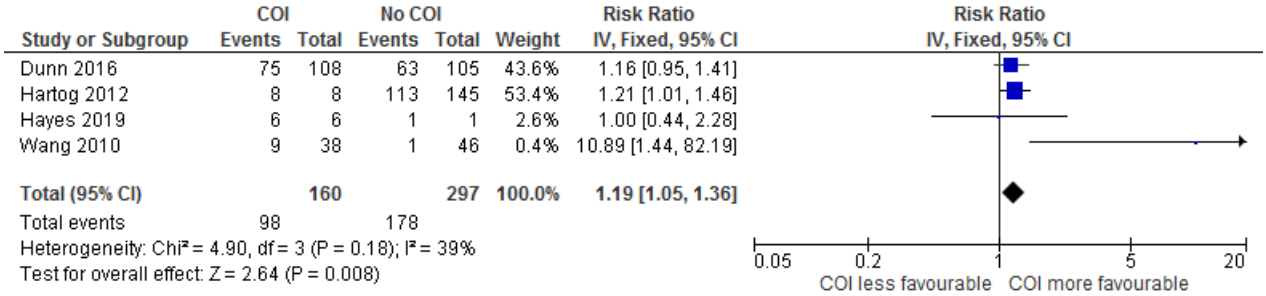


COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Re-analysing our primary analyses using fixed-effect meta-analyses

Our re-analysis of our primary analysis on narrative reviews using a fixed-effect model had somewhat similar results compared to our primary analysis (from RR: 1.20, 95% CI: 0.97 to 1.49 in the primary analysis to RR: 1.19, 95% CI: 1.05 to 1.36, eFigure 29).

eFigure 29. Sensitivity analysis of the association between financial conflicts of interest and favourable recommendations in narrative reviews using fixed-effect model

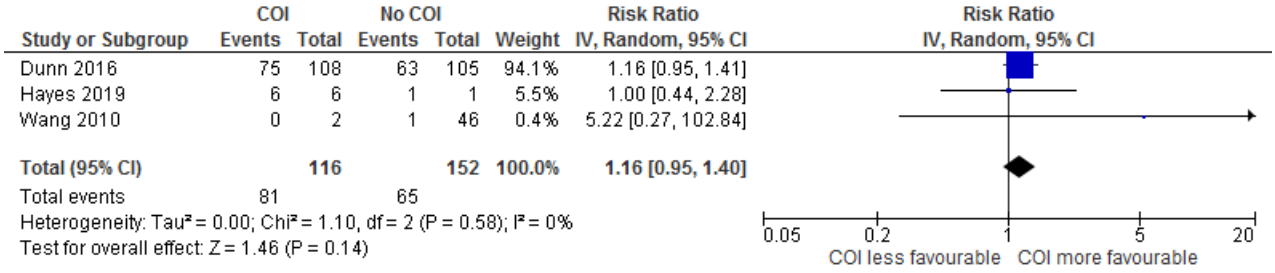


COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

Re-categorising financial conflicts of interest into financial conflicts of interest related to the manufacturer and financial conflicts of interest related to any for-profit company

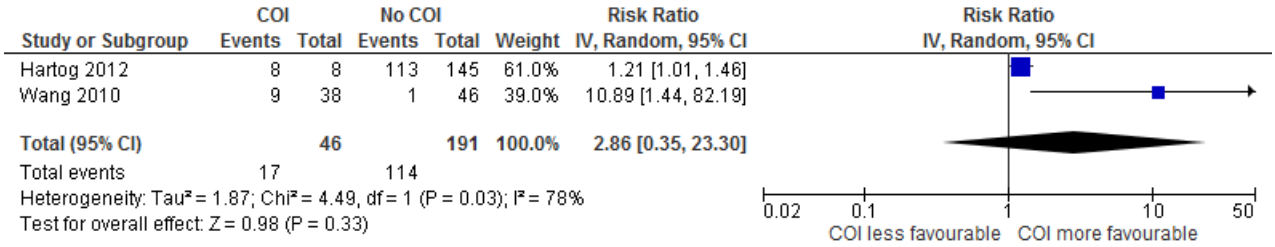
Two of the studies on narrative reviews investigated financial conflicts of interest related to the manufacturer of the drug or device of interest,[7,14] one study investigated financial conflicts of interest related to both the manufacturer and any for-profit company,[23] and the remaining study investigated financial conflicts of interest related to any for-profit company.[10] Both our sensitivity analyses showed somewhat similar results as our primary analysis (from RR: 1.20, 95% CI: 0.97 to 1.49 in the primary analysis to RR: 1.16, 95% CI: 0.95 to 1.40 for financial conflicts of interest related to the manufacturer, eFigure 30; and to: RR: 2.86, 95% CI: 0.35 to 23.30 for financial conflicts of interest related to any for-profit company, eFigure 31).

eFigure 30. Sensitivity analysis of the association between financial conflicts of interest related to the manufacturer and favourable recommendations in narrative reviews



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

eFigure 31. Sensitivity analysis of the association between financial conflicts of interest related to any for profit company and favourable recommendations in narrative reviews



COI: conflicts of interest; IV: inverse-variance; CI: confidence interval

The estimate of heterogeneity should be interpreted with caution as the estimate using a random-effects model is not reliable when only two studies are included in the analysis

Supplementary appendix 9. Summary of findings table

We assessed the certainty of the evidence for our primary outcome using both the GRADE approach for intervention studies[31] (observational studies preliminary graded as providing low certainty evidence) and prognostic studies[32] (observational studies preliminary graded as providing high certainty evidence).

eTable 1. Summary of findings

Document type	Absolute effect (95% CI)*		Relative effect RR (95% CI)	Number of studies	Certainty of the evidence using the GRADE approach for intervention studies**	Certainty of the evidence using the GRADE approach for prognostic studies***
	Event rate in documents with conflicts of interest	Event rate in documents without conflicts of interest				
Financial conflicts of interest						
Clinical guidelines	54 (40 to 72) clinical guidelines with favourable recommendations per 100 clinical guidelines with financial conflicts of interest****	43 clinical guidelines with favourable recommendations per 100 clinical guidelines without financial conflicts of interest	**1.26** (0.93 to 1.69)	4 studies including 86 clinical guidelines	**Very low** Downgraded due to study limitations (four studies with inadequate methodological quality) and imprecision (wide confidence interval*****)	**Low**
Advisory committee reports	78 (64 to 94) advisory committee reports with favourable recommendations per 100 advisory committee reports with financial conflicts of interest	65 advisory committee reports with favourable recommendations per 100 advisory committee reports without financial conflicts of interest	**1.20** (0.99 to 1.45)	4 studies including 629 advisory committee reports	**Very low** Downgraded due to study limitations (two studies with inadequate methodological quality) and imprecision (wide confidence interval*****)	**Low**
Opinion pieces	71 (25 to 100******) opinion pieces with favourable recommendations per 1000 opinion pieces with financial conflicts of interest	27 opinion pieces with favourable recommendations per 100 opinion pieces without financial conflicts of interest	**2.62** (0.91 to 7.55)	4 studies including 284 opinion pieces	**Very low** Downgraded due to study limitations (three studies with inadequate methodological quality), imprecision (wide confidence interval*****), and inconsistency (substantial statistical heterogeneity)	**Very low**

Narrative reviews	72 (58-89) narrative reviews with favourable recommendations per 100 narrative reviews with financial conflicts of interest	60 narrative reviews with favourable recommendations per 100 narrative reviews without financial conflicts of interest	**1.20** (0.97-1.49)	4 studies including 457 narrative reviews	**Very low** **Low** Downgraded due to study limitations (three studies with inadequate methodological quality) and imprecision (wide confidence interval[*****])
Non-financial conflicts of interest					
Clinical guidelines	90 (39-100[*****]) clinical guidelines with favourable recommendations per 100 clinical guidelines with one or more radiology authors	43 clinical guidelines with favourable recommendations per 100 clinical guidelines without radiology authors	**2.10** (0.92-4.77)	1 study including 12 clinical guidelines	**Very low** **Low** Downgraded due to study limitations (one study with inadequate methodological quality) and imprecision (wide confidence interval[*****])

CI: confidence interval; RR: relative risk; GRADE: Grading of Recommendations Assessment, Development and Evaluation

*The event rate of the control group (i.e. no conflicts of interest group) was calculated as the mean risk (i.e. number of documents with favourable recommendations divided by total number of documents). The event rate (and its 95% confidence interval (CI)) in the intervention group (i.e. conflicts of interest group) is based on the assumed risk in the control group and the relative effect of the intervention (and its 95% CI).

**The procedure for assessing the certainty of the evidence followed the GRADE approach for intervention studies (observational studies preliminary graded as providing low certainty evidence).

***The procedure for assessing the certainty of the evidence followed the GRADE approach for prognostic studies (observational studies preliminary graded as providing high certainty evidence).

****Numbers on clinical guidelines do not account for panel data in the Norris 2013 study (i.e. 13 clinical guidelines with 24 recommendations each).

*****We used an effect size of 0.05 on a relative scale (i.e. RR<0.95 or RR>1.05) as a methodologically important difference.[33] This cut-off was based on effect sizes of important study design biases in trials.[34]

******Upper event rate truncated at 100.

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Appendix 6. Submitted manuscript for sub-study III – first part

The first part of sub-study III is reported in:

Nejstgaard CH, Laursen DRT, Lundh A, Hróbjartsson A. Commercial funding and estimated intervention effects in randomized clinical trials: a systematic review of meta-epidemiological studies. *Submitted January 2021*

The manuscript is formatted as a research letter and has been submitted to JAMA Internal Medicine in January 2021.

Commercial funding and estimated intervention effects in randomized clinical trials: a systematic review of meta-epidemiological studies

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Word count: 597

Introduction

Drug or device companies often fund randomized trials[1] and it is widely suspected that financial conflicts of interest are associated with results that favor the commercial funder.

This perception was reinforced by a systematic review of 75 methodological studies finding that commercially funded trials had a 34% higher chance of favorable conclusions than non-commercial trials.[2] However, interpretation of the result is hampered by risk of confounding, as compared trials may differ in other aspects than funding source, e.g. trial populations, interventions and outcomes.

The risk of confounding is markedly reduced in meta-epidemiological studies. Such studies sample meta-analyses and, within each, compare the results of trials with a characteristic, e.g. commercial funding, with the results of similar trials without the characteristic.[3] These intended 'like with like' comparisons are then summarized across meta-analyses, providing an estimate of the average impact.

Several meta-epidemiological studies have addressed commercial funding in trials. Here, we report the first systematic review of such studies.

Methods

We searched five bibliographic databases for meta-epidemiological studies of the impact of commercial funding on estimated intervention effects in randomized trials. We included studies aimed at exploring: 1) commercial funding per se, and 2) commercial funding with increased risk of funder influence (assessed by meta-epidemiological study authors, e.g. the combination of commercial funding and direct funder influence on trial design, conduct, analysis or reporting) (eAppendix).

Two reviewers independently included studies and extracted data. We used study authors' definition of commercial funding and selected one result per meta-epidemiological study, preferably unadjusted ratio of odds ratios (ROR), e.g. odds ratio(commercial funding)/odds ratio(non-commercial funding), or converted other measures (e.g. difference in standardized mean differences) to ROR. We harmonized direction of

effect, so ROR<1 indicated larger effect estimates in trials with commercial funding, and we pooled the RORs with random-effects meta-analysis, sub-grouped by meta-epidemiological study aim.

Results

We included seven meta-epidemiological studies in our review (Table 1; eAppendix) and six in our main analysis. Based on 166 meta-analyses of 1545 trials, ROR in included studies ranged from 0.76 to 1.10, with a pooled average of 0.92 (95% confidence interval 0.80 to 1.03, I^2= 51%) and no clear subgroup difference (Figure 1).

Discussion

We found an uncertain impact of commercial funding on estimated intervention effects in randomized trials. On average, odds ratios in trials with commercial funding, or with high risk of funder influence, were exaggerated by 8%, with 95% confidence interval ranging from a 20% exaggeration to a 3% underestimation.

The strength of our study is a comparatively low risk of confounding and inclusion of data from as many as 1545 trials. However, we only included published summary data, vulnerable to reporting biases. Also, some trials or meta-analyses may have been included in multiple meta-epidemiological studies. Our result is compatible with no impact of commercial funding on trial results or insufficient statistical power to detect an important impact. Inclusion of additional studies may clarify this and elucidate whether commercial funding with increased risk of funder influence affects trial results more than commercial funding per se.

The discrepancy between our finding and that of previous reviews may be caused by differences in trial or meta-analysis outcomes. Commercially funded trials frequently have surrogate primary outcomes,[4] whereas the meta-analyses included in our meta-epidemiological studies often analyzed mortality. Furthermore, we studied the impact of commercial funding on estimated intervention effects, whereas the largest review[2] studied impact on trial conclusions, vulnerable to spin (and not necessarily strongly associated with intervention effects).

In conclusion, based on a systematic review of seven meta-epidemiological studies, we found an uncertain impact of commercial funding on estimated intervention effects in randomized trials.

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Author contributions

CHN 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.

Concept and design: CHN, AL, AH.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: CHN, AL, AH.

Critical revision of the manuscript for important intellectual content: All authors.

Conflicts of interest disclosures

All authors declare no conflicts of interest.

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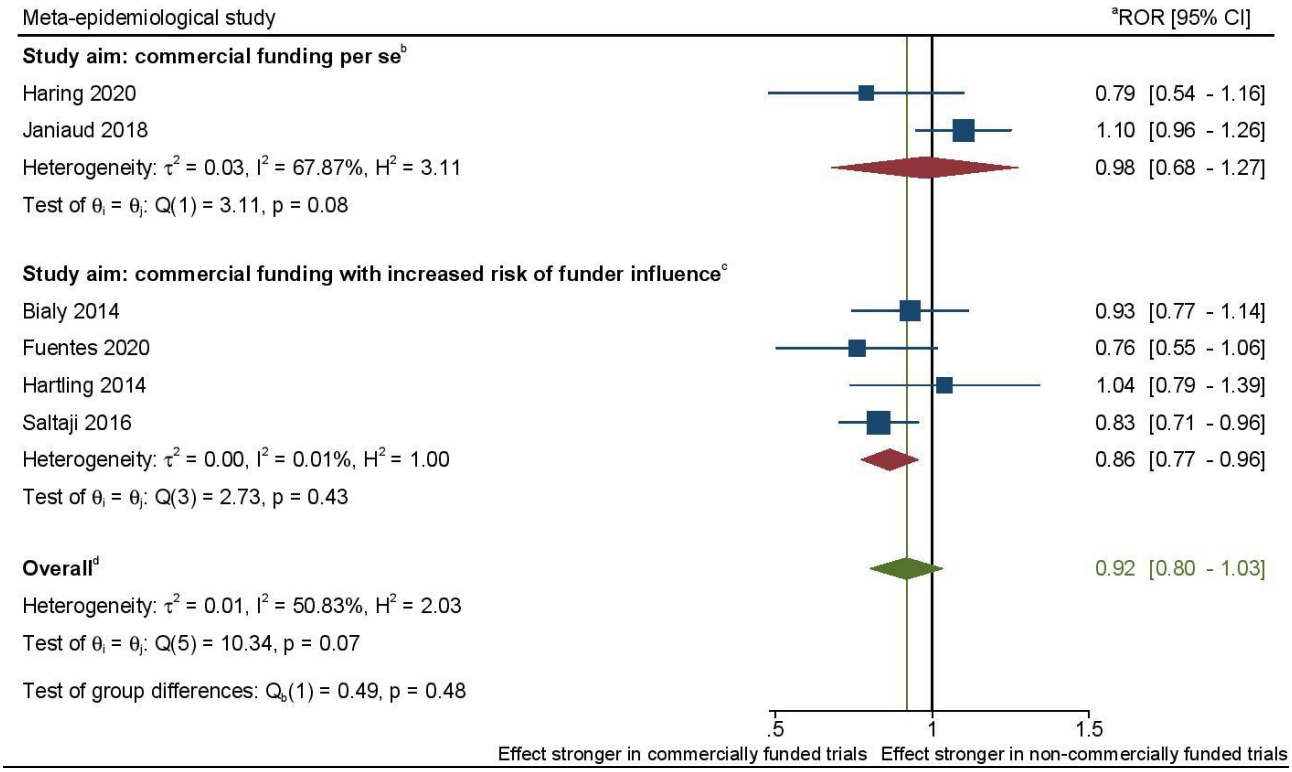
Table 1. Characteristics of included meta-epidemiological studies

Study	Study aim	N meta-analyses (trials)	Type of trials		Within meta-analysis comparison		
			Patients and interventions	Outcomes[c]			
Haring 2020	Commercial funding per se	16 (120)[a]	Men receiving testosterone therapy, drugs	Mixed, binary and continuous	Commercial funding (fully or partially)	VS	Non-commercial funding, no funding received or funding source not reported
Janiaud 2018	Commercial funding per se	33 (226)[a]	Critical care, drugs and devices	Mixed, binary (mainly mortality)	Commercial funding (fully or partially)	VS	Non-commercial funding or only the intervention supplied by commercial companies[d]
Bialy 2014	Commercial funding with increased risk of funder influence	23 (207)[b]	Neonatal care, drugs and devices	Mixed, binary (mainly mortality)	Commercial funding with high or unclear risk of funder influence (high or unclear risk of bias due to funding source[e])	VS	No commercial funding or commercial funding with low risk of funder influence (low risk of bias due to funding source[e])
Fuentes 2020	Commercial funding with increased risk of funder influence	40 (377)[a]	Physical therapy, non-drugs and devices	Mixed, continuous	Commercial funding with increased or unclear risk of funder influence (authors working for the funder or a funder with involvement in trial conduct)	VS	No commercial funding or no increased risk of commercial funder influence (commercial funder with no involvement in trial conduct)
Hartling 2014	Commercial funding with increased risk of funder influence	17 (287)[b]	Pediatric, drugs and non-drugs	Mixed, binary and continuous	Commercial funding with high or unclear risk of funder influence (high or unclear risk of bias due to funding source[e])	VS	No commercial funding or commercial funding with low risk of funder influence (low risk of bias due to funding source[e])
Saltaji 2016	Commercial funding with increased risk of funder influence	37 (328)[a]	Oral health, drugs and non-drugs	Mixed, continuous	Commercial funding with increased or unclear risk of funder influence (authors working for the funder or a funder with involvement in trial conduct)	VS	No commercial funding or no increased risk of commercial funder influence (commercial funder with no involvement in trial conduct)
Unverzagt 2013[f]	Commercial funding with increased risk of funder influence	12 (82)[b]	Critical care, drugs and devices	Mortality	Commercial funding with high or unclear risk of funder influence (authors or funder may financially benefit from the trial and lacking safeguards against bias)	VS	No commercial funding or commercial funding with low risk of funder influence (non-industry-initiated trial or independent monitoring, audit or analyzes)

[a]Number of meta-analyses (trials) included in eligible analysis. [b]Number of meta-analyses (trials) included in meta-epidemiological study. [c]Mixed outcomes indicate that the meta-epidemiological study included meta-analyses of trials with a range of different outcomes. [d]The authors excluded trials without reported funding source. [e]The authors did not publish their specific assessment criteria (e.g. no description of when trials were considered to have high risk of bias due to funding source). [f]The study was reported in two publications (2013 and 2015), and the ROR for the same eligible analysis differed between the two publications. Contact to the corresponding author did not reveal reason for inconsistency. The study was included in our systematic review, and informed sensitivity analyses, but was excluded from our main analysis.

Figure 1. Meta-analysis of results from meta-epidemiological studies on the association between commercial funding and estimated intervention effects in randomized clinical trials



[a]ROR: ratio of odds ratio; CI: confidence interval. [b]Commercial funding vs no commercial funding. [c]Commercial funding with increased risk of funder influence vs no commercial funding or commercial funding with low risk of funder influence. [d]A seventh study, investigating commercial funding with increased risk of funder influence, was included in our systematic review, but excluded from our main analysis, as the ROR for the same analysis differed between two publications (Unverzagt 2013 and 2015). Contact to the corresponding author did not reveal reason for the inconsistency. Sensitivity analyses including either result did not alter our main finding importantly. When including ROR of 0.92, 95% CI: 0.75-1.12 from the 2013 publication, the pooled ROR was 0.92, 95% CI: 0.82-1.02, and when including ROR of 1.01, 95% CI: 0.87-1.15 from the 2015 publication, the pooled average ROR was 0.94, 95% CI: 0.84-1.04.

Content of eAppendix

Secondary objectives

As secondary objectives, we wanted to investigate to which degree commercial funding is associated with:

1. Frequency of statistically favorable results in randomized clinical trials (e.g. results that are favorable towards the experimental intervention based on direction and statistical significance)
2. Frequency of favorable conclusions in randomized clinical trials (e.g. conclusions that are favorable towards the experimental intervention)
3. Concordance between results and conclusions in randomized clinical trials (e.g. whether favorable conclusions are supported by statistically favorable results)

We report the findings for our three secondary objectives in appendix due to word limitations in the main text.

Methods

Eligibility criteria

We defined meta-epidemiological studies as studies of samples of meta-analyses of randomized clinical trials in which trials with and without a characteristic were compared within meta-analyses before summarizing results across meta-analyses. We included meta-epidemiological studies that investigated estimated intervention effects (i.e. our primary outcome) and published ratio of odds ratios (ROR) or effect measures that could be converted to ROR (e.g. difference in standardized mean difference (dSMD)) for the impact of commercial funding. We also included meta-epidemiological studies that investigated statistically favorable results, favorable conclusions, or concordance between results and conclusions (i.e. our secondary outcomes) and published any measure for the impact of commercial funding.

Commercial funding per se related solely to the type of funding source of the trial. Commercial funding with increased risk of funder influence combined information on trial funding source with an assessment (done by authors of the meta-epidemiological studies) of whether a commercial funder had an influence on the trial design, conduct, analysis, or reporting (e.g. a trial funded by a pharmaceutical company that also conducted the statistical analyses).

Search for meta-epidemiological studies

We searched PubMed, Embase and Cochrane Methodology Register (up to June 2020). We used the search strategy for PubMed presented below and adapted it for the other databases. One contributor (CHN) screened titles and abstracts for obvious exclusions, and two contributors (CHN and either AF, SA or MHAG) independently assessed full text publications of studies for inclusion.

Two contributors (CHN and either SA or MHAG) independently screened studies included in a systematic review of meta-epidemiological studies,[1] and studies included and excluded in two versions of a Cochrane review on industry funding in primary research studies.[2]

One contributor (CHN) searched reference lists of included meta-epidemiological studies, Web of Science (up to February 2020) for studies citing any of the included meta-epidemiological studies or any of the studies included in the updated Cochrane review on industry funding in trials from 2017,[2] and conference proceedings from Cochrane Colloquia (available at http://abstracts.cochrane.org/), Peer Review Congresses (available at https://peerreviewcongress.org/past-congresses/), and the Clinical Trials Methodology Conference (available at http://www.methodologyhubs.mrc.ac.uk/workshops/methodology-conference/). One contributor (CHN) searched Google Scholar (up to March 2020).

Data extraction

Two contributors (CHN and either DRTL or AH) independently extracted data on basic characteristics, definitions of commercial funding per se or commercial funding with increased risk of funder influence, definitions of estimated intervention effects, definition of statistically favorable results, definition of favorable conclusions, definition of concordance between results and conclusions, and outcome data from the included meta-epidemiological studies.

When a meta-epidemiological study published multiple RORs for the impact of commercial funding on estimated intervention effects, we used the following algorithm. We preferred unadjusted ROR, and if several unadjusted RORs (or measures convertible to ROR) were published, we used the ROR from the main analysis, as defined by the meta-epidemiological study authors. In all but one of the included meta-epidemiological studies, several RORs were published. The meta-epidemiological study authors published results from both adjusted and unadjusted analyses, stratified and non-stratified analyses, sensitivity analyses comparing different types of commercial funding, and analyses based on different statistical models (eTable 1).

eTable 1. Number and data on published RORs in the included meta-epidemiological studies

Study	Study aim	N ROR[a,b]	Range of ROR[b,c]	Median ROR[b,c]	Main ROR[d] (95% CI)	ROR (95% CI) selected for our main analysis
Haring 2020	Commercial funding per se	3	0.73-0.85	0.79	0.79 (0.54-1.16)	0.79 (0.54-1.16)
Janiaud 2018	Commercial funding per se	16	0.85-1.22	1.10	1.10 (0.96-1.26)	1.10 (0.96-1.26)
Bialy 2014	Commercial funding with increased risk of funder influence	1	-	0.93[e]	0.93[e] (0.77-1.14)	0.93[e] (0.77-1.14)
Fuentes 2020	Commercial funding with increased risk of funder influence	9	0.40-1.00	0.76[f]	0.76[f] (0.55-1.06)	0.76[f] (0.55-1.06)
Hartling 2014	Commercial funding with increased risk of funder influence	9	0.76-1.09	1.04[g]	1.04[g] (0.79-1.39)	1.04[g] (0.79-1.39)
Saltaji 2016	Commercial funding with increased risk of funder influence	10	0.49-0.88	0.82[h]	0.83[h] (0.71-0.96)	0.83[h] (0.71-0.96)
Unverzagt 2013[i]	Commercial funding with increased risk of funder influence	7	0.92-1.08	1.04	1.05[j] (0.88-1.24)	Not included in main analysis

[a]Number of published RORs or measures convertible to ROR. [b]Numbers based on data extraction done by a single review author. [c]We report only point estimates. [d]Published result from the main analysis, as defined by the meta-epidemiological study authors. [e]We converted direction of the published ROR of 1.07, 95% CI: 0.88-1.30. [f]We converted published study results from dSMD of 0.15, 95% CI: -

0.03-0.33 to ROR and converted the direction. [g]We converted published study results from dSMD of 0.02, 95% CI: -0.13-0.18 to ROR. [h]We converted published study results from dSMD of 0.10, 95% CI: 0.02-0.19 to ROR and converted the direction. [i]The study was reported in two publications published in 2013 and 2015,[9,10] and the ROR for the same eligible analysis differed between the two publications. Contact to the corresponding author did not reveal reason for inconsistency. The study was included in our systematic review, and informed sensitivity analyses, but excluded from our main analysis. [j]ROR adjusted for trial characteristics (e.g. double blinding and baseline imbalances).

Assessing risk of bias in included meta-epidemiological studies

As no tool has been developed for assessing risk of bias in meta-epidemiological studies, we did not formally assess risk of bias.

Data handling and synthesis

We converted dSMD to log ROR by multiplying by $\frac{\pi}{\sqrt{3}} = 1.814$.[11] We harmonized directions of effect by using the reciprocals when necessary. If inconsistent results for the same analysis were published in multiple study publications of the same meta-epidemiological study, we contacted the authors for clarification. If the authors were not able to clarify, we excluded the study from our main analysis and undertook sensitivity analyses including the inconsistent results separately.

In three secondary analyses, we analyzed statistically favorable results, favorable conclusions, and concordance between results and conclusions. We planned to pool effect measures with random-effects meta-analyses, when findings from two or more meta-epidemiological studies were available. If meta-analysis was not considered meaningful, we summarized the findings qualitatively.

PubMed Search Strategy

Block 1: Investigation of commercial funding or bias

1. "Conflict of Interest"[MeSH]

2. (Conflict[Title/Abstract] OR conflicts[Title/Abstract] OR conflicting[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])

3. (Competing[Title/Abstract] OR vested[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])

4. (Industry[Title] OR industries[Title] OR company[Title] OR companies[Title] OR manufacturer[Title] OR manufacturers[Title] OR finance[Title] OR financial[Title]) AND (funded[Title] OR funding[Title] OR sponsor[Title] OR sponsors[Title] OR sponsorship[Title] OR sponsoring[Title] OR support[Title] OR supported[Title] OR involvement[Title] OR involving[Title] OR payment[Title] OR payments[Title] OR relationship[Title] OR relationships[Title] OR relation[Title] OR relations[Title] OR tie[Title] OR ties[Title] OR collaboration[Title] OR collaborations[Title])

5. Industry-funded[Title/Abstract] OR industry-funding[Title/Abstract] OR industry-sponsor*[Title/Abstract] OR company-funded[Title/Abstract] OR company-funding[Title/Abstract] OR company-sponsor*[Title/Abstract] OR industry-support[Title/Abstract] OR industry-supported[Title/Abstract] OR company-support[Title/Abstract] OR company-supported[Title/Abstract]

6. (Commercial-academic[Title/Abstract] OR academic-commercial[Title/Abstract] OR industry-academic[Title/Abstract] OR academic-industry[Title/Abstract] OR commercial-industry[Title/Abstract] OR industry-commercial[Title/Abstract] OR industry-physician[Title/Abstract] OR physician-industry[Title/Abstract]) AND (interaction[Title/Abstract] OR interactions[Title/Abstract] OR relationship[Title/Abstract] OR relationships[Title/Abstract] OR relation[Title/Abstract] OR relations[Title/Abstract] OR collaboration[Title/Abstract] OR collaborations[Title/Abstract])

7. "Bias"[MeSH]

8. (Bias[Title/Abstract] OR biases[Title/Abstract]) AND (quantify[Title/Abstract] OR quantified[Title/Abstract] OR quantification[Title/Abstract] OR measure[Title/Abstract] OR measured[Title/Abstract] OR classify[Title/Abstract] OR classified[Title/Abstract] OR classification[Title/Abstract])

9. (Methodological[Title] OR methodologic[Title]) AND (quality[Title] OR qualities[Title])

10. (Trial[Title] OR trials[Title]) AND (characteristic[Title] OR characteristics[Title])

11. "Randomized Controlled Trials as Topic"[Majr]

12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11

Block 2: meta-epidemiological studies

13. Meta[Title/Abstract] AND (epidemiological[Title/Abstract] OR epidemiologically[Title/Abstract] OR epidemiology[Title/Abstract] OR epidemiologic[Title/Abstract])

14. Meta-epidemiological[Title/Abstract] OR meta-epidemiology[Title/Abstract] OR meta-epidemiological[Title/Abstract] OR meta-epidemiologic[Title/Abstract]

15. Meta-meta[Title/Abstract] AND (analysis[Title/Abstract] OR analyses[Title/Abstract] OR review[Title/Abstract] OR reviews[Title/Abstract] OR overview[Title/Abstract] OR overviews[Title/Abstract])

16. Meta-meta-analysis[Title/Abstract] OR meta-meta-analyses[Title/Abstract]

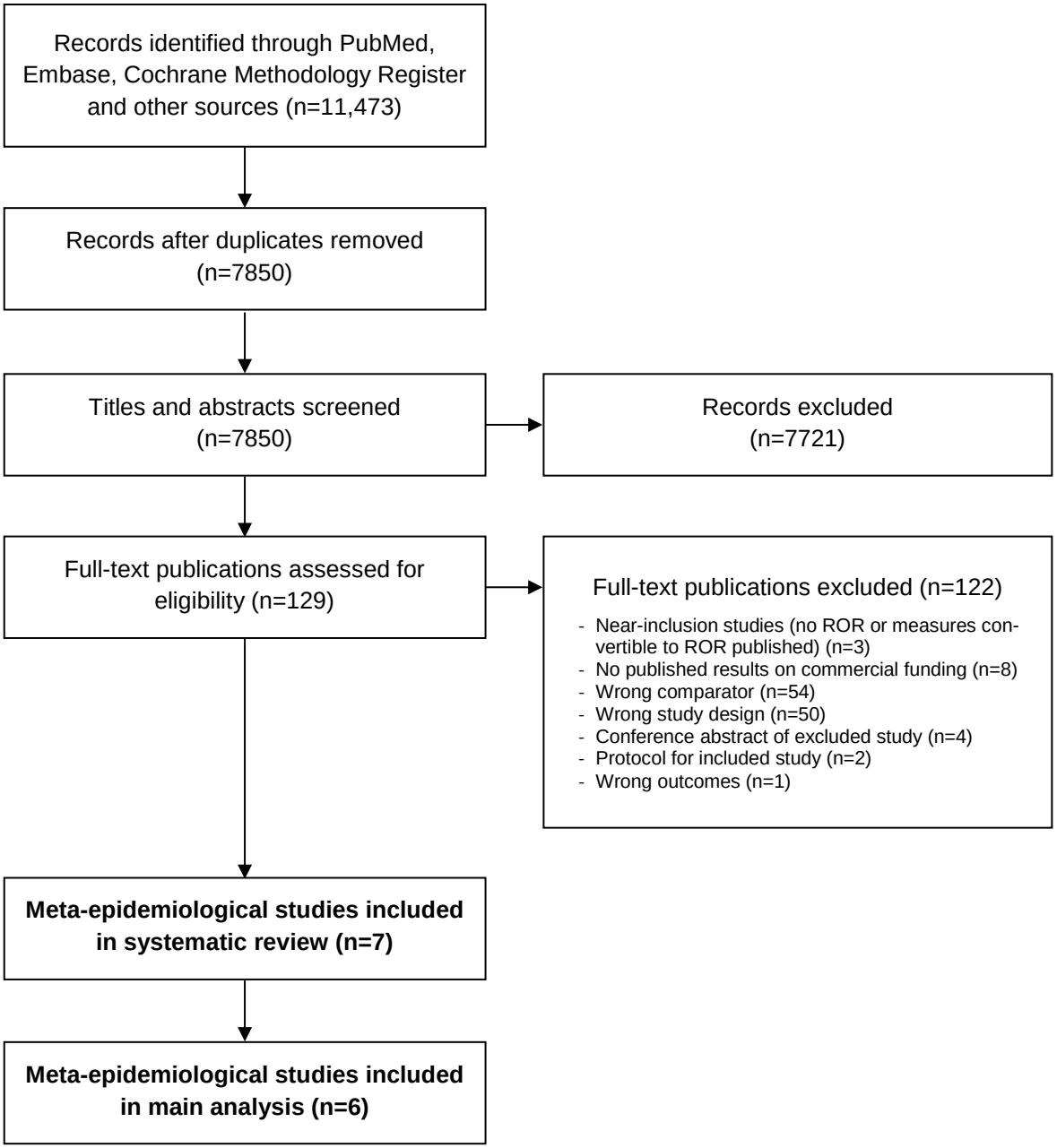
17. (Systematic[Title/Abstract] OR Cochrane[Title/Abstract]) AND (review[Title/Abstract] OR reviews[Title/Abstract]) AND ((randomised[Title/Abstract] OR randomized[Title/Abstract]) AND (trial[Title/Abstract] OR trials[Title/Abstract]))

19. Empirical[Title] AND (evaluation[Title] OR evaluations[Title] OR investigation[Title] OR investigations[Title])

20. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19

Combined searches
21. 12 AND 20

eFigure 1. Flow chart of meta-epidemiological study inclusion



Secondary findings on statistically favorable results, favorable conclusions, and concordance between results and conclusions

None of the included meta-epidemiological studies investigated the impact of commercial funding on statistically favorable results in clinical randomized trials.

One of the included meta-epidemiological studies investigated the impact of commercial funding on favorable conclusions in randomized clinical trials. Conclusions were considered unfavorable when trials clearly did not recommend the experimental intervention; or when trials concluded that the experimental intervention was less effective, more harmful, or not more effective without any mentioning of positive trade-offs (e.g. lesser cost). All other scenarios were considered favorable. The authors estimated the arcsine difference, first within each meta-analysis and then across meta-analyses using a random-effects model. A summary arcsine estimate>0 indicated that conclusions were more favorable in randomized clinical trials with commercial funding per se. The authors found no statistically significant difference in frequency of favorable conclusions between commercially and non-commercially funded trials (arcsine estimate of having negative conclusions in randomized trials with versus without commercial funding per se: 0.04, 95% CI: -0.09 to 0.17).[4]

None of the included meta-epidemiological studies investigated the impact of commercial funding on concordance between results and conclusions in randomized clinical trials.

Near-inclusion meta-epidemiological studies

We identified three meta-epidemiological studies that investigated the association between commercial funding and estimated intervention effects, but did not publish RORs or measures that were convertible to ROR based on a within meta-analysis comparison. The studies were therefore not eligible, but would have been if they had reported their results differently. It is therefore interesting to which degree their results cohere with ours.

Als-Nielsen and colleagues investigated 25 systematic reviews including 370 randomized drug trials. They investigated commercial funding per se and compared four groups of trials with different funding source (for-profit, for-profit and non-profit, non-profit, and not reported) across meta-analyses. They estimated z-scores (log odds ratio (OR) divided by standard error to log OR) for each trial and p-values using a Kruskal-Wallis test (the higher the z-score the smaller the benefit of the experimental drug). The authors found no significant difference in estimated intervention effects between trials with different types of commercial funding source (mean z-score: for-profit trials: -1.48, for-profit and non-profit trials: -1.77, non-profit trials: -1.20, and not reported trials: -1.20).[12] Thus, the published findings by Als-Nielsen and colleagues are somewhat similar to what we found.

In addition, Als-Nielsen and colleagues also investigated the impact of commercial funding on favorable conclusions in randomized drug trials. Conclusions were graded on a six-point scale ranging from recommending the control intervention without disclaimers (1 point) to recommending the experimental intervention without disclaimers (6 points). Only conclusions graded as 6 points were considered favorable. The authors estimated OR across meta-analyses using a logistic regression model adjusted for treatment effect, double blinding, and meta-analysis level (i.e. the meta-analysis the trials were included from). OR>1 indicated that conclusions were more favorable in randomized drug trials with commercial funding per se. Compared with non-profit trials, the authors found that for-profit trials more often had favorable conclusions (OR: 5.3, 95% CI: 2.0 to 14.4). Differences in favorable conclusions were also found for comparisons between for-profit and non-profit trials versus non-profit (OR: 2.6, 95% CI: 0.9 to 7.9) as well as not reported trials versus non-profit (OR: 2.4, 95% CI: 0.9 to 6.8), though these were not statistically significant.[12]

Alahdab and colleagues investigated 70 meta-analyses including 930 randomized trials on patients with chronic medical conditions. They investigated commercial funding per se and compared two groups of trials with different funding source (for-profit/unclear versus non-profit). The authors investigated whether the largest effect size was reported in the first or second earliest trials (defined as the Proteus effect). They sorted trials within meta-analyses by publication date and assessed proportions of trials with and without the Proteus effect between the different types of funding source. P-values were estimated using a chi-square test or Fisher's exact test depending on the sample size. The authors found no statistically significant association between commercial funding source and the Proteus effect (p-value: 0.6).[13] Thus, Alahdab and colleagues did not publish results that can be directly compared to what we found.

Bolvig and colleagues investigated 20 meta-analyses including 126 randomized osteoarthritis trials on a mix of drug and non-drug interventions. They investigated commercial funding per se and compared two groups of trials with different funding source (for-profit/unclear versus non-profit). They estimated effect estimates for the two groups of trials across meta-analyses by using a random-effects meta-analysis model with the systematic review level (i.e. the systematic review or meta-analysis the trials were included from) included as a fixed factor. The authors found no statistically significant difference in estimated intervention effects between the two groups of trials (effect size for trials with for-profit or unclear funding: 0.46, effect size for trials with non-profit funding: 0.36, relative difference in estimated intervention effects: 28%, p-value for interaction: 0.20).[14] Thus, Bolvig and colleagues found a non-statistically significant impact of commercial funding, but their published effect measures are not directly comparable to our ROR (based on within meta-analysis comparisons).

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Appendix 7. Draft manuscript for sub-study III – second part

The second part of sub-study III is reported in:

Nejstgaard CH, Lundh A, Abdi S, et al. Methods and development of a combined database of primary meta-epidemiological studies of commercial funding of randomised clinical trials: the COMFIT study. ***Draft manuscript***

The manuscript is formatted to fit the requirements of Research Synthesis Methods.

Methods and development of a combined database of meta-epidemiological studies of commercial funding of randomised clinical trials: the COMFIT study

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Word count: 4646

ABSTRACT

Introduction

It is widely believed that commercial funding influences results and conclusions of randomised clinical trials, in part based on numerous methodological studies. However, their results are often hampered by a high risk of confounding, because trials likely differ for reasons other than funding source. The risk of confounding is markedly reduced in meta-epidemiological studies, where trials are compared within meta-analyses, thus ensuring fairly comparable groups of patients, interventions, controls, and outcomes.

In this paper, we describe the aims and methods of the COMFIT study (COMmercial Funding In Trials). The idea of the COMFIT study is to identify meta-epidemiological studies with data on funding source and estimated intervention effects in randomised trials and to establish a consortium of researchers to enable trial-level data sharing for the construction of a combined database. Below, we describe the establishment of the COMFIT consortium, detail the procedures for constructing the COMFIT database, and provide core baseline data of the meta-epidemiological studies included.

Methods

We included meta-epidemiological studies with data on trial funding source and trial results or conclusions. We searched PubMed, Embase, Cochrane Methodology Register, Web of Science, and Google Scholar. We also read reference lists of included studies, and scanned conference proceedings, studies included in a systematic review of meta-epidemiological studies, and studies (included and excluded) in two versions of a Cochrane review on industry funding in trials.

We invited authors of meta-epidemiological studies to join the COMFIT consortium based on data sharing of trial-level data. We plan to construct the COMFIT database by checking data quality of each dataset; identifying references for the included trials; harmonising categories used for the variables across the meta-epidemiological studies; and removing non-informative meta-analyses (e.g. meta-analyses where all trials have the same type of funding) as well as correlated or duplicate meta-analyses and trials.

Results

We included 18 meta-epidemiological studies and obtained trial-level data from 17. The 17 meta-epidemiological studies contributed with 728 meta-analyses (median 33, range 6 to 156) and 6841 trials (median 326, range 32 to 1236) that will be integrated into the COMFIT database. The final number of included meta-analyses and trials has yet to be determined, but will be lower.

Conclusions

We established the COMFIT consortium and database of combined trial-level data on commercial funding and estimated intervention effects from 6841 trials included in 728 meta-analyses and 17 meta-epidemiological studies. When the database has been completed, it will enable comprehensive and statistically powerful analyses with a reduced risk of both confounding and reporting bias.

KEYWORDS

Commercial funding, meta-epidemiology, data sharing, data management, randomised clinical trials, meta-analyses

INTRODUCTION

Results from randomised clinical trials often have substantial impact on patient care. When several trials are summarised and analysed in systematic reviews, these reviews may also impact on treatment recommendations and clinical practice.[1,2] It is therefore essential that results from trials are unbiased.

Randomised clinical trials are often funded by commercial companies and trial reports are often written by authors with financial ties to such companies. In a random sample of 195 drug trials, 69% of the trials were funded by the industry and 68% had principal authors with financial ties to trial drug manufacturers.[3] These ties create financial conflicts of interest and it is widely believed that this influences trial results and conclusions.

The perception that financial conflicts of interest impact on trial results and conclusions is supported by numerous methodological studies. A large Cochrane review identified and analysed 75 methodological studies investigating the impact of commercial funding on primary research studies, mainly randomised trials. The authors reported that commercially funded studies more often had favourable conclusions than non-commercially funded studies (RR 1.34, 95% confidence interval 1.19 to 1.51). Moreover, commercially funded studies more often had favourable efficacy results (based on direction and statistical significance of the results) than non-commercially funded studies (RR 1.27, 95% confidence interval 1.17 to 1.37).[4]

However, the review was based on methodological studies with a high risk of confounding, because most studies compared trials that likely differ for other reasons than funding source. This means that the reported association between funding and favourable conclusions may be confounded by other factors, for example differences in trial populations between commercially and non-commercially funded trials. Furthermore, the review included 24 studies that compared estimated intervention effects (e.g. odds ratios (OR) or relative risks) between trials with and without commercial funding, but they could not be combined in a meta-analysis. The studies had mixed findings and the results were uncertain.[4]

Therefore, despite widespread suspicion that trial funding source impacts directly on estimated intervention effects, this is not supported empirically by an overview of methodological studies with low risk of confounding. In the context of systematic reviews the impact from funding source on estimated intervention effects is the relevant outcome, as trial effect estimates and not trial conclusions are used in meta-analyses.

The risk of confounding is considerably reduced in meta-epidemiological studies. A meta-epidemiological study analyses samples of meta-analyses of randomised clinical trials. Estimated intervention effect (e.g. OR) is summarised separately for trials with and without a certain characteristic (e.g. commercial funding) within each meta-analysis. This ensures comparison of trials with fairly similar groups of patients, interventions, controls, and outcomes. The results of each within-meta-analysis comparison are then summarised across meta-analyses providing an estimate of the average impact, for example in the form of a ratio of odds ratios (ROR). A ROR is based on the

ratio between the summary OR for trials with the characteristic and the summary OR for trials without the characteristic (e.g. $OR_{commercial\ funding}/OR_{non\text{-}commerical\ funding}$).[5]

Interpretation of findings from methodological or meta-epidemiological studies and from systematic reviews based solely on published data from such studies may be influenced by reporting bias. Reporting bias occurs when the publication of research findings is influenced by the nature and direction of results.[6] As a consequence, available results may differ systematically from unpublished results. Reporting bias therefore is a potential threat to the validity of studies.

In response to the uncertainty regarding the impact of commercial funding on estimated intervention effects and to the risk of confounding and reporting bias in existing methodological studies, we initiated the COMFIT (COMmercial Funding In Trials) study. We wanted to identify meta-epidemiological studies with data on funding source and estimated intervention effects in randomised clinical trials and to establish a consortium of researchers to enable the sharing of trial-level data for the construction of a combined database. Below, we describe the establishment of the COMFIT consortium to share trial-level data, detail the procedures for constructing the COMFIT database, and provide core baseline data of the meta-epidemiological studies included.

AIMS OF THE COMFIT STUDY

The primary aim of the COMFIT study is to investigate the impact of commercial funding on estimated intervention effects in randomised clinical trials.

The secondary aims are to investigate 1) the impact of commercial funding on occurrence of statistically favourable results, favourable conclusions, and the concordance between results and conclusions; and 2) the impact of commercial funding with increased risk of funder influence on estimated intervention effects; and 3) trial authors' financial conflicts of interest on estimated intervention effects.

Supplementary aims are to investigate a dose-response relation of the impact of degree of commercial funding on estimated intervention effects in trials as well as the association between risk of bias assessments in trials and their source of funding.

METHODS

Eligibility criteria for meta-epidemiological studies

We included meta-epidemiological studies that enabled a comparison of trials with and without: 1) commercial funding per se (related solely to type of funding source), 2) commercial funding with increased risk of funder influence (assessment done by the authors of the meta-epidemiological studies of whether a commercial funder had an influence on trial design, conduct, analysis, or reporting, e.g. trials funded by pharmaceutical companies that also conducted the statistical analyses), and 3) trial authors' financial conflicts of interest (financial ties between the authors of the trials and commercial companies).

Some included meta-epidemiological studies had data on commercial funding, but with no analysed or reported impact on trial results or conclusions, as funding source was considered a basic characteristic or adjustment factor. This was, for example, the case in a study of the impact of single-centre trial status on effect estimates which performed analyses adjusted for trial funding source.[7] With access to trial level data, we could calculate the direct impact of commercial funding on estimated intervention effects.

Types of outcomes

We included meta-epidemiological studies in which it was possible to extract or calculate ROR for our primary or secondary outcomes. Our primary outcome was estimated intervention effects. Our three secondary outcomes were occurrence of statistically favourable results (whether effect estimates are favourable towards the experimental intervention and statistically significant), favourable conclusions (whether conclusions are favourable towards the experimental intervention), and concordance between results and conclusions (whether favourable conclusions are supported by statistically favourable results).

Search strategy and study inclusion

We searched PubMed, Embase, and Cochrane Methodology Register (from inception to June 2020) for eligible meta-epidemiological studies. We used the search strategy for PubMed presented in eAppendix 1 and adapted it for the other databases. We searched Web of Science for studies citing any of the included meta-epidemiological studies or any of the studies included in the updated Cochrane review on industry funding in trials from 2017.[4] We searched Google Scholar using standard phrases (eAppendix 2). We sorted by relevance and screened the first 30 records of each search.

We read references of included meta-epidemiological studies. We searched 2014-2020 proceedings from Cochrane Colloquia,[8] Peer Review Congresses,[9] and the Clinical Trials Methodology Conference[10] for published and unpublished meta-epidemiological studies. We assessed all meta-epidemiological studies included in a systematic review of meta-epidemiological studies by Dechartres and colleagues from 2016,[11] all included and excluded studies in the updated Cochrane review on industry funding in trials from 2017,[4] and all excluded studies from the previous version from 2012 for eligibility.[12]

Finally, we searched for additional meta-epidemiological studies using the search strategy in eAppendix 3 and randomly choose a sample of 20 studies for further assessment. For each meta-epidemiological study, we contacted the authors and enquired whether they collected trial funding information.

One author (CHN) screened titles and abstracts for evident exclusions, and two authors (CHN and SA, MHAG, or DRTL) assessed full text of potentially eligible meta-epidemiological studies. One author (CHN) read references, searched Web of Science, Google Scholar, and conference proceedings.

Establishing the COMFIT consortium

To enable analysis of trial-level data we established a collaborative network, the COMFIT consortium. The consortium is based on sharing trial-level data from all included meta-epidemiological studies.

The COMFIT consortium consists of authors of the included meta-epidemiological studies and methodologists with expertise in meta-epidemiology. We invited lead authors (e.g. first, senior, or corresponding authors) of each included meta-epidemiological study to join the consortium and share meta-epidemiological datasets with trial-level data. We contacted corresponding authors, or in some cases first/senior authors, by email and/or telephone.

We developed a data stewardship plan outlining our principles for data sharing. The plan stated that data would not be shared or used for other purposes than the COMFIT study without consent.

Constructing the COMFIT database

We plan to construct the COMFIT database through the steps outlined below, inspired by the methods used in the BRANDO[13] study: checking data quality, identifying references for included trials, assigning unique identity numbers, constructing trial-level data for one meta-epidemiological study, classifying variables, removing non-informative meta-analyses, and removing correlated or duplicate meta-analyses and trials. The data were handled by Excel, STATA, and Python.

Checking data quality

In principle, each meta-epidemiological dataset involves three information levels: 1) systematic reviews, 2) meta-analyses included from the systematic reviews, and 3) randomised trials included from the meta-analyses.

For each meta-epidemiological dataset, one author will check the data quality by comparing datasets with the study publication. First, we plan to check that the number of included meta-analyses and trials in the dataset match the numbers reported in the study publication. In case of any discrepancies, we will consult with the authors. If the authors are not able to clarify, we plan to exclude the meta-analyses and trials not included in the study publication.

Second, we plan to check that the number of trials with and without commercial funding in the dataset match the numbers reported in the study publication. For meta-epidemiological studies that primarily investigate a different trial characteristic, but have data on commercial funding as a basic characteristic or adjustment factor, we plan to check that the number of trials with and without the essential trial characteristic (e.g. blinding) in the dataset match the numbers reported in the study publication. If these are consistent, we will proceed with the dataset.

Identifying references for included randomised trials

If some of the meta-epidemiological datasets do not list references for the included trials (but solely use ID numbers), one author will attempt to identify references. First, we plan to identify the relevant meta-analysis. From all the meta-analyses included in the concerned systematic review, we will identify the one where the intervention, comparison, and outcome measure match the infor-

mation in the meta-epidemiological dataset. Next, we plan to identify the relevant trials. From the meta-analysis, we will compare number of patients in the experimental and control groups with the meta-epidemiological dataset for each trial. When these numbers match, we will retrieve the trial reference. If we are not able to identify a reference, we plan to exclude the trial.

We plan to implement a script in Python based on PubMed's Entrez application programming interface (API) to automatically obtain PubMed identifier numbers (PMID numbers) for meta-analyses and trials when this information is not available in the meta-epidemiological publication or dataset. Based on information on first author, publication year, and publication title, the script automatically searches the PubMed database. From the list of returned results, it determines the most likely by calculating the difference between the expected title and each of the returned titles. This calculation is based on the FuzzyWuzzy Python package's Levenshtein distance[14,15] implemented using 95% as the minimum match threshold. The PMID number of the results with the highest matching scores are retrieved and stored against the corresponding record. We will not obtain identification numbers from other databases, when meta-analyses and trials are not indexed in PubMed.

Assigning unique identity numbers
We plan to assign each meta-analysis and trial included in the COMFIT database with a unique identity number.

Constructing trial-level data for one meta-epidemiological study
For one meta-epidemiological study, results from the same analysis differed between two study publications.[16,17] Contact to the corresponding author did not reveal the reason for the inconsistency nor access to the underlying trial-level data. However, it was possible to re-construct a dataset with trial-level data based on the published information and the included meta-analyses. Two authors (CHN and DRTL) independently selected meta-analyses from included systematic reviews, extracted data, and coded type of trial funding and trial authors' financial conflicts of interest (eAppendix 4).

Classification of commercial funding and trial authors' financial conflicts of interest variables, outcome variables, and subgroup and adjustment variables for the COMFIT database
The COMFIT database will contain variables on: commercial funding (i.e. commercial funding per se, and commercial funding with increased risk of funder influence), trial authors' financial conflicts of interest, trial results and conclusions (i.e. estimated intervention effects, statistically favourable results, favourable conclusions, and concordance between results and conclusions), primary purpose of the meta-epidemiological study, risk of bias in trials (i.e. sequence generation, allocation concealment, blinding, incomplete outcome data, and overall risk of bias), type of systematic review (e.g. Cochrane reviews and non-Cochrane reviews), clinical area, type of trial intervention, type of trial outcome (e.g. objective and subjective), intention of trial outcome (i.e. whether the outcome is related to benefits or harms), and number of analysed patients (eAppendix 5).

For each variable, we plan to develop coding categories for the COMFIT database based on the categorisation used by the individual meta-epidemiological studies. In this way, we will harmonise

categories across the meta-epidemiological studies, and convert the categorisation from individual meta-epidemiological studies into common categorisations for the COMFIT database. Two authors will discuss and agree on the categorisation of each meta-epidemiological study and third author will verify the categorisation of commercial funding. For example, if a meta-epidemiological study codes trial conclusions using the following three categories: negative with harmful effects, negative with no benefits, and positive; we plan to convert into the following COMFIT categorisation: unfavourable (covering trials coded as negative with harmful effects and negative with no benefits) and favourable (covering trials coded as positive).

For each meta-analysis, two authors will independently note the direction of estimated intervention effects in included randomised trials based on reporting of the meta-epidemiological study or dataset. If not clear from the reporting, we plan to look within each included meta-analysis to determine direction. We will ensure that OR<1 or SMD<0 indicate a beneficial effect of the experimental intervention and reverse the effect estimates if necessary. If we are not able to confirm the direction, we plan to exclude the meta-analysis. Any disagreements will be resolved by discussion or arbitration.

Removing non-informative meta-analyses
For meta-analyses to be included in the COMFIT database they have to include at least one trial with and without at least one type of commercial funding (i.e. they have to be informative). For example, if all trials in a meta-analysis have commercial funding, this meta-analysis would not be informative. We plan to remove non-informative meta-analyses, defined as meta-analyses not contributing to the analysis of at least one of our primary and secondary aims.

Removing correlated or duplicate meta-analyses and trials
As we will combine data from several meta-epidemiological studies, the same systematic review or two versions of the same Cochrane review may provide several meta-analyses for the COMFIT database. Likewise, the same trial or different comparisons from the same trial may be included more than once. Correlated or duplicate meta-analyses and trials may impact on effect estimates from any analyses made on the basis of the COMFIT database. For example, if a commercially funded trial showing a large effect of the experimental intervention is included more than once, this may overestimate the average impact from commercial funding. Also, this dependency in data may cause standard errors to be too small and thus confidence intervals to be too narrow. Therefore, we plan to remove correlated or duplicate meta-analyses and trials. Based on first author and publication year, title, and PMID number, we will use Excel and STATA to identify correlated and duplicate meta-analyses and trials.

We define correlated or duplicate meta-analyses as meta-analyses included from the same systematic review. The meta-analyses may be duplicates, when the same meta-analysis is included more than once, or they may be correlated, when separate meta-analyses are included from the same systematic review (e.g. meta-analyses investigating different outcomes). Likewise, we define correlated or duplicate trials as the same trial result being included more than once (i.e. duplicate trials) or separate trial results being included from the same trial (i.e. correlated trials). We will not distin-

guish between duplicate and correlated meta-analyses and trials, and will not compare correlated meta-analyses and trials to identify the amount of overlap.

For correlated or duplicate meta-analyses, we will first exclude the non-informative ones. If all correlated or duplicate meta-analyses are informative, we will exclude the ones with the fewest included trials. If all correlated or duplicate meta-analyses include the same number of trials, we will exclude meta-analyses at random.

For correlated or duplicate trials, we will first exclude trials that do not turn an informative meta-analysis non-informative by excluding them. If this rule cannot yield a decision, we will exclude the trials with the fewest included patients. If all correlated or duplicate trials include the same number of patients, we will exclude trials at random.

Data analysis plan

Based on the COMFIT database, we plan to use Bayesian hierarchical models (model developed by Rhodes and colleagues[18]) to estimate ROR and heterogeneity statistics (Phi and Lambda) for each meta-epidemiological study. We will then pool measures across the meta-epidemiological studies using inverse-variance random-effects meta-analyses.

In our primary analysis, we plan to analyse estimated intervention effects between randomised trials with and without commercial funding per se. In our secondary analyses, we plan to analyse occurrence of statistically favourable results, favourable conclusions, and concordance between results and conclusions between randomised trials with and without commercial funding per se. We also plan to analyse estimated intervention effects between randomised trials with commercial funding with increased risk of funder influence versus no commercial funding or commercial funding with low risk of funder influence; as well as between randomised trials with versus without trial authors' financial conflicts of interest. In supplementary analyses, we plan to investigate a dose-response relation by analysing estimated intervention effects between randomised trials with full commercial funding, some commercial funding (e.g. trials receiving the intervention only by commercial companies), and no commercial funding. We also plan to analyse the association between risk of bias in trials (i.e. assessments of random sequence generation, allocation concealment, blinding, incomplete outcome data, and overall risk of bias) and their source of funding through adjustment and interaction analyses. Finally, we plan to conduct sensitivity and subgroup analyses, for example by comparing different types of trial interventions.

RESULTS

The COMFIT database

We identified 18 eligible meta-epidemiological studies and included data from 17 of them in the COMFIT database (Figure 1). The authors of sixteen studies supplied us with a dataset with trial-level data[7,19-33] and we constructed a dataset for one study.[16] Data had been lost from the last meta-epidemiological study from 1998 and the study data (11 meta-analyses and 127 trials)[34] could therefore not be included.

The 17 meta-epidemiological studies contributed with 728 meta-analyses (median 33, range 6 to 156) and 6841 trials (median 326, range 32 to 1236). These meta-analyses and trials will be integrated into the COMFIT database, but the number will decrease as part of our procedures for checking data quality, identifying references for included trials, confirming the direction on estimated intervention effects, excluding non-informative meta-analyses, and removing correlated or duplicate meta-analyses and trials.

The 17 meta-epidemiological studies were published between 2003 and 2020. Ten studies investigated trials within specific clinical specialties or diseases (e.g. critical care or osteoarthritis), whereas the remaining seven studies sampled trials from multiple specialties. Fourteen studies investigated a mixture of outcomes, two studies included only patient-reported pain outcomes, and one study included only mortality outcomes (Table 1). Seven of the studies had published findings on the impact of commercial funding on estimated intervention effects based on a within-meta-analysis approach and three additional studies had reported other effect measures of the impact.[35] The remaining seven studies had collected data on commercial funding as a descriptive or adjustment factor, but had not reported any analyses on the impact of commercial funding in the study publication.

DISCUSSION

We established a consortium for data sharing and initiated the development of a database combining trial-level data on commercial funding and trial results and conclusions from 17 meta-epidemiological studies including 728 meta-analyses and 6841 trials. The COMFIT database will enable comprehensive and statistically powerful analyses with a reduced risk of both confounding and reporting bias.

Strengths and challenges of the COMFIT study

To our knowledge, the COMFIT study will be the largest study of multiple meta-epidemiological datasets. We identified 18 meta-epidemiological studies with data on commercial funding and obtained trial-level data from 17 (99% of meta-analyses and 98% of trials) of them. The only other study that combined trial-level data from meta-epidemiological studies is the BRANDO study that aimed at investigating the impact from study design characteristics on estimated intervention effects. The BRANDO study combined data from seven meta-epidemiological studies and contained 234 meta-analyses and 1973 trials.[36] Thus, the size of COMFIT will likely surpass quite considerably that of the BRANDO study.

The COMFIT database provides an opportunity to perform analyses with a reduced risk of confounding as the compared trials will have fairly similar groups of patients, interventions, controls, and outcomes. Moreover, the analyses will be more reliable than simply conducting a meta-analysis of individual meta-epidemiological summary results, because we removed correlated or duplicate meta-analyses and trials between the meta-epidemiological studies. Also, we included unpublished data, thus limiting the risk of reporting bias. Additionally, the analyses will have more statistical power than single meta-epidemiological studies. Our procedures will ensure high data quality, for example by ensuring correct directionality in effect estimates. Finally, the database will provide an opportunity to investigate the potential dose-response relation of the impact of degree of commer-

cial funding on estimated intervention effects as well as the possible association between risk of bias and source of funding.

Nevertheless, there are some challenges. First, the definitions and coding criteria differed between the meta-epidemiological studies. For example, some meta-epidemiological studies perceived provision of trial material to be funding, whereas other meta-epidemiological studies did not. As a consequence, non-commercially funded trials that received trial material from commercial companies were coded differently and not all meta-analyses and trials in the COMFIT database will inform the analyses of all study aims. Second, some studies primarily investigated commercial funding, while other studies solely used commercial funding as a descriptive or adjustment factor. Therefore, data on funding source may be collected using different methods.

Despite a reduced risk of confounding in meta-epidemiological studies, findings from such studies may be influenced by residual confounding. The comparison of trials within meta-analyses may control imperfectly for patient group, intervention, and control,[37] and other trial characteristics (e.g. sample size) may confound the association between commercial funding and estimated intervention effects.[38] Furthermore, the sampling of trials included in meta-epidemiological studies is not random. The comparison is restricted to trials that are included in meta-analyses, and to meta-analyses that include both trials with and without commercial funding. Meta-analyses from clinical areas with a very high or low prevalence of commercially funded trials may therefore not be included in the meta-epidemiological studies. Finally, characterising trial intervention arms as experimental and control may be challenging. Errors in labelling trial intervention arms may affect the overall estimate of impact in the meta-epidemiological study.[39] Only some of the included meta-epidemiological studies addressed this problem, for example by excluding head-to-head comparisons[19] or restricting the inclusion to meta-analyses of active interventions versus sham, placebo, or no intervention controls.[24] However, these approaches will likely affect applicability of the meta-epidemiological study findings.[39]

Comparison with other studies

Our methods for the COMFIT study are based on experiences from the construction of a database used in the BRANDO study.[13] Even though the methods used in the two studies are very similar, there are some differences. For example, we had different approaches to handling correlated trials. When different results from the same trial were available, the BRANDO study combined different treatment groups if appropriate (e.g. in multi-arm trials where the same control group is compared with two different treatment groups).[13] Combining treatment groups requires considerable resources and requires making somewhat subjective judgements in regards to when it is appropriate to merge different treatments. Therefore, we plan to exclude correlated trials, accepting that it will reduce the COMFIT database sample size. Nevertheless, none of the approaches is likely to influence the results of the analyses based on the databases.

Potential implications for research and practice

The COMFIT study is enabled because of a willingness to share trial-level data by the authors of the included meta-epidemiological studies. Many scientific journals have data sharing policies, but

with wide variation in the requirements.[40] Obtaining trial-level data enables analyses that are not possible to do on the basis of published summary data. Our approach, procedures, and reflections may be useful for future investigations planning to combine primary data from multiple meta-epidemiological studies.

The revised Cochrane tool to assess risk of bias in randomised trials does not include commercial funding as a separate bias domain.[41] The Cochrane Handbook for Systematic Reviews of Interventions discourages the inclusion of commercial funding directly in the risk of bias assessments when conducting systematic reviews, as this would be inconsistent with the conceptual structure of the tool that is based on fundamental, independent bias mechanisms.[42] However, a methodological study of 100 Cochrane reviews reported that approximately 30% of the reviews incorporated information on funding and authors' conflicts of interest directly into the risk of bias assessment.[43] Currently, there is little practical guidance for how to tackle commercial funding and there is a need for a broader consensus on how information of funding source and authors' conflicts of interest should be addressed in systematic reviews.[44] The COMFIT database will enable analysis of the potential interaction from the traditional bias domains on the association between commercial funding and estimated intervention effects. These findings will inform the debate.

Conclusion

We established a consortium for data sharing and initiated the development of a database combining trial-level data on commercial funding and estimated intervention effects in randomised clinical trials from meta-epidemiological studies. The COMFIT database will enable comprehensive and statistically powerful analyses with a reduced risk of both confounding and reporting bias. It will provide an opportunity to address possible dose-response relations of the impact of degree of commercial funding on estimated intervention effects in randomised clinical trials as well as the possible association between risk of bias and sources of funding.

HIGHLIGHTS

What is already known?

It is widely suspected that commercial funding impacts on results and conclusions of randomised trials. This perception is based on methodological studies that have a high risk of confounding. Risk of confounding is markedly reduced in meta-epidemiological studies where trials are compared within meta-analyses, thus ensuring broadly similar groups of patient, interventions, controls, and outcomes.

What is new?

We established a consortium for data sharing and initiated the development of the COMFIT database combining trial-level data on commercial funding and trial results and conclusions from meta-epidemiological studies. We included data from 17 meta-epidemiological studies including 728 meta-analyses and 6841 trials. The use of trial-level data will enable us to ensure data quality, harmonise coding categories across meta-epidemiological studies, ensure directionality in estimated intervention effects, and remove correlated or duplicate meta-analyses and trials.

Potential impact for *Research Synthesis Methods* readers outside the authors' field

The COMFIT database will enable comprehensive and statistically powerful analyses with a reduced risk of both confounding and reporting bias.

DECLARATIONS

Conflicts of interest
None.

Funding
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Ethics
Ethical approval was not required for this study.

Author contributions
CHN, AL, and AH developed the idea for the project and constitute the COMFIT steering group. CHN and AH contacted authors to establish the COMFIT consortium. CHN, AL, DRTL, and AH coded data for the COMFIT database. CHN, JS, and AH developed procedures for constructing the database and removing correlated or duplicate meta-analyses and trials. BKO developed the code to obtain PMIDs for the meta-analyses and trials in the database. CHN and AH wrote the draft for the article and all authors contributed in revising the article.

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Figure 1. Flow diagram of meta-epidemiological study inclusion

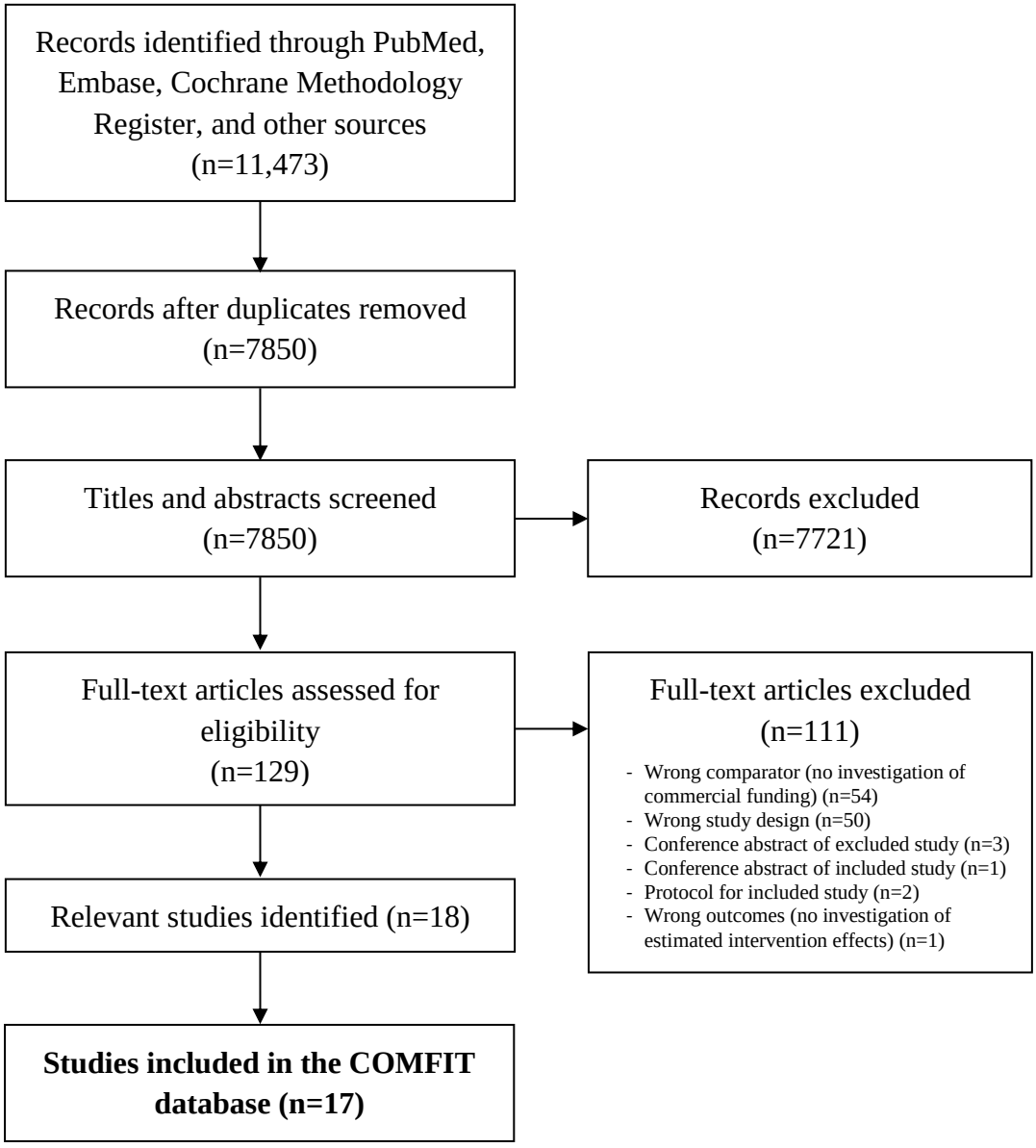

Table 1. Characteristics of meta-epidemiological studies in the COMFIT database

First author and year	Type of trials[a]	Type of trial outcomes[b]	Number of meta-analyses (trials)
Abraha 2015	Generic cohort of trials	Mixed binary	51 (326)
Alahdab 2018	Trials on chronic medical conditions	Mixed binary	70 (930)
Als-Nielsen 2003	Generic cohort of trials	Mixed binary	29 (370)
Bafeta 2012	Generic cohort of trials	Mixed continuous	27 (298)
Bialy 2014	Neonatal trials	Mixed binary (mainly mortality)	24 (208)
Bolvig 2018	Osteoarthritis trials	Patient-reported pain	20 (140)
daCosta 2013	Osteoarthritis trials	Patient-reported pain	21 (292)
Dechartres 2011	Generic cohort of trials	Mixed binary	48 (421)
Dechartres 2016	Generic cohort of trials	Mixed binary	67 (322)
Fuentes 2020	Physical therapy trials	Mixed continuous	43 (578)
Haring 2020	Trials on testosterone therapy in men	Mixed binary and continuous	19 (132)
Hartling 2014	Pediatric trials	Mixed binary and continuous	17 (287)
Janiaud 2018	Critical care trials	Mixed binary (mainly mortality)	33 (369)
Moustgaard 2020	Generic cohort of trials	Mixed binary and continous	156 (1236)
Saltaji 2016	Oral health trials	Mixed continuous	62 (523)
Tsujimoto 2020	Generic cohort of trials	Mixed binary	35 (377)
Unverzagt 2013	Critical care trials	Mortality	6 (32)

[a]Generic cohort of trials indicate that the meta-epidemiological study authors sampled trials from multiple specialties. [b]Mixed outcomes indicate that the meta-epidemiological study authors included trials regardless of their outcome measure and therefore investigated a sample of trials with a range of different outcomes.

eAPPENDIX 1. PUBMED SEARCH STRATEGY

Block 1: Investigation of conflicts of interest or bias

1. "Conflict of Interest"[MeSH]

2. (Conflict[Title/Abstract] OR conflicts[Title/Abstract] OR conflicting[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])

3. (Competing[Title/Abstract] OR vested[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])

4. (Industry[Title] OR industries[Title] OR company[Title] OR companies[Title] OR manufacturer[Title] OR manufacturers[Title] OR finance[Title] OR financial[Title]) AND (funded[Title] OR funding[Title] OR sponsor[Title] OR sponsors[Title] OR sponsorship[Title] OR sponsoring[Title] OR support[Title] OR supported[Title] OR involvement[Title] OR involving[Title] OR payment[Title] OR payments[Title] OR relationship[Title] OR relationships[Title] OR relation[Title] OR relations[Title] OR tie[Title] OR ties[Title] OR collaboration[Title] OR collaborations[Title])

5. Industry-funded[Title/Abstract] OR industry-funding[Title/Abstract] OR industry-sponsor*[Title/Abstract] OR company-funded[Title/Abstract] OR company-funding[Title/Abstract] OR company-sponsor*[Title/Abstract] OR industry-support[Title/Abstract] OR industry-supported[Title/Abstract] OR company-support[Title/Abstract] OR company-supported[Title/Abstract]

6. (Commercial-academic[Title/Abstract] OR academic-commercial[Title/Abstract] OR industry-academic[Title/Abstract] OR academic-industry[Title/Abstract] OR commercial-industry[Title/Abstract] OR industry-commercial[Title/Abstract] OR industry-physician[Title/Abstract] OR physician-industry[Title/Abstract]) AND (interaction[Title/Abstract] OR interactions[Title/Abstract] OR relationship[Title/Abstract] OR relationships[Title/Abstract] OR relation[Title/Abstract] OR relations[Title/Abstract] OR collaboration[Title/Abstract] OR collaborations[Title/Abstract])

7. "Bias"[MeSH]

8. (Bias[Title/Abstract] OR biases[Title/Abstract]) AND (quantify[Title/Abstract] OR quantified[Title/Abstract] OR quantification[Title/Abstract] OR measure[Title/Abstract] OR measured[Title/Abstract] OR classify[Title/Abstract] OR classified[Title/Abstract] OR classification[Title/Abstract])

9. (Methodological[Title] OR methodologic[Title]) AND (quality[Title] OR qualities[Title])

10. (Trial[Title] OR trials[Title]) AND (characteristic[Title] OR characteristics[Title])

11. "Randomized Controlled Trials as Topic"[Majr]

12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11

Block 2: meta-epidemiological studies

13. Meta[Title/Abstract] AND (epidemiological[Title/Abstract] OR epidemiologically[Title/Abstract] OR epidemiology[Title/Abstract] OR epidemiologic[Title/Abstract])

14. Meta-epidemiological[Title/Abstract] OR meta-epidemiology[Title/Abstract] OR meta-epidemiological[Title/Abstract] OR meta-epidemiologic[Title/Abstract]

15. Meta-meta[Title/Abstract] AND (analysis[Title/Abstract] OR analyses[Title/Abstract] OR review[Title/Abstract] OR reviews[Title/Abstract] OR overview[Title/Abstract] OR overviews[Title/Abstract])

16. Meta-meta-analysis[Title/Abstract] OR meta-meta-analyses[Title/Abstract]

17. (Systematic[Title/Abstract] OR Cochrane[Title/Abstract]) AND (review[Title/Abstract] OR reviews[Title/Abstract]) AND ((randomised[Title/Abstract] OR randomized[Title/Abstract]) AND (trial[Title/Abstract] OR trials[Title/Abstract]))

18. Empirical[Title] AND (evaluation[Title] OR evaluations[Title] OR investigation[Title] OR investigations[Title])

19. 13 OR 14 OR 15 OR 16 OR 17 OR 18

Combined searches

20. 12 AND 19

eAPPENDIX 2. SEARCH STRATEGY FOR GOOGLE SCHOLAR

Search phrases

All the searches were sorted by relevance. We screened the first 30 records for each search.

1. Meta-epidemiological study
2. Meta-epidemiological studies
3. Meta-epidemiological methods
4. Meta-epidemiological synthesis
5. Randomised trials included in systematic reviews
6. Randomised trials included in Cochrane reviews
7. Randomised trials included in meta-analyses
8. Randomized trials included in systematic reviews
9. Randomized trials included in Cochrane reviews
10. Randomized trials included in meta-analyses
11. Association between funding and conclusions in randomised trials
12. Association between funding and conclusions in randomized trials
13. Identified randomised trials from Cochrane reviews
14. Identified randomized trials from Cochrane reviews
15. Identified randomised trials from systematic reviews
16. Identified randomized trials from systematic reviews
17. Identified systematic reviews containing a meta-analysis with randomised trials
18. Identified systematic reviews containing a meta-analysis with randomized trials

eAPPENDIX 3. PUBMED SEARCH STRATEGY TO GENERATE RANDOM SAMPLE OF 20 META-EPIDEMIOLOGICAL STUDIES

1. Meta-epidemiological[Title] AND (study[Title] OR studies[Title] OR review[Title] OR reviews[Title] OR analysis[Title] OR analyses[Title])

2. Meta[Title] AND epidemiological[Title] AND (study[Title] OR studies[Title] OR review[Title] OR reviews[Title] OR analysis[Title] OR analyses[Title])

3. Meta-meta[Title] AND (study[Title] OR studies[Title] OR review[Title] OR reviews[Title] OR analysis[Title] OR analyses[Title])

4. Metaepidemiological[Title] AND (study[Title] OR studies[Title] OR review[Title] OR reviews[Title] OR analysis[Title] OR analyses[Title])

5. 1 OR 2 OR 3 OR 4

eAPPENDIX 4. CONSTRUCTING A DATASET FOR ONE META-EPIDEMIOLOGICAL STUDY

For one meta-epidemiological study in which we did not have access to trial-level data, we reconstructed a dataset. The meta-epidemiological study findings were reported in two study publications,[1,2] and in one of these, the authors' coding of sequence generation, allocation concealment, blinding, selective outcome reporting, and commercial funding with increased risk of funder influence was reported for each included trial.[1]

The meta-epidemiological study included six systematic reviews and reported information on outcome and intervention in the included meta-analyses as well as references for the included trials. Two authors (CHN and DRTL) independently compared information between the meta-epidemiological study publications and the meta-analyses, and selected the first reported meta-analysis from each systematic review that 1) had matching information and 2) reported either number of events and participants in each group or summary effect estimates (e.g. OR).

Two authors (CHN and DRTL) independently extracted number of events and participants in the experimental and control groups, summary effect estimates with 95% confidence intervals, direction of effect, and type of intervention from the included meta-analyses. We also extracted information on sequence generation, allocation concealment, blinding, selective outcome reporting, and commercial funding with increased risk of funder influence from the meta-epidemiological study publication. One author (CHN) extracted verbatim declarations of conflicts of interest and funding as well as affiliations of authors from each trial. Two authors (CHN and DRTL) independently coded type of trial funding and trial authors' financial conflicts of interest for each trial.

eAPPENDIX 5. VARIABLES IN THE COMFIT DATABASE

eTable 1. Variables that will be included in the COMFIT database

COMFIT variable	Description
Commercial funding and trial authors' financial conflicts of interest variables	
Commercial funding per se	Type of trial funding (i.e. not considering any potential influence on trial design, conduct, analysis, or reporting as well as any financial ties between the trial authors and commercial companies) Categories for the COMFIT database may, for example, include: - Not reported or unclear - No funding or non-commercial funding - Intervention only supplied by commercial companies - Combined commercial and non-commercial funding - Commercial funding
Commercial funding with increased risk of funder influence	Assessment (done by the authors of the meta-epidemiological studies) of funding source and its perceived influence of trial design, conduct, analysis, or reporting Categories for the COMFIT database may, for example, include: - Low risk of commercial funding with funder influence - High risk of commercial funding with funder influence - Unclear risk of commercial funding with funder influence
Trial authors' financial conflicts of interest	Financial ties between trial authors and commercial companies Categories for the COMFIT database may, for example, include: - Not reported or unclear - No author financial conflicts of interest - Author financial conflicts of interest
Outcome variables	
Estimated intervention effects	Odds ratio (OR) and standard error (SE) in each randomised trial
Statistically favourable results	Whether estimated intervention effects are favourable towards the experimental intervention and statistically significant Categories for the COMFIT database may, for example, include: - Favourable - Unfavourable
Favourable conclusions	Whether conclusions are favourable towards the experimental intervention Categories for the COMFIT database may, for example, include: - Favourable - Unfavourable
Concordance between results and conclusions	Whether favourable conclusions are supported by statistically favourable results or whether unfavourable conclusions are supported by statistically unfavourable results Categories for the COMFIT database may, for example, include: - In concordance - Not in concordance

Subgroup and adjustment variables	
Primary purpose of meta-epidemiological study	The primary purpose of the meta-epidemiological study Categories for the COMFIT database may, for example, include: - Investigating commercial funding - Investigating a different trial characteristic and adjusting for commercial funding - Investigating a different trial characteristic and collecting descriptive information on commercial funding
Risk of bias	Assessment of risk of bias in relation to sequence generation, allocation concealment, blinding, incomplete outcome date, and overall risk of bias Categories for the COMFIT database may, for example, include: - Low risk of bias - High risk of bias or unclear
Type of systematic review	Type of systematic review that the meta-analysis is included from Categories for the COMFIT database may, for example, include: - Cochrane review - Non-Cochrane review
Clinical area	Type of clinical area for each trial
Trial intervention	Type of experimental intervention for each trial Categories for the COMFIT database may, for example, include: - Drug and device intervention - Non-drug and non-device intervention - Mixed drug/device and non-drug/non-device interventions - Not possible to classify
Type of trial outcome	Type of outcome for each trial Categories for the COMFIT database may, for example, include: - All-cause mortality - Cause-specific mortality - Other objective outcomes - Subjective outcomes - Not possible to classify
Intention of trial outcome	Whether the outcome of the trial is intended to measure benefit or harms. Categories for the COMFIT database may, for example, include: - Benefit - Harms - Not possible to classify
Number of analysed patients	Number of patients analysed in each randomised trial

Commercial funding and trial authors' financial conflicts of interest variables

The COMFIT database will contain the following variables on commercial funding: commercial funding per se and commercial funding with increased risk of funder influence. In addition, it will contain a variable on trial authors' financial conflicts of interest.

If the meta-epidemiological study does not code funding source for each randomised trial, but provide information on funding declarations (e.g. verbatim extractions of funding declarations), two authors will independently code this. Any disagreements will be resolved by discussion.

Outcome variables

The COMFIT database will contain the following outcome variables: estimated intervention effects, statistically favourable results, favourable conclusions, and concordance between results and conclusions.

For each trial, we will extract OR and SE or standardised mean difference (SMD) and SE. If the meta-epidemiological dataset contains data on number of patients with and without the event in the experimental and control groups, but no estimated ORs, we will calculate the OR and its SE.[3] For trials with zero events in any of the intervention groups, we will use the standard continuity correction of 0.5 in order to include all relevant data.[4] If the dataset contains data on mean difference and standard deviations, and number of trial participants for the experimental and control groups, we will calculate the SMD and its SE and convert to log OR and SE for log OR. For each meta-analysis, two authors will independently note the direction of effect estimates in included randomised trials based on reporting of the meta-epidemiological study or dataset, or included meta-analyses, if necessary. We will ensure that OR<1 or SMD<0 indicate a beneficial effect of the experimental intervention. If not, we will reverse OR by using the reciprocals and SMD by multiplying with -1. If we are not able to confirm the direction, we plan to exclude the meta-analysis.

If the meta-epidemiological study does not code statistically favourable results, we will categorise results based on trial data. We will code effect estimates that are favourable towards the experimental intervention (e.g. OR<1, SMD<0) and statistically significant (based on 95% confidence intervals) as statistically favourable results.

If the authors of the meta-epidemiological studies use a scale to categorise favourable conclusions, we will dichotomise the scale according to the dichotomisation used by the authors.

Subgroup and adjustment variables

The COMFIT database will contain the following subgroup and adjustment variables: primary meta-epidemiological purpose, risk of bias variables (sequence generation, allocation concealment, blinding, incomplete outcome data, and overall risk of bias), type of systematic review, clinical area, type of trial intervention, type of trial outcome, intention of the trial outcome, and number of analysed patients.

Two authors will independently code primary purpose of each meta-epidemiological study.

For our variables on sequence generation, allocation concealment, and incomplete outcome data, we plan to comply with the definitions used by the authors of the meta-epidemiological studies. For blinding, we define trials to have low risk of bias if the trial is coded (by the meta-epidemiological study authors) as double blinded or low risk of bias in either blinding of the patients or blinding of

the outcome assessors. We define trials as having overall low risk of bias, if all four bias domains are assessed as low risk of bias. Otherwise, we define it as overall high/unclear risk of bias.

Two authors will independently code clinical area for each meta-epidemiological study, meta-analysis, or trial as necessary.

If the meta-epidemiological study does not categorise the intervention of each meta-analysis or use categories adaptable with ours, two authors will independently code the interventions based on information supplied in the dataset, the corresponding paper, or supplementary material. For the coding, we will consider vaccines of any kind to be drug and device interventions. We will consider nutritional interventions (e.g. vitamins) and dental interventions (e.g. toothpaste) to be non-drug and non-device interventions. Surgery interventions will be classified as drug and device interventions, unless it is clearly specified that the type of surgery does not involve use of devices (e.g. sutures).

If the meta-epidemiological study does not code the type of trial outcome or use categories adaptable with ours, two authors will independently code the trial outcome based on information supplied in the dataset, the corresponding paper, or supplementary material on meta-analysis level. When possible, we will code whether the outcome is intended to measure benefit or harms.

If the meta-epidemiological study does not code number of patients analysed, we plan to use number of randomised patients as a proxy.

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