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Industry sponsorship and research outcome (Review)

Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L

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[Methodology Review]

Industry sponsorship and research outcome

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ABSTRACT

Background

Clinical research affecting how doctors practice medicine is increasingly sponsored by companies that make drugs and medical devices. Previous systematic reviews have found that pharmaceutical-industry sponsored studies are more often favorable to the sponsor's product compared with studies with other sources of sponsorship. A similar association between sponsorship and outcomes have been found for device studies, but the body of evidence is not as strong as for sponsorship of drug studies. This review is an update of a previous Cochrane review and includes empirical studies on the association between sponsorship and research outcome.

Objectives

To investigate whether industry sponsored drug and device studies have more favorable outcomes and differ in risk of bias, compared with studies having other sources of sponsorship.

Search methods

In this update we searched MEDLINE (2010 to February 2015), Embase (2010 to February 2015), the Cochrane Methodology Register (2015, Issue 2) and Web of Science (June 2015). In addition, we searched reference lists of included papers, previous systematic reviews and author files.

Selection criteria

Cross-sectional studies, cohort studies, systematic reviews and meta-analyses that quantitatively compared primary research studies of drugs or medical devices sponsored by industry with studies with other sources of sponsorship. We had no language restrictions.

Data collection and analysis

Two assessors screened abstracts and identified and included relevant papers. Two assessors extracted data, and we contacted authors of included papers for additional unpublished data. Outcomes included favorable results, favorable conclusions, effect size, risk of bias and whether the conclusions agreed with the study results. Two assessors assessed risk of bias of included papers. We calculated pooled risk ratios (RR) for dichotomous data (with 95% confidence intervals (CIs)).

Main results

Twenty-seven new papers were included in this update and in total the review contains 75 included papers. Industry sponsored studies more often had favorable efficacy results, RR: 1.27 (95% CI: 1.17 to 1.37) (25 papers) (moderate quality evidence), similar harms results RR: 1.37 (95% CI: 0.64 to 2.93) (four papers) (very low quality evidence) and more often favorable conclusions RR: 1.34 (95% CI: 1.19 to 1.51)

(29 papers) (low quality evidence) compared with non-industry sponsored studies. Nineteen papers reported on sponsorship and efficacy effect size, but could not be pooled due to differences in their reporting of data and the results were heterogeneous. We did not find a difference between drug and device studies in the association between sponsorship and conclusions (test for interaction, P = 0.98) (four papers). Comparing industry and non-industry sponsored studies, we did not find a difference in risk of bias from sequence generation, allocation concealment, follow-up and selective outcome reporting. However, industry sponsored studies more often had low risk of bias from blinding, RR: 1.25 (95% CI: 1.05 to 1.50) (13 papers), compared with non-industry sponsored studies. In industry sponsored studies, there was less agreement between the results and the conclusions than in non-industry sponsored studies, RR: 0.83 (95% CI: 0.70 to 0.98) (six papers).

Authors' conclusions

Sponsorship of drug and device studies by the manufacturing company leads to more favorable efficacy results and conclusions than sponsorship by other sources. Our analyses suggest the existence of an industry bias that cannot be explained by standard 'Risk of bias' assessments.

PLAIN LANGUAGE SUMMARY

Industry sponsorship and research outcome

Results from clinical studies on drugs and medical devices affect how doctors practice medicine and thereby the treatments offered to patients. However, clinical research is increasingly sponsored by companies that make these products, either because the companies directly perform the studies, or fully or partially fund them. Previous research has found that pharmaceutical industry sponsored studies tend to favor the sponsors' drugs more than studies with any other sources of sponsorship. This suggests that industry sponsored studies are biased in favor of the sponsor's products.

This review is an update of a previous review that looked at sponsorship of drug and device studies. The primary aim of the review was to find out whether the published results and overall conclusions of industry sponsored drug and device studies were more likely to favor the sponsors' products, compared with studies with other sources of sponsorship. The secondary aim was to find out whether such industry sponsored studies used methods that increase the risk of bias, again compared with studies with other sources of sponsorship. In this update, we carried out a comprehensive search of all relevant papers of empirical studies published from 2010 to February 2015 and included 27 new papers, yielding a total of 75 papers included in our review.

Industry sponsored drug and device studies more often had efficacy results that were favorable to the sponsors' products, (risk ratio (RR): 1.27, 95% confidence interval (CI): 1.17 to 1.37), similar harms results (RR: 1.37, 95% CI: 0.64 to 2.93) and favorable overall conclusions (RR: 1.34, 95% CI: 1.19 to 1.51), compared with non-industry sponsored drug and device studies. We did not find a difference between industry and non-industry sponsored studies with respect to standard methodological factors that may increase the risk of bias, except for blinding: industry sponsored studies reported satisfactory blinding more often than non-industry sponsored studies. In industry sponsored studies, there was less agreement between the results and the conclusions than in non-industry sponsored studies, RR: 0.83 (95% CI: 0.70 to 0.98).We did not find a difference between drug and device studies in the association between sponsorship and conclusions. Our analysis suggests that industry sponsored drug and device studies are more often favorable to the sponsor's products than non-industry sponsored drug and device studies due to biases that cannot be explained by standard 'Risk of bias' assessment tools.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Industry sponsored compared to non-industry sponsored studies for research outcome

Results and conclusions: Industry sponsored compared to non-industry sponsored studies

Patient or population: industry sponsorship and study results
Intervention: industry sponsored studies
Comparator: non-industry sponsored studies

Outcomes	Illustrative comparative risks* (95% CI)		Risk ratio (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Non-industry sponsored studies	Industry sponsored studies				
Number of studies with favorable efficacy results	502 per 1000	638 per 1000 (588 to 688)	1.27 (1.17 to 1.37)	25 papers including 2923 studies	⊕⊕⊕○ MODERATE	Upgraded as control for confounders and analysis of low risk of bias papers gave similar results.
Number of studies with favorable harms results	474 per 1000	649 per 1000 (303 to 1388)	1.37 (0.64 to 2.93)	4 papers including 826 studies	⊕○○○ VERY LOW	Downgraded due to substantial heterogeneity (inconsistency) and wide confidence intervals (imprecision).
Number of studies with favorable conclusions	644 per 1000	863 per 1000 (766 to 972)	1.34 (1.19 to 1.51)	29 papers including 4583 studies	⊕⊕○○ LOW	Downgraded due to substantial heterogeneity (inconsistency). Upgraded as control for confounders and analysis of low risk of bias papers gave similar results.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

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.

The assumed risk of the control group (i.e. non-industry group) was calculated as the mean risk (i.e. number of studies with favorable results divided by total number of studies).

BACKGROUND

Description of the problem or issue

Clinical research sponsored by the pharmaceutical industry affects how doctors practice medicine (PhRMA 2008; Wyatt 1991). An increasing number of clinical trials at all stages in a product's life cycle are funded by the pharmaceutical industry, and the industry now spends more on medical research than do the National Institutes of Health in the USA (Moses 2015). Results and conclusions that are unfavorable to the sponsor (i.e. studies that find an expensive drug similarly or less effective or more harmful than drugs used to treat the same condition) can pose considerable financial risks to companies.

Several systematic reviews have documented that pharmaceutical industry sponsorship of drug studies is associated with findings that are favorable to the sponsor's product (Bekelman 2003; Lexchin 2003; Schott 2010a; Sismondo 2008a). There are several ways that industry can sponsor a study, including single-source sponsorship, shared sponsorship, and provision of free drugs or devices only. There are also several potential ways that industry sponsors can influence the outcome of a study, including the framing of the question, the design of the study, the conduct of the study, how data are analyzed, selective reporting of favorable results, and spin in reporting conclusions (Bero 1996; Lexchin 2012; Sismondo 2008b). Although some journals now require that the role of the sponsor in the design, conduct and publication of the study be described, this practice is not widespread (Tuech 2005). In addition, some have argued that because industry sponsored studies are often conducted for regulatory purposes, their methods must meet high standards (Rosefsky 2003). Therefore, it is important to examine differences not only in the outcomes of industry versus non-industry sponsored studies, but also differences in the methods or risks of bias.

Why it is important to do this review

This systematic review is the update of an original systematic review by three of the authors (Lundh 2012), which investigated whether sponsorship by industry is associated with the publication of outcomes favorable to the sponsor. That review is now out of date. Developments, such as the adoption of trial registration could lessen the bias associated with industry sponsorship, as publication bias can be more readily detected (DeAngelis 2004). Furthermore, companies now publish results in trial registries suggesting a move toward increased transparency (Potthast 2014; Schwartz 2016). However, this may not be the case as a recent study found that reporting bias is also prevalent in registered trials, particular in industry sponsored trials (Jones 2013). In addition, the release of internal industry documents as a result of settlement agreements resulting from litigation against drug companies has revealed examples of industry manipulation of the conduct and publication of studies (Fugh-Berman 2010; Ross 2008; Steinman 2006; Vedula 2009).

OBJECTIVES

The objectives were to investigate whether:

- sponsorship of drug and device studies by the pharmaceutical and device industries is associated with outcomes, including conclusions, that are favorable to the sponsor;
- drug and device studies sponsored by the pharmaceutical and device industries differ in their risk of bias compared with studies with other sources of sponsorship.

METHODS

Criteria for considering studies for this review

Types of studies

This review includes reports of empirical studies that investigate samples of primary research studies. To avoid confusion we will use the terms 'studies' for the primary research studies and 'papers' for the reports of empirical studies of primary research studies. We will use the term trials to describe studies of a randomized clinical trial design.

We included papers of cross-sectional studies, cohort studies, systematic reviews or meta-analyses that quantitatively compared primary research of human drug or medical device studies sponsored by the pharmaceutical or device industries with studies that had other sources of sponsorship. These papers could report the results of methodological studies or systematic reviews that had a pre-specified subgroup or sensitivity analysis by sponsorship source. We also included papers investigating sources of heterogeneity (e.g. using meta-regression) if sponsorship was investigated. Drugs were defined as medications that require approval by a regulatory authority as a prescription drug, recognizing that these approval standards vary worldwide. Devices were defined based on the Food and Drug Administration (FDA) definition as instruments intended for use in the diagnosis, treatment or prevention of disease.

We excluded papers without quantitative data related to our primary or secondary outcomes. We excluded papers of the effects of sponsorship by non-pharmaceutical or non-device (e.g. tobacco, food or chemical) industries, and papers that evaluated the effectiveness of herbal supplements or medical procedures. Papers examining mixed interventions (e.g. pharmaceuticals and educational interventions) were included if drug or device data were reported separately or could be obtained from the authors.

We excluded papers that quantitatively compared the association of sponsorship and results of syntheses of research studies (i.e. systematic reviews or meta-analyses) or pharmacoeconomic studies of drugs or devices. We also excluded analyses of pharmacokinetic studies and studies restricted to non humans (e.g. animal or cell cultures).

Only papers published in full, including structured research letters, were included. We excluded unstructured letters to the editor and conference abstracts. This decision was based on the poor reporting quality of data in letters and conference abstracts encountered in a previous version of our review (Lexchin 2003). A comment to the previous version of our review (Lundh 2012) suggested that the exclusion of conference abstracts and letters could have introduced publication bias. Therefore, we included conference abstracts and all types of letters in a sensitivity analysis (see below). We had no language restrictions.

Types of data

Drug and device papers including human research studies comparing drug to placebo, device to sham, drug to drug, drug

to device, device to device, or mixed comparisons where the effectiveness, efficacy or harms of the drug or device were evaluated. A few papers included data from both unpublished and published studies. If data were reported separately for the published studies or were available from the authors we used data from published studies only. The reason for this decision was that published studies represent what is available to users of the medical literature and our focus was on assessing biases in published studies.

Types of methods

We defined sponsorship as funding or provision of free drug or devices. Drug or device studies with pharmaceutical or device industry funding versus those with other or undisclosed funding were included. We extracted the definition of industry funding verbatim from the included papers (see Data extraction and management) and reported this in the 'Characteristics of included studies' table. For analysis, we grouped the definitions into a variety of categories, including 100% pharmaceutical or device company funding, 100% non-industry funding, mixed funding (e.g. non-industry and industry collaboration), free provision of drug or device only, and undisclosed funding.

We included papers that compared industry sponsored studies with non-industry sponsored studies and also papers that compared studies of products by competing manufacturers (i.e. studies sponsored by the manufacturer of the test treatment with studies sponsored by the manufacturer of the control treatment); we analyzed the two types of papers separately.

Types of outcome measures

Primary outcomes

We included two primary outcomes.

- Whether the results were favorable to the sponsor.
- Whether the conclusions were favorable to the sponsor.

We used the definition of favorable results as described in the methods of the included papers. For efficacy results, most papers considered favorable results to be those that were statistically significant (e.g. $P < 0.05$ or a 95% confidence interval excluding the possibility of no difference) in favor of the sponsor's product. Based on the previous review (Lundh 2012), which found very few studies that reported results unfavorable to the sponsor, unfavorable results were combined with studies that reported results that were neutral or not statistically significant. For harms results, most papers regarded favorable results to be those where harms results were not statistically significant (e.g. $P > 0.05$ or a 95% confidence interval including the possibility of no difference) or results that had a statistically significant higher number of harms in the comparator group.

Conclusions in which the sponsor's product was preferred over the control treatment were considered favorable to the sponsor. For conclusions we did not distinguish between efficacy and harms, as conclusions are often overall qualitative judgements based on a benefit to harm balance.

Secondary outcomes

We included three secondary outcomes.

- The size of the effect estimate in industry sponsored studies versus those with other sources of sponsorship.
- The risk of bias in industry sponsored studies versus those with other sources of sponsorship.
- The concordance between study results and conclusions, i.e. whether the conclusions agreed with the study results, in industry sponsored studies versus those with other sources of sponsorship.

We included papers that reported at least one of these secondary outcomes, even if it reported neither of the primary outcomes.

Search methods for identification of studies

Electronic searches

In this update, we searched Ovid MEDLINE (R) In-Process and other non-indexed citations and Ovid MEDLINE (R) (2010 to February 2015), Ovid Embase (2010 to February 2015) and the Cochrane Methodology Register (2015, Issue 2) (Wiley InterScience Online). We searched the Web of Science (June 2015) for papers that cited any of the papers included in our review.

Search strategy

We used the strategy shown in Appendix 1 for Ovid MEDLINE and adapted it for the other databases.

Searching other resources

Other sources of data included author files, searches of reference lists of included papers and previous systematic reviews.

Data collection and analysis

Selection of studies

Two pairs of assessors (LB and JS or BM and JL) screened the titles and abstracts, when available, of all retrieved records for obvious exclusions, and assessed the remaining papers based on full text. Any disagreements were resolved by consensus and reasons for exclusions of potentially eligible papers are described in the 'Characteristics of excluded studies' table. There was no need for translation of non-English papers.

Data extraction and management

Two pairs of assessors (AL and JS or BM and JL) independently extracted data from included papers; differences in data extraction were resolved by consensus.

We extracted data on the following.

- Year published.
- Country of corresponding author.
- Study objective.
- Study design used in the paper (cohort, cross-sectional, systematic review or meta-analysis, other).
- Study domain - descriptive (e.g. oncology drug trials).
- Study domain - category (drug/device class, specific disease, medical specialty/type of diseases, mixed).
- Type of studies (drug, device, drug and device, mixed).
- Type of comparisons (drug versus drug, drug versus placebo, device versus device, device versus sham, device versus drug, mixed, other).

- Sample strategy used to locate research studies (electronic search only, electronic plus other, sampling of journals, sampling by venue (e.g. conference abstracts)).
- Whether there were language restrictions on the search.
- Number of studies included in the sample.
- Time period covered by studies in the paper.
- Sponsorship categories coded in the paper. Categories were:
- * 100% pharmaceutical/device company funded;
  * 100% non-profit funded;
  * mixed funding - e.g. non-industry and industry collaboration;
  * provision of drug or device only; and
  * undisclosed funding.
- Sponsorship categories used in analysis in the paper (e.g. 100% industry funded grouped with mixed funding for industry category).
- Description of role of the sponsor (if any). For example, definition of the sponsor's role in the design, implementation or reporting in the sample of studies.
- Criteria used to assess risk of bias of the studies included in the paper.
- Primary purpose of the study.
- Whether the paper commented on appropriateness of comparators.
- Data on sponsorship and results.
- Data on sponsorship and conclusions.
- Data on sponsorship and effect size.
- Data on sponsorship and risk of bias.
- Data on sponsorship and concordance between study results and conclusions.
- Additional relevant data.
- Funding source of included paper. As this item was not included in the previous version of the review we also extracted data from papers included in the previous version.

Assessment of risk of bias in included studies

Since there are no validated criteria for assessing risk of bias in these types of papers, we developed our own criteria. We reviewed papers for high, low or unclear risk of bias for each of four criteria. If a criterion was met, it was regarded as having low risk of bias, and high risk of bias otherwise. If we could not determine whether a criterion was met, we coded it as unclear. We used the following criteria:

- whether explicit and well-defined criteria that could be replicated by others were used to select studies for inclusion/exclusion;
- whether there was an adequate study inclusion method, with two or more assessors selecting studies;
- whether the search for studies was comprehensive; and
- whether methodological differences and other characteristics that could introduce bias were controlled for or explored.

Measures of the effect of the methods

We performed a meta-analysis of the papers that reported the association of sponsorship with favorable study outcomes in cases where a pooled risk ratio (RR) and its 95% confidence interval could be computed.

The definition of a favorable outcome varied among papers. In some papers favorable outcomes were defined as those that were favorable to the sponsor's product and in others favorable to the test treatment. This difference in terminology did not matter when the comparison was between active treatment and placebo, since the sponsor's product was the active treatment and not placebo. For head-to-head comparisons, however, the sponsor could be either the manufacturer of the test treatment or the control treatment. In these cases, when data were available, we recoded outcomes as to whether they were favorable to the sponsor's product.

We separately analyzed papers of industry sponsored head-to-head studies, comparing studies sponsored by the manufacturer of the test treatment with studies sponsored by the manufacturer of the comparator treatment. This was done by assigning the newest treatment (most recent FDA approval date) as the 'test' treatment and the older treatment as the 'comparator' treatment using similar methods as described by Bero and colleagues (Bero 2007) and comparing the number of studies favorable to the test treatment in the two groups (i.e. sponsor produces test treatment or sponsor produces comparator treatment).

At the time many of the papers were published, the approach was to assess the methodological quality of studies as opposed to an assessment of the risk of bias of studies. We therefore recoded the data on methodological quality into 'Risk of bias' categories. So, for example, a trial with adequate concealment of allocation was coded as low risk of bias and a trial with inadequate concealment of allocation as high risk of bias. Some papers assessed risk of bias by summarizing results for individual domains into an overall methodological quality score (i.e. a scale approach). There are substantial methodological problems related to quality scales (Jüni 1999), and their use is not recommended. We therefore did not combine the results obtained with these scales, but report the results descriptively. The included papers assessed blinding using different approaches. Some papers rated blinding for the study overall, for example whether a study used matching placebo tablets (which could be considered blinded) and some papers assessed who was blinded, similar to the Cochrane 'Risk of bias' tool. The Cochrane 'Risk of bias' tool assesses blinding to protect against performance bias (e.g. clinicians or patients are blinded) and to protect against detection bias (e.g. outcome assessors are blinded). We therefore categorized each 'Risk of bias' assessment into the items blinding-overall, blinding-performance bias and blinding-detection bias.

Dealing with missing data

We contacted authors of the original papers in an attempt to obtain missing data. If papers included studies reporting conflicts of interest, but not the source of funding, we contacted the authors in order to obtain separate data for funding. In total, we contacted authors of eight papers included in this update and received additional data for five of these papers.

Assessment of heterogeneity

We assessed heterogeneity using I^2. We defined substantial statistical heterogeneity as an $I^2 > 50\%$ (Higgins 2011a).

Data synthesis

We used Review Manager (RevMan 2014) to analyze data. For dichotomous data we used the Mantel-Haenszel random-effects model to create a pooled RR. In the previous version of this review (Lundh 2012), we used a fixed-effect model as default and a random-effects model when substantial heterogeneity was observed. However, due to the large clinical heterogeneity between papers (e.g. study domains, study designs and definition of outcomes), we decided that a random-effects model was more appropriate.

Subgroup analysis and investigation of heterogeneity

We considered the following factors as potential explanations for heterogeneity and investigated them in separate subgroup analyses for our primary outcomes.

- We hypothesized that the association of industry sponsorship and favorable outcomes may be larger in high risk of bias papers. We assessed overall risk of bias of the included papers using the criteria described in 'Assessment of risk of bias in included studies'. We regarded papers with adequate study inclusion, a comprehensive search and controlling for bias as having a low risk of bias; others as having a high risk. We compared low risk of bias papers with high risk of bias papers in a subgroup analysis.
- We compared papers of drug studies with device studies, as the mechanisms of influencing study outcomes may differ between the industries. For example, drug trials are more regulated than device trials, which could have an influence on biases in the design, conduct and reporting of the trials. We compared this in a subgroup analysis.
- As the study domain might contribute to heterogeneity, we compared papers on specific treatments or diseases with papers of mixed domains in another subgroup analysis.

Sensitivity analysis

We undertook the following sensitivity analyses to test the robustness of our findings for our primary outcomes.

- The primary analyses compared the number of favorable results and conclusions in papers with industry sponsorship to those with other sources of sponsorship; 'industry sponsorship' included 100% pharmaceutical/device company funding, mixed funding and provision of drug or device only. 'Non-industry sponsorship' included 100% government funding, 100% non-industry funding and undisclosed funding. In a sensitivity analysis, we excluded those studies with mixed funding sources and those with funding consisting solely of free product from the 'industry sponsorship' category, and excluded studies with undisclosed funding from the category of 'non-industry sponsorship', to determine if these had an impact on the initial analysis. As noted under 'Data extraction and management', we were reliant on how the studies in our review defined 'funding'.
- A sensitivity analysis restricted to papers that adjusted for confounders (e.g. adjusted for sample size and concealment of allocation using logistic regression) using adjusted estimates. We used the generic inverse variance method to pool adjusted odds ratios in a random-effects model.
- A sensitivity analysis where all analyses were based on a fixed-effect model.
- One paper (Finucane 2004), included unpublished abstracts from conference proceedings. One paper (Lynch 2007), included manuscripts submitted to a medical journal of which the majority were never published. However, based on the reported data it was not possible to extract data from the published studies separately. As these two papers included unpublished data and we planned to analyze only published data, we conducted a sensitivity analysis that excluded these two papers.
- Many of the included papers investigated similar domains (e.g. antidepressants or oncology drugs) or included studies from similar journals in overlapping time-periods. This is likely to lead to double counting if data from the same studies are included more than once and to an overestimate of the precision of effect estimates. Due to the way data were reported in the papers, it was not possible ensure that data was not double counted. Instead we performed a sensitivity analysis restricted to papers on specific treatments or diseases where none of the other included papers were related to the same domain.
- We included letters and conference abstracts reporting quantitative data in a sensitivity analysis.

Quality of Evidence

We created a 'Summary of findings' table using the GRADE approach (Higgins 2011a) and using the MAGICapp software (MAGICapp; Vandvik 2013).

RESULTS

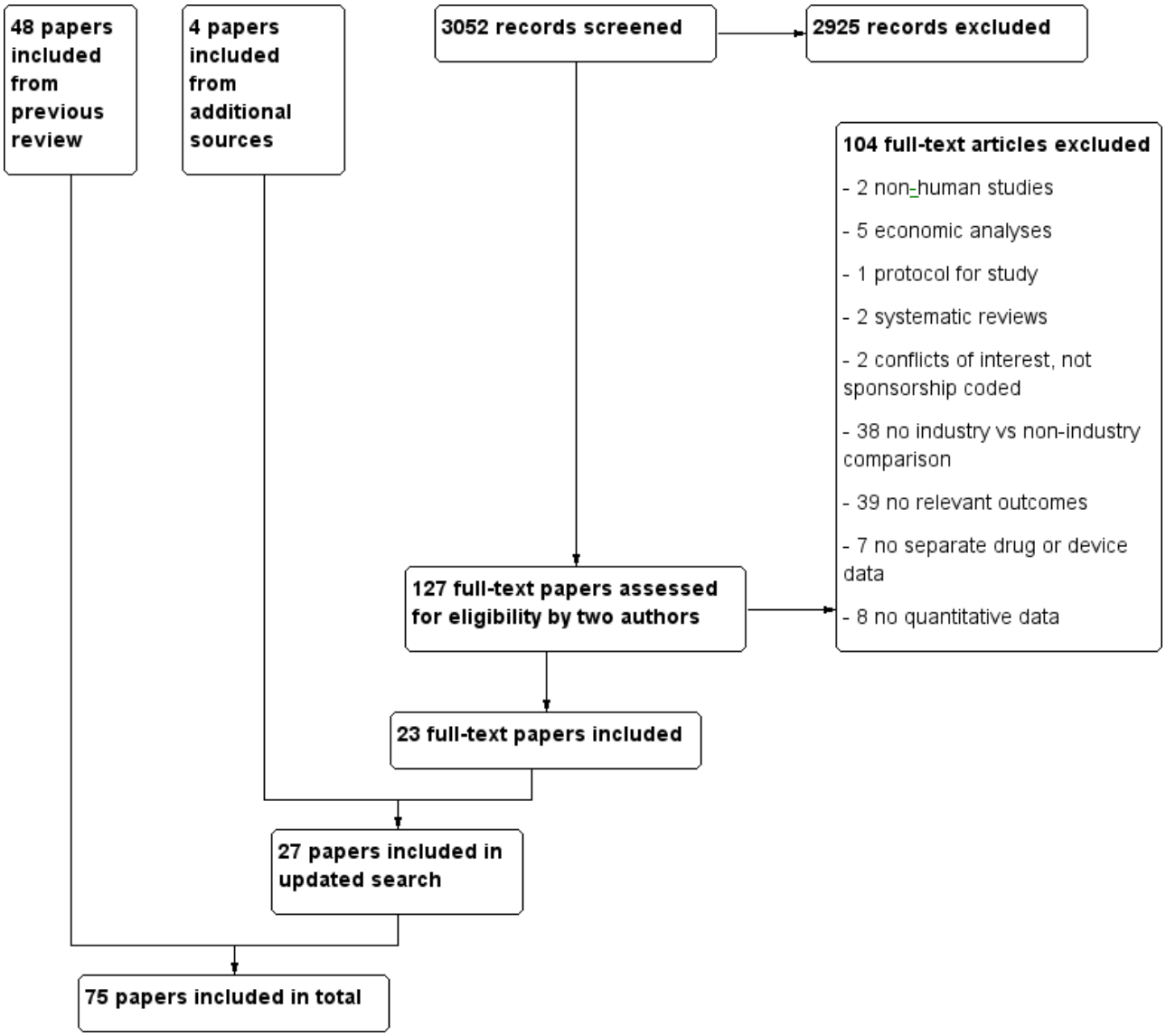
Description of studies

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

Results of the search

See: Figure 1.

Figure 1. Study flow diagram.



After removal of duplicates, 3052 references were identified. From reading titles and abstracts, 2925 were eliminated as being not relevant to the review. Full-text papers were obtained for 127 references. From these 127 papers, 104 papers were excluded (see Characteristics of excluded studies) and 23 included (see Characteristics of included studies). Four additional papers were included from searching additional sources and 48 were included from the previous version of the review (see Characteristics of included studies). In total, 75 papers were included.

Included studies

See: Characteristics of included studies.

The 75 papers were published between 1986 and 2015. Seventy-two papers included mainly published studies, one included studies presented at a conference, one included studies submitted to a medical journal, and one included studies submitted to eight medical journals. Fifty-seven papers included only drug studies, three only device studies, two drug and device studies and 13 included different types of interventions (e.g. drugs, devices, behavioral interventions). Thirty-four papers included studies related to specific drug classes, 16 related to specific medical specialties or types of diseases (e.g. endocrinology), 10 related to a specific disease, three related to a specific type of device, 11 included all types of research studies, and one did not state the domain. Various aspects of medicine were covered, but 16 (21%) papers were restricted to psychiatric diseases or drugs and eight (11%) to cancer treatment. Fifty-eight papers included only clinical trials, two only observational studies, and 15 both clinical trials and observational studies. Thirteen papers included only drug versus drug comparisons, eight only drug versus placebo, 49 mixed comparisons (e.g. drug versus drug, drug versus placebo) and five did not describe the kind of comparisons. The median number of included studies per paper was 105 (range: nine to 930). Of the 75 papers, 27 reported data on both favorable outcomes and risk of bias, 44 on favorable outcomes only, and four on risk of bias only. Twenty-five papers were non-industry funded, two were industry funded (Freemantle 2000; van Lent 2014), one was funded by both

industry and non-industry sources (Lynch 2007), 17 reported that they did not receive funding and 30 did not reported on funding.

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 papers.

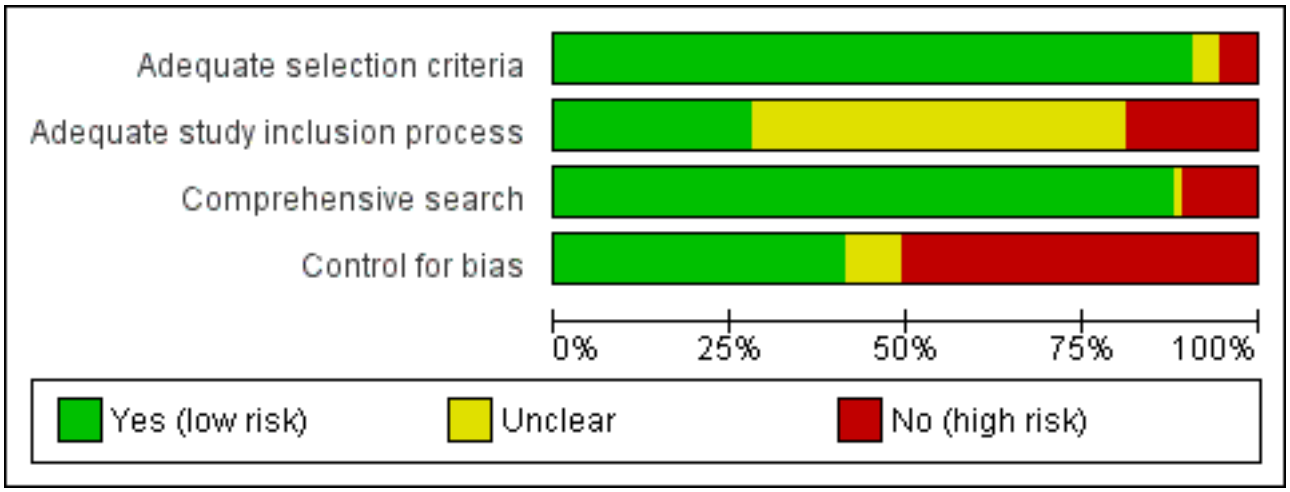


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included paper.

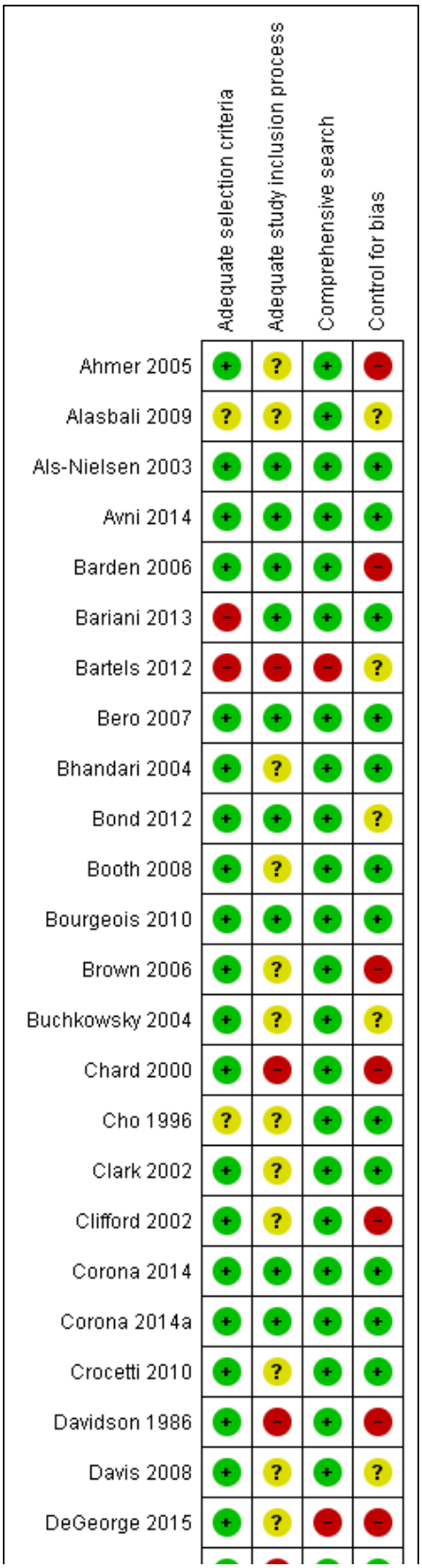


Figure 3. (Continued)

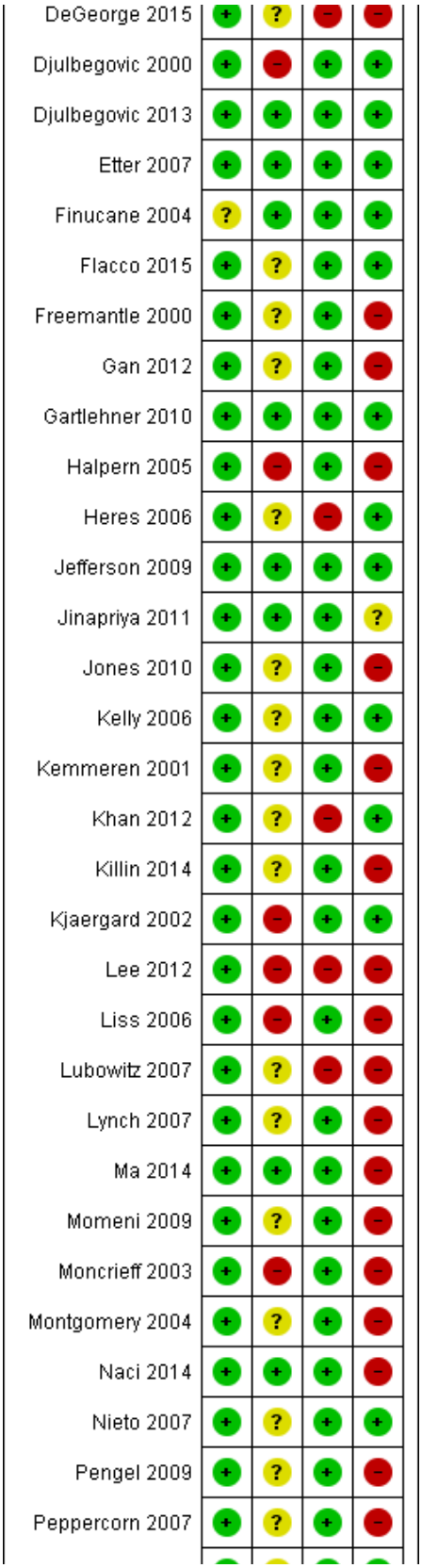
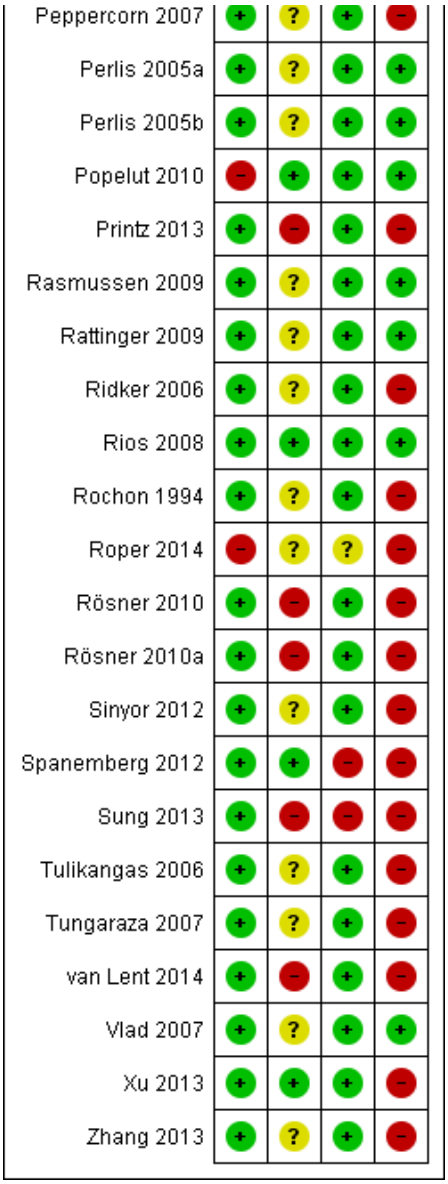


Figure 3. (Continued)



Sixty-eight papers had low risk of bias for the selection criteria for inclusion of studies, three were unclear and four had high risk. Twenty-one papers had low risk of bias for the study inclusion process, 40 were unclear and 14 had high risk. Sixty-six papers had low risk of bias from the search, one was unclear and eight had high risk. Thirty-one papers had low risk of bias due to lack of control for bias in the studies, five were unclear and 39 had high risk. Fourteen papers were regarded as having an overall low risk of bias and 61 as a high risk of bias according to our criteria.

Effect of methods

See: **Summary of findings for the main comparison** Industry sponsored compared to non-industry sponsored studies for research outcome

Favorable results: industry sponsored versus non-industry sponsored studies

See: Summary of findings for the main comparison

Twenty-six papers, including 3081 studies (3062 drug studies and 19 device studies), reported on sponsorship and efficacy results; 25 could be combined in a pooled analysis. An analysis based on these 25 papers, including 2923 studies, found that industry sponsored studies more often had favorable efficacy results (e.g. those with significant P values) compared with non-industry sponsored studies, risk ratio (RR): 1.27 (95% confidence interval (CI): 1.17 to 1.37), I^2: 28% (Analysis 1.1). The paper that could not be included in the pooled analysis (Bhandari 2004), which had included 158 drug studies in general medicine, found similar results, odds ratio (OR): 1.6 (95% CI: 1.1 to 2.8).

Four papers, including 826 studies, did not find a difference in favorable harms results in industry sponsored studies compared

with non-industry sponsored studies, RR: 1.37 (95% CI: 0.64 to 2.93), I^2: 96%. (Analysis 1.2). The results of one paper (Als-Nielsen 2003), were opposite in direction to the other papers and resulted in the substantial heterogeneity. .

Favorable results: industry sponsorship by test treatment company versus industry sponsorship by comparator treatment company

Three papers, including 151 studies (all drug trials), compared efficacy results of trials sponsored by the manufacturer of the test treatment with trials sponsored by the manufacturer of the comparator treatment; two could be combined in a pooled analysis. An analysis based on these two papers (Bero 2007; Rattinger 2009), which included 131 industry sponsored trials of statins and thiazolidinediones, found that trials were much more likely to favor the test treatment when they were sponsored by the manufacturer of the test treatment than when they were sponsored by the manufacturer of the comparator treatment, RR: 3.88 (95% CI: 1.26 to 11.94), I^2: 50% (Analysis 2.1). The paper that could not be included in the pooled analysis, which had included 20 selective serotonin reuptake inhibitor head-to-head trials, found that two trials favored the sponsor's drug, 18 had similar efficacy and none favored the comparator drug (Gartlehner 2010).

Favorable conclusions: industry sponsored versus non-industry sponsored studies

See: Summary of findings for the main comparison

Thirty-two papers, including 5258 studies (4761 drug studies and 497 device studies), reported on sponsorship and conclusions, 29 of which could be combined in a pooled analysis. An analysis based on these 29 papers, including 4583 studies (4179 drug studies and 404 device studies), found that industry sponsored studies more often had favorable conclusions than non-industry sponsored studies, RR: 1.34 (95% CI: 1.19 to 1.51), I^2: 92% (Analysis 3.1). Three papers could not be included in the pooled analysis due to the reporting of data. Of these, one paper reporting on 301 psychiatric drug studies (Kelly 2006) found that industry sponsored studies more often had favorable conclusions than non-industry sponsored studies (P < 0.001) and similar findings were reported in a paper of 59 trials of antipsychotics (P = 0.02) (Montgomery 2004). A paper on 315 gastroenterology trials (222 drug trials and 93 device trials) did not find a difference in conclusions between industry sponsored trials and non-industry sponsored trials (industry: 86% favorable, non-industry: 83% favorable; P = 0.57) (Brown 2006).

Favorable conclusions: industry sponsorship by test treatment company versus sponsorship by comparator treatment company

Five papers, including 348 drug trials, compared conclusions of studies sponsored by the manufacturer of the test treatment with studies sponsored by the manufacturer of the comparator treatment, and three could be combined in a pooled analysis. These three papers (Bero 2007; Heres 2006; Rattinger 2009) including 154 industry sponsored trials of statins, antipsychotics and thiazolidinediones, found that trials were much more likely to favor the test treatment when they were sponsored by the manufacturer of the test treatment than when they were sponsored by the manufacturer of the control treatment, RR: 5.92 (95% CI: 2.80 to 12.54). No heterogeneity was observed (Analysis 4.1). A paper including 138 psychiatric drug studies (Kelly 2006) had similar findings, RR 2.80 (95% CI: 2.02 to 3.88), and a paper on 56 non-steroidal anti-inflammatory drug (NSAID) trials (Rochon 1994), found that 16 trials favored the sponsor's drug, 40 concluded that the drugs had similar effect and none favored the comparator drug.

Effect size: industry sponsored versus non-industry sponsored studies

Twenty-four papers, including 1517 studies (1476 drug studies and 41 device studies), reported on sponsorship and effect size, but could not be pooled due to differences in reporting of data. The results were heterogeneous and are described in Table 1 below.

Table 1. Effect size in industry and non-industry sponsored studies.

Paper ID	Study domain	Effect size of industry versus non-industry studies
Efficacy		
Als-Nielsen 2003	370 drug RCTs in Cochrane reviews	Primary outcome. Mean z-scores: industry: -1.48 (95% CI: -1.77 to -1.19); mixed: -1.77 (95% CI: -2.28 to -1.26); non-industry: -1.20 (95% CI: -1.81 to -0.59); not stated: -1.20 (95% CI: -1,49 to -0.91) (P > 0.05).
Avni 2014	36 RCTs of antibiotics for pneumonia	No difference in mortality and clinical failure.
Barden 2006	176 acute pain and migraine drug RCTs	No difference in pain relief.
Clark 2002	19 RCTs of erythropoietin for cancer-related anemia	Number of transfusions: industry: OR: 0.43 (95% CI: 0.35 to 0.54); non-industry OR: 0.22 (95% CI: 0.11 to 0.45).
Corona 2014a	25 RCTs of testosterone for male sexual dysfunction	Erectile dysfunction. Standardized mean difference (SMD): industry: SMD: 1.36 (95% CI: 0.55 to 1.16); non-industry: SMD: 0.33 (95% CI: 0.13 to 0.54) (P = 0.02).

Davis 2008	124 RCTs of 2nd generation versus 1st generation antipsychotics	Effect on psychotic symptoms (P = 0.57).
Djulbegovic 2013	126 oncology drug RCTs	Primary outcome: industry: OR/hazard ratio (HR): 0.61 (99% CI: 0.47 to 0.78); non-industry OR/HR: 0.86 (99% CI: 0.74 to 1.00) (P = 0.003). Overall survival (P = 1.00).
Etter 2007	34 RCTs of nicotine replacement therapy	Effect: industry: OR: 1.90 (95% CI: 1.67 to 2.16); non-industry: OR: 1.61 (95% CI: 1.43 to 1.80) (P = 0.06).
Freemantle 2000	105 RCTs of selective serotonin reuptake inhibitors versus alternative antidepressants	No difference in effect.
Jinapriya 2011	31 of prostaglandin analogues for open-angle glaucoma	Effect on intraocular pressure (P = 0.83).
Killin 2014	14 RCTs of donepezil for Alzheimer's disease	Effect on cognitive scales: industry: SMD: 0.46 (95% CI: 0.38 to 0.54); non-industry: SMD: 0.33 (95% CI: 0.18 to 0.48) (P = 0.13).
Lubowitz 2007	23 studies of chondrocyte implantation	No difference in effect on various outcomes.
Moncrieff 2003	9 RCTs of clozapine versus conventional antipsychotics	Psychotic symptoms: industry: SMD: -0.83 (95% CI: -1.06 to -0.61); non-industry: SMD: -0.21 (95% CI: -0.34 to -0.07) (P < 0.001).
Naci 2014	183 statin RCTs	No difference in effect on mean change in LDL levels, after controlling for statin dose.
Popelut 2010	41 clinical studies of dental implants	Failure rates. Industry versus non-industry: OR: 0.21 (95% CI: 0.12 to 0.38).
Rösner 2010	24 RCTs of acamprosate for alcohol dependence	Return to any drinking: industry: RR: 0.88 (95% CI: 0.80 to 0.97); mixed: RR: 0.84 (95% CI: 0.78 to 0.89); non-industry: RR: 0.86 (95%: CI 0.81 to 0.91).
Rösner 2010a	26 RCTs of opioid antagonists for alcohol dependence	Return to any drinking: industry: RR: 0.90 (95% CI: 0.78 to 1.05); non-industry: RR: 0.84 (95% CI: 0.77 to 0.91).
Vlad 2007	15 RCTs of glucosamine for osteoarthritis	Primary outcome: industry: SMD: 0.47 (95% CI: 0.24 to 0.70); non-industry: SMD: 0.05 (95% CI: -0.32 to 0.41) (P = 0.05).
Zhang 2013	12 RCTs of 2nd generation versus 1st generation antipsychotics	Short-term symptom reduction and response (P = 0.007 and P = 0.046).
Harms		
Corona 2014	26 RCTs of testosterone therapy for men	Cardiovascular events: industry: OR: 1.07 (95% CI: 0.54 to 2.24); non-industry: OR: 0.94 (95% CI: 0.39 to 2.24).
Kemmeren 2001	9 observational studies of 3rd generation versus 2nd generation oral contraceptives	Thrombosis: industry: OR: 1.3 (95% CI: 1.0 to 1.7); non-industry: OR 2.3 (95% CI: 1.7 to 3.2).
Ma 2014	4 RCTs of fluoxetine for major depressive disorder	Harms: industry: OR: 2.34 (95% CI: 1.62 to 3.36); non-industry: OR: 2.78 (95% CI:1.76 to 4.38).

Xu 2013	27 RCTs of testosterone therapy for men	Cardiovascular events: industry: OR 0.89 (95%: CI 0.50 to 1.60); non-industry: OR 2.06 (95% CI: 1.34 to 3.17) (P = 0.03).
Efficacy and dosage		
Sinyor 2012	58 industry head-to-head RCTs of antidepressants	Remission: sponsor's drug at higher dose OR: 1.28 (95% CI: 1.11 to 1.47) versus sponsor's drug at comparable or lower dose OR: 1.06 (95% CI: 0.96 to 1.17) (P = 0.04).

Most papers (19 out of 24) compared effect sizes for efficacy results. Twelve of these papers, including 1131 drug studies, did not find a difference in effect sizes for efficacy estimates between industry sponsored studies and non-industry sponsored studies. In contrast, seven papers, including 262 studies (221 drug studies and 41 device studies) found higher effect sizes of efficacy estimates in industry sponsored studies. Two papers, including 30 drug studies, did not find a difference in effect size of harms between industry sponsored studies and non-industry sponsored studies. In contrast, two papers, including 36 drug studies, found lower effect size of harms in industry sponsored studies. Lastly, a paper on 58 industry-sponsored head-to-head trials of antidepressants (Sinyor 2012), found that the sponsor's antidepressants were often given at a higher dose than the comparator. Effects on remission were higher when the sponsor's drug was given at a higher dose, as compared to trials in which the sponsor's drug was given in comparable or lower dose OR: 1.28 (95% CI: 1.11 to 1.47) versus OR: 1.06 (95% CI: 0.96 to 1.17) (P = 0.04).

Risk of bias: industry sponsored versus non-industry sponsored studies

Twelve papers, including 1660 studies (1482 drug studies and 178 device studies), compared risk of bias in industry versus non-industry studies using six different composite quality scales (Brown, Cho, Cochrane, Jadad, PEDro or Sackett) and the results were heterogeneous. Seven papers did not find a difference in risk of bias between industry sponsored and non-industry sponsored studies (Cho 1996; Clark 2002; Corona 2014; Jefferson 2009; Lynch 2007; Sung 2013; Vlad 2007), whereas five papers found lower risk of bias (i.e. higher methodological quality scores) in industry sponsored studies (Brown 2006; Djulbegovic 2000; Montgomery 2004; Pengel 2009; Perlis 2005a).

Nine papers, including 913 drug trials, did not find a difference in risk of bias from sequence generation in industry sponsored trials compared with non-industry sponsored trials, RR: 0.99 (95% CI: 0.78 to 1.27), I^2: 73% (Analysis 5.1). Sixteen papers, including 1886 trials (1867 drug trials and 19 device trials), did not find a difference in risk of bias from concealment of allocation in industry sponsored trials compared with non-industry sponsored trials, RR: 1.06 (95% CI: 0.85 to 1.31), I^2: 71% (Analysis 5.2). Thirteen papers, including 1578 trials (1559 drug trials and 19 device trials), found that industry sponsored trials more often had low risk of bias from overall blinding compared with non-industry sponsored trials, RR: 1.25 (95% CI: 1.05 to 1.50), I^2: 72% (Analysis 5.3). Three papers, including 128 drug trials, did not find a difference in risk of performance bias (e.g. blinding of clinicians or patients) in industry sponsored trials compared with non-industry sponsored trials, RR: 1.26 (95% CI: 0.60 to 2.62), I^2: 66% (Analysis 5.4). Four papers, including 307 drug trials, found that industry sponsored trials more often had low risk of detection bias (e.g. blinding of outcome assessors) compared with non-industry sponsored trials, RR: 1.47 (95% CI: 1.02 to 2.12). No heterogeneity was observed (Analysis 5.5). Six papers, including 416 drug trials, did not find a difference in risk of bias from loss to follow-up in industry sponsored trials compared with non-industry sponsored trials, RR: 1.05 (95% CI: 0.92 to 1.18), I^2: 2% (Analysis 5.6). Two papers, including 193 drug trials, did not find a difference in risk of reporting bias in industry sponsored trials compared with non-industry sponsored trials, RR: 1.49 (95% CI: 0.61 to 3.60), I^2: 79% (Analysis 5.7).

Concordance between study results and conclusions: industry sponsored versus non-industry sponsored studies

Six papers, including 751 drug studies, reported on concordance between study efficacy results (e.g. as judged by their P values) and conclusions. Industry sponsored studies were less concordant than non-industry sponsored studies, RR: 0.83 (95% CI: 0.70 to 0.98), I^2: 63% (Analysis 6.1). One paper (Alasbali 2009), including 39 drug studies, found markedly higher lack of concordance in industry studies than the other four papers, and this was the reason for the high heterogeneity between papers.

One paper, of 211 corticosteroid studies with statistically significant harms results, found that industry sponsored studies more often concluded that the drug was safe than non-industry sponsored studies, RR: 3.68 (95% CI: 2.14 to 6.33) (Nieto 2007).

Subgroup analysis and investigation of heterogeneity

For efficacy results, the association between industry sponsorship and favorable results was stronger in papers with a low risk of bias than in those with a high risk of bias, RR: 1.46 (95% CI: 1.25 to 1.71) versus RR: 1.20 (95% CI: 1.11 to 1.30) (test for subgroup differences P = 0.03) (Analysis 7.1). For harms results, the association between industry sponsorship and favorable harms results differed in papers with a low risk of bias compared with those with a high risk of bias, RR: 0.82 (95%: 0.72 to 0.93) versus RR: 1.87 (95% CI: 1.54 to 2.27) (test for subgroup differences P < 0.0001) (Analysis 7.2). For conclusions, the differences between the groups went in the same direction as for efficacy results, RR: 1.42 (95% CI: 1.12 to 1.79) versus RR: 1.32 (95% CI: 1.15 to 1.50) (test for subgroup differences P = 0.60) (Analysis 7.3).

For efficacy results, the association between industry sponsorship and favorable results were opposite in direction in drug studies compared with device studies, RR: 1.27 (95% CI: 1.17 to 1.38) versus RR: 0.50 (95% CI: 0.26 to 0.97) (test for subgroup differences P = 0.006) (Analysis 7.4). However, the analysis only included 19 device studies, of which only three were non-industry. We did not find a difference in the association between sponsorship and conclusions in drug studies compared with device studies

(test for subgroup differences P = 0.98) (Analysis 7.5) or between sponsorship and efficacy results or conclusion in studies limited to specific treatments or diseases compared with studies of mixed domains (test for subgroup differences P = 0.67 and P = 0.49) (Analysis 7.6; Analysis 7.8). However, for harms results the association between industry sponsorship and favorable harms results differed in papers with mixed study domain compared with those of specific treatments or diseases, RR: 0.82 (95%: 0.72 to 0.93) versus RR: 1.87 (95% CI: 1.54 to 2.27) (test for subgroup differences P < 0.0001) (Analysis 7.7).

Sensitivity analysis

Our re-analyses of the outcomes using variations in definition of sponsorship categories gave similar results as our main analyses for efficacy results, harms results and conclusions (Analysis 8.1; Analysis 8.2; Analysis 8.3). Our analyses, taking into account papers that adjusted for confounding, based on pooling adjusted odds ratios, confirmed our findings that industry sponsored trials compared with non-industry sponsored trials more often had favorable results, OR: 3.15 (95% CI: 2.07 to 4.80), I^2: 0% and favorable conclusions, OR: 3.13 (95% CI: 1.66 to 5.93), I^2: 38% (Analysis 8.4; Analysis 8.5). Similarly, sensitivity analyses using a fixed-effect model rather than a random-effects model did not affect our results (Analysis 8.6; Analysis 8.8; Analysis 8.9; Analysis 8.10), except for harms results where they changed from RR: 1.37 (95% CI: 0.64 to 2.93) to RR: 1.29 (95% CI: 1.15 to 1.46) (Analysis 8.7). When we excluded papers sampling unpublished studies, it did not affect our analysis on favorable conclusions (Analysis 8.11). The same was found when we limited our analyses to papers from specific domains (i.e. papers on specific treatments or diseases where none of the other included papers were related to the same domain) (Analysis 8.12; ; Analysis 8.14; Analysis 8.15; Analysis 8.16), except for harms results where they changed from RR: 1.37 (95% CI: 0.64 to 2.93) to RR: 1.87 (95% CI: 1.54 to 2.27) (Analysis 8.13). Lastly, if we included the two additional papers that were only published as letters (Mandelkern 1999; Thomas 2002) our analysis on the association between sponsorship and favorable conclusions gave similar results RR: 1.35 (95% CI: 1.20 to 1.52), I^2: 91%.

DISCUSSION

Summary of main results

We found that drug and device studies sponsored by the manufacturing company more often had favorable efficacy results (e.g. those with statistically significant results, usually defined using P values) and conclusions than those that were sponsored by other sources. The findings were consistent across a wide range of diseases and treatments. We did not find any differences in harms results and risk of bias of drug and device trials sponsored by industry compared with non-industry sponsored trials, except in relation to blinding, where industry sponsored trials seemed to have lower risk of bias. Industry sponsored studies also had less concordance between results and conclusions than non-industry sponsored studies. The evidence from device studies was limited due to fewer data, but the association between sponsorship and favorable conclusions was similar to drug studies.

Reasons for observed heterogeneity

For the association between sponsorship and favorable efficacy results of drug and device studies the data had acceptable heterogeneity, but heterogeneity for the association between sponsorship and harms results and study conclusions was substantial with an I^2 of 96% and 92%, respectively.

The reason for the large heterogeneity related to harms results is attributed to the results of the Als-Nielsen paper (Als-Nielsen 2003), that was opposite in direction to the other papers (i.e. industry had less favorable harms results as opposed to more favorable harms results) (Halpern 2005; Kemmeren 2001; Nieto 2007), and the interaction tests in the subgroup analyses were statistically significant. The Als-Nielsen paper differs in some aspects from the three other included papers. First, it samples trials from various therapeutic areas, whereas the other papers each deal with harms results of single-drug classes (HIV drugs, oral contraceptives and inhaled corticosteroids). Second, the three papers related to single-drug classes had harms results as their primary outcome and only included studies with quantitative data, but Als-Nielsen had harms as a secondary outcome and also included trials without quantitative harms data. The number of trials without harms data was high, particularly in the non-industry group, 28% and 52%, respectively. Third, Als-Nielsen only included trials, whereas Halpern 2005 included both trials and observational studies and Kemmeren 2001 and Nieto 2007 only included observational studies. Finally, we assessed Als-Nielsen 2003 as having an overall low risk of bias, compared to high risk of bias in the other three papers.

In relation to the substantial heterogeneity for study conclusions, one reason was likely that the coding of favorable results was similar across the different papers, using statistical significance as the cut-off, but coding varied for favorable conclusions. Some papers did not describe what they considered a favorable conclusion and this would involve some judgement. Others used scales, but for similar scales the cut-off varied between papers. For example, on the same six-point scale one paper used four as the cut-off (Djulbegovic 2000) and another used six as the cut-off (Als-Nielsen 2003).

Also, the proportion of studies with favorable conclusions in the non-industry sponsored group might have contributed to the size of the association and thereby the heterogeneity. For example, while the Chard and Liss papers (Chard 2000; Liss 2006) had a similar proportion of favorable industry sponsored studies (both 98%), they reported very different proportions of favorable non-industry sponsored studies (32% and 97%) and this explains why the risk ratios reported in the two studies were not the same: RR: 3.03 in Liss and RR: 1.01 in Chard. Variations in the definition of favorable conclusions might explain why the risk ratios reported in the two papers were not similar. For example, in the Chard paper, a conclusion was coded as favorable if the study authors supported the use of the treatment, even in the absence of a statistically significant result.

Our subgroup analyses stratifying papers in relation to risk of bias (low versus high), type of intervention (drug versus device) or study domain (mixed versus specific treatments or diseases) did not explain the observed heterogeneity, though this was a simplistic comparison and other factors might also contribute to heterogeneity.

We found mixed results on the relationship between sponsorship and effect size, with most papers not finding a difference. All but one of these papers were restricted to specific treatments, which

may explain the different findings. A recent study of systematic reviews of nine different drugs found that the influence of reporting biases on effect sizes varied considerably between drugs (Hart 2012). Furthermore, one paper found that even when adjusting for effect size, industry sponsored studies more often had favorable conclusions, compared with non-industry sponsored studies (Als-Nielsen 2003). Therefore, while the direction of the relationship between sponsorship and favorable outcomes was consistent, the size of the effect likely varies depending on the type of treatment or treated condition.

Reasons for favorable outcomes in industry sponsored studies

The pharmaceutical and medical device industries have strong interests in scientific publications that present their products positively, as publications are the basis of regulatory, purchasing, and medical decisions. These interests can influence the design, conduct and publication of studies in ways that make the sponsor's product appear better than the comparator product (Bero 1996).

Several possible factors can explain the relationship between industry sponsorship and favorable outcomes. It has been argued that since many industry sponsored studies are undertaken to fulfill regulatory requirements, industry sponsored studies could have a lower risk of bias than non-industry sponsored studies (Rosefsky 2003). Even if this were true, it would not explain the association of industry sponsorship and favorable efficacy results and conclusions. In addition, we did not find evidence for differences in risk of bias except in relation to blinding, where industry sponsored trials tended to have a lower risk of bias, even when restricted to head-to-head trials (Bero 2007). The papers comparing blinding between trials with different sponsorship often used a description of double blinding as an indicator for low risk of bias. Double blinding is an inconsistent term and does not ensure that, for example, outcome assessors are blinded (Devereaux 2001). The more frequent use of double blinding may therefore be a reporting issue, with industry trials being better reported. This is further substantiated by the fact that nearly all the papers finding a higher methodological quality score in industry studies used the Jadad scale, a scale which has been criticized for having more focus on the quality of reporting than on methodological quality (Lundh 2008).

A few papers assessing a more specific definition of blinding related to performance bias and detection bias also found that industry sponsored studies had lower risk of bias. Evidence also suggests that for non-industry trials, companies may prevent proper blinding by restricting access to placebo drugs (Christensen 2012), and therefore differences in adequate blinding may be real. In addition, double blinding can be used as a proxy for low risk of bias and trials without double blinding are on average more likely to have favorable results (Pildal 2007). The effect of this bias is in the opposite direction of our findings, as it would lead to industry sponsored studies having less favorable results and conclusions, and our findings can therefore, not be explained by differences in risk of bias related to blinding between industry and non-industry sponsored studies.

Another possible explanation for our findings could be that industry studies have larger sample sizes, and would have a higher chance of achieving statistically significant results. Although industry trials seem in general to be of larger size (Als-Nielsen 2003; Booth 2008; Bourgeois 2010; Djulbegovic 2013; Etter 2007; Flacco 2015; Perlis 2005a), when we restricted our analysis to studies controlling for sample size and other confounders, the relationship between industry sponsorship and favorable results or conclusions was still present.

Industry representatives argues that the trials they sponsor are more likely to have favorable outcomes because they fund research that has a high chance of achieving success (Palmer 2003). However, when independent investigators conduct non-industry sponsored trials, they in most cases test treatments that have been approved based on favorable industry trial results. Non-industry sponsored trials would therefore also be expected to achieve successful results, unless they are designed to answer different questions than industry sponsored trials. For example, non-industry sponsored studies may test a new treatment against a well-established treatment, while industry sponsored studies might test the new treatment against placebo or against an outdated, inferior treatment.

Accordingly, it seems most plausible that industry achieves overly positive results through a variety of biasing choices in the design, conduct and reporting of their studies. For example, industry protocols might include inferior comparators that will increase the chance of their product's success. Djulbegovic and colleagues (Djulbegovic 2003) have argued that industry sponsored studies violate equipoise by choosing inferior competing treatment alternatives. Previous studies have found that industry sponsored trials more often use placebo control (Als-Nielsen 2003; Djulbegovic 2000; Dunn 2013; Estellat 2012; Katz 2006; Lathyris 2010), active comparators in inferior doses (Rochon 1994; Safer 2002; Sinyor 2012), or inappropriate administration of the drugs (Johansen 1999). Industry may also selectively choose less clinical relevant outcomes as their primary outcome in order to get a higher chance of achieving an effect. For example, in the paper by Djulbegovic (Djulbegovic 2013) industry sponsored trials had higher effect size than non-industry sponsored trials on primary outcomes, but not overall survival. This could also be one of the possible explanations as to why industry sponsored trials more often have favorable results and conclusions while the effect sizes are often similar when comparing similar outcomes.

Industry sponsored studies may also be biased in the coding of events and their data analysis (Furukawa 2004; Psaty 2008; Psaty 2010). Industry and its sponsored investigators also may selectively report favorable outcomes, fail to publish whole studies with unfavorable results, or publish studies with favorable results multiple times (Chan 2004; Dwan 2008; Gøtzsche 2011; McGauran 2010; Melander 2003; Rising 2008; Vedula 2009). While such biases in analyses and reporting have been documented in a number of cases, the papers included in this review focused on comparisons of published studies. Only two papers (Killin 2014; Naci 2014) included in our review compared risk of selective reporting between industry sponsored trials and non-industry sponsored trials and found no difference. However, confidence intervals were wide and the analysis was limited to two types of drugs (donepezil for Alzheimer's disease and statins). Therefore, we are unable to determine the extent to which selective analysis or reporting contribute to our findings. Similarly, we found no difference in harms results between industry sponsored and non-industry sponsored studies. Under-reporting of harms seems to be a major problem in both industry and non-industry sponsored studies with 28% of trials included in Als-Nielsen 2003 not reporting

any harms data, which is in line with a recent systematic review that found that a median of 54% studies do not report harms data (Golder 2016).

Favorable conclusions in industry-sponsored trials may also be reached by over-interpreting results and use of spin in conclusions (Boutron 2010). We found that industry sponsored studies had less concordance between results and conclusions compared with non-industry sponsored studies, suggesting that conclusions of industry sponsored studies are less reliable.

It should also be noted that some studies in the non-industry group likely had authors with conflicts of interest related to the pharmaceutical or device industry, which may have influenced their interpretation of study results (Stelfox 1998; Wang 2010), thereby diluting the measured effect of industry bias on study conclusions. Also, we coded studies as non-industry sponsored if they did not state who sponsored the study. As some of these studies were likely industry sponsored, this misclassification will have led to similar bias towards the null. However, in our sensitivity analyses, we excluded studies without sponsorship statements and did not see a change in results.

Further evidence for industry bias stems from our comparison of studies sponsored by the manufacturer of the test treatment with those sponsored by the manufacturer of the control treatment. These studies had the advantage of comparing like with like, as they are restricted to specific drug classes or types of devices and have similar methodologies. Though limited to only three papers on drug trials, the findings show associations that are stronger than the comparison between industry and non-industry sponsored studies. These comparisons are restricted to drugs competing for the same market, which may put pressure on companies to influence outcomes to a greater degree than what is needed in placebo-controlled trials to present the drug in a good light.

In sum, the industry bias associated with favorable efficacy results and conclusions may be mediated by factors other than traditional measures of the risk of bias (e.g. lack of concealment of allocation, blinding and dropout) and sample size. This industry bias may be partially mediated by such factors as the choice of comparators, dosing and timing of comparisons, choice of outcomes, selective analysis, and selective reporting.

Quality of the evidence

The majority of included papers were regarded as having a high risk of bias. Many lacked information on study conduct and did not control for confounders that could influence the relationship. Nevertheless, we did identify 14 papers with low risk of bias and analyses restricted to these papers actually strengthened the relationship between industry sponsorship and conclusions. In general, there is convincing and consistent evidence for the existence of an industry bias in studies; however, the body of evidence for device studies is not as strong as for drug studies. While many papers, including studies of devices and other interventions, have been published in the surgical field (Amiri 2014; Cunningham 2007; Khan 2008; Leopold 2003; Roach 2008; Shah 2005; Sun 2013; Yao 2007), the papers do not report separate data for device studies.

Potential biases in the review process

We did a comprehensive search, our methods were based on pre-specified criteria in a protocol as outlined in *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Higgins 2011a), and this updated review has substantially increased the number of included papers from our previous review (Lundh 2012). Nevertheless, there are some limitations. First, we decided only to include published papers. In our first version of the review (Lexchin 2003), we found problems with the completeness and quality of the data in conference abstracts and unstructured letters and therefore decided not to include them in this review. A comment to the previous version of this review (Lundh 2012), suggested that the exclusion of conference abstracts and letters could have introduced publication bias. In this update, we decided to include these papers in a sensitivity analysis, which gave similar results. However, we could only include quantitative data from two papers and we might have missed relevant papers. We expect that due to the high number of included papers such unidentified papers would not have major impact on our results. Due to the heterogeneity of included papers we decided not to assess publication bias using a funnel plot as it would be difficult to interpret.

Second, our assessment of risk of bias in the included papers was not based on validated criteria similar to 'Risk of bias' assessment for clinical trials (Higgins 2011b). As no validated assessment tools exist for these type of papers, we developed our own criteria and included items similar to assessment tools for systematic reviews (Oxman 1991; Shea 2007).

Third, one item not included in our assessment of risk of bias in the papers was whether coders of outcomes were blinded to the sponsorship status of the studies. If these types of papers were undertaken by authors with a particular view on the drug industry, knowledge of sponsorship status could introduce bias in the assessment of whether outcomes were favorable, particularly for conclusions, as this is an outcome that is qualitative in nature. Some of the included papers were written by authors who had published multiple times in the area, and as such could be at increased risk of bias. These papers used coders who were both blinded and unblinded to the sponsorship status of the studies. The agreement in coding was high, suggesting a lack of bias (Als-Nielsen 2003; Bero 2007; Kjaergard 2002). Likewise, all review authors (AL, BM, JL, JS, LB) have published several times in the field and one review author (LB) is the author of four of the included papers (Bero 2007; Cho 1996; Rasmussen 2009; Rattinger 2009), which could have introduced bias. Because of the way data were presented in the papers, it was not possible to blind our data extraction process. None of the data extractors were co-authors of the included papers. Furthermore, our data extraction of outcomes did not involve any qualitative interpretation as we extracted actual numbers.

Fourth, if the papers included in this review included some of the same studies, their findings would not be independent. Furthermore, some papers included some of the same studies (Corona 2014; Xu 2013), but had different results, which could be explained by differences in inclusion criteria and data extraction. In the majority of cases, it was not possible to assess the potential overlap of studies as most papers did not provide a reference list of included studies and we rarely had access to raw data. Instead we undertook sensitivity analyses restricted to papers on specific treatments or diseases where none of the other included papers were related to that domain. The analyses gave similar results, however with wider confidence intervals.

Agreements and disagreements with other studies or reviews

Our results are in agreement with previous systematic reviews (Bekelman 2003; Lexchin 2003; Schott 2010a; Sismondo 2008a), though the risk ratios for the associations are less than previous quantitative estimates, but similar to our previous estimates (Lundh 2012). Previous reviews did not distinguish between favorable efficacy results or conclusions, but looked at the association between sponsorship and outcomes. Bekelman 2003 found OR 3.60 (95% CI: 2.63 to 4.91) and Lexchin 2003 OR 4.05 (95% CI: 2.98 to 5.51). Translated to odds ratios, we found 2.05 (95% CI: 1.66 to 2.52) for results and 2.69 (95% CI 2.04 to 3.54) for conclusions in our review. This difference could be due to chance or it could be because the earlier reviews also included pharmacoeconomic analyses, non-drug studies, unstructured letters and conference abstracts. It is also possible that the degree of industry bias has diminished over time, for example with a decrease in reporting bias due to trial registration. One paper on oncology drug trials (Djulbegovic 2013), suggested that the treatment effect size between industry sponsored and non-industry trials became more similar over time. However, the analysis included both published and unpublished trials and did not investigate the association between sponsorship and results or conclusions over time. In contrast, a recent paper found that reporting bias is also prevalent in registered trials, particular in industry sponsored trials (Jones 2013). Second, one of the most recent papers (Flacco 2015) sampled drug trials published in 2011 and found OR: 2.8 (95% CI: 1.6 to 4.7) for results, suggesting that industry bias has not changed over time.

For harms results one other systematic review (Golder 2008) has been published. Due to the anticipated heterogeneity of the data, the authors decided not to perform a meta-analysis. The results of the review are in line with our findings of no differences in harms results between industry sponsored and non-industry sponsored studies, but there are large variation in findings among individual papers.

AUTHORS' CONCLUSIONS

Implication for methodological research

Currently, the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* acknowledges problems in relation to sponsorship, but does not recommend assessing industry sponsorship as a separate domain in the 'Risk of bias' assessment (Higgins 2011b). The assumption is that the influence of the sponsor will be mediated through the mechanisms of bias that are currently assessed, such as selective reporting of favorable outcomes. A Cochrane review that examined the association of sponsorship and selective outcome reporting bias (Dwan 2011), found uncertain evidence for the association; however, assessment of selective outcome reporting is complex and bias may be difficult to detect (Kirkham 2010). Some studies that have documented the extensive selective reporting of favorable outcomes have examined only industry sponsored studies (Rising 2008; Vedula 2009), thus making comparison with non-industry sponsored studies impossible.

Our data suggest that the more favorable outcomes in industry sponsored studies are mediated by factors other than those documented in the 'Risk of bias' assessment tool in Cochrane reviews. It has been suggested that industry bias should be regarded as a meta-bias, as industry sponsorship in itself is not a bias-producing process – as for example lack of concealment of allocation is – but a risk factor for bias (Goodman 2011). However, the characteristics currently assessed in the standard risk of bias approach in Cochrane reviews likely do not capture the additional risk of bias in industry sponsored studies. For example, the *Handbook* states that design issues, such as dosage of comparators are not issues of bias, but of generalizability. Yet, pharmacological interventions have dose-response curves, and testing drugs that are not in comparable places on their dose-response curves sets up a systematic, unfair and biased comparison (Safer 2002).

Consequently, our data suggest that industry sponsorship should be treated as bias-inducing and industry bias should be treated as a separate domain. There are many subtle mechanisms through which sponsorship may influence outcomes, and an assessment of sponsorship should therefore be used as a proxy for these mechanisms. Interestingly, the AMSTAR tool for methodological quality assessment of systematic reviews includes funding and conflicts of interest as a domain (Shea 2007). Adaptations of Cochrane tools for assessing risk of bias in studies assessing environmental risks have also included funding source and conflicts of interest as a domain (Johnson 2016). Methods for reporting, assessing and handling industry bias and other biases in future systematic reviews must be developed. Specifically, further methodological research should focus on how industry bias is handled in Cochrane reviews.

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CHARACTERISTICS OF STUDIES

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

Ahmer 2005

Methods	To study the association between study support and outcome in randomized controlled trials (RCTs) of psychotropic drugs. All RCTs published in *Acta Psychiatrica Scandinavica* (APS), *American Journal of Psychiatry* (AJP), *Archives of General Psychiatry* (AGP) and *British Journal of Psychiatry* (BJP) from July 1998 to June 2003.
Data	188 psychotropic drug RCTs (various comparators).
Comparisons	Manufacturer support and no support.
Outcomes	Study conclusions.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.

Ahmer 2005 *(Continued)*

Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Database and handsearch.
Control for bias?	No	Subgroup analysis, but only of journal name.

Alasbali 2009

Methods	To investigate the relationship between industry vs non-industry funded publications comparing the efficacy of topical prostaglandin analogs by evaluating the correspondence between the statistical significance of the publication's main outcome measure and its abstract conclusions. Studies published from 1966 to November 2007.
Data	39 reports of head-to-head comparisons of topical prostaglandins in ophthalmology (various study designs).
Comparisons	Industry and non-industry funding.
Outcomes	Study conclusions, study results and concordance between study results and conclusions.
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Unclear	Not clear which study designs and whether placebo-controlled studies were included, cannot be replicated.
Adequate study inclusion process?	Unclear	Three assessors for data extraction, but unclear in relation to study inclusion.
Comprehensive search?	Yes	MEDLINE and handsearching.
Control for bias?	Unclear	Not described.

Als-Nielsen 2003

Methods	To explore whether the association between funding and conclusions in randomized drug trials reflects treatment effects or adverse events. All randomized trials included in eligible meta-analyses from a random sample of Cochrane reviews obtained in May 2001 (RCTs from 1971 to 2000).
Data	370 drug RCTs (mixed comparisons).
Comparisons	Funding from non-profit organizations, not reported, both non-profit and for-profit organizations, and for-profit organizations.
Outcomes	Study conclusions, effect size and risk of bias (generation of randomization sequence, concealment of allocation and double-blinding).

Als-Nielsen 2003 *(Continued)*

Funding	Danish Centre for Evaluation and Health Technology Assessment (DACEHTA), The Danish Medical Research Council, and The Copenhagen Hospital Corporation's Medical Research Council.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	One assessor screened and two involved in final inclusion.
Comprehensive search?	Yes	Identification via Cochrane reviews.
Control for bias?	Yes	Logistic regression adjusting for treatment effect, adverse events, and other potentially confounding trial variables (methodological quality, sample size, whether preset sample size was estimated and reached, meta-analysis, year of publication, and journal impact factor). Adjusted for treatment effect and double-blinding in final model.

Avni 2014

Methods	To compare effect estimates for clinical failure and all-cause mortality in clinical trials of antibiotic treatment of pneumonia. Trials assessing adults with pneumonia, comparing different antibiotics published between 2005 and 2012.
Data	36 antibiotic RCTs for pneumonia (drug vs drug).
Comparisons	Industry-sponsored and not industry-sponsored.
Outcomes	Effect size and risk of bias (sequence generation, concealment of allocation and blinding).
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two authors included studies.
Comprehensive search?	Yes	PubMed, the Cochrane Library, LILACS, KOREAMED, NLM gateway and reference lists.
Control for bias?	Yes	Meta-regression was used.

Barden 2006

Methods	To study if industry-sponsored trials yield a better result than trials not sponsored by industry, and if a particular drug would perform better as the test drug in trials funded by its manufacturer and worse as the comparator drug in trials funded by a competitor. RCTs from published systematic reviews in acute pain and migraine (reviews from 1999 to 2004).
Data	176 acute pain or migraine drug RCTs (active comparator or placebo-controlled).
Comparisons	Industry versus non-industry and manufacturer versus competitor funding.
Outcomes	Effect size and risk of bias (Jadad score, 0-5 point scale).
Funding	The study was supported by Pain Research funds and the Oxford Pain Relief Trust.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	From Cochrane reviews, seems more than one assessor was used.
Comprehensive search?	Yes	Identification via Cochrane reviews.
Control for bias?	No	No control for bias.

Bariani 2013

Methods	To study the association between authors' conclusions and self-reported conflicts of interest or trial sponsorship in cancer studies. Phase III oncology RCTs (from January 2008 to October 2011) published in *JCO, Journal of the National Cancer Institute,The Lancet Oncology,Annals of Oncology, and The Cancer Journal*.
Data	150 oncology RCTs of which 105 are testing oncology drugs (mixed comparisons).
Comparisons	Industry, mixed, non-industry and not stated.
Outcomes	Study results and study conclusions.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	No	Not objective inclusion criteria.

Bariani 2013 *(Continued)*

Adequate study inclusion process?	Yes	Two authors included trials.
Comprehensive search?	Yes	Handsearching of journals.
Control for bias?	Yes	Multivariate logistic regression analysis adjusted for conflicts of interest, study results, type of intervention, type of outcome and sponsorship for outcome study conclusions.

Bartels 2012

Methods	To determine what effect reporting a financial disclosure has on the conclusion of an article. Articles on interspinous devices and cervical disc prostheses, published from January 2008 to December 2010.
Data	160 interspinous device and cervical disc prosthesis studies (comparison not stated).
Comparisons	Commercial versus non-commercial funding.
Outcomes	Study conclusions.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	No	Not objective inclusion criteria.
Adequate study inclusion process?	No	Not adequate study inclusions process.
Comprehensive search?	No	Only English written papers from PubMed search in limited time period.
Control for bias?	Unclear	Not reported.

Bero 2007

Methods	To examine the associations between research funding source, study design characteristics aimed at reducing bias, and other factors that potentially influence results and conclusions in randomized controlled trials of statin–drug comparisons. All statin RCTs with active comparators from January 1999 to May 2005.
Data	192 statin RCTs (active comparators).
Comparisons	Industry, none disclosed/no funding and government/private non-profit funding.
Outcomes	Study results, study conclusions, risk of bias (concealment of allocation, blinding and follow-up) and concordance between study results and conclusions.

Bero 2007 *(Continued)*

Funding	California Tobacco-Related Disease Research Program Grant.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two or more assessors included studies.
Comprehensive search?	Yes	MEDLINE and references.
Control for bias?	Yes	Multivariate logistic regression analysis. Final model controlled for journal Impact Factor, sample size and blinding.

Bhandari 2004

Methods	To study the association between industry funding and the statistical significance of results in recently published medical and surgical trials. RCTs from January 1999 to June 2001 in 8 leading surgical journals (*Journal of Bone and Joint Surgery* [American and British volumes], *Clinical Orthopaedics and Related Research*, *Acta Orthopaedica Scandinavica*, *Annals of Surgery*, *American Journal of Surgery*, *Plastic and Reconstructive Surgery and Journal of Neurosurgery*) and 5 medical journals (*Lancet, BMJ, JAMA, Annals of Internal Medicine and New England Journal of Medicine*).
Data	332 RCTs of drug, surgery, and other types of interventions (no description of comparisons).
Comparisons	Industry-for-profit, not-for-profit and undeclared funding.
Outcomes	Study results and risk of bias (Detsky quality index, 0-21 point scale).
Funding	Mohit Bhandari is funded, in part, by a Clinical Scientist Fellowship, Department of Clinical Epidemiology and Biostatistics, McMaster University. Jason Busse is funded by a Canadian Institutes of Health Research Fellowship Award. P.J. Devereaux is funded by a Heart and Stroke Foundation of Canada/Canadian Institutes of Health Research Fellowship Award.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearch and MEDLINE used.
Control for bias?	Yes	Multivariate logistic regression with adjustment for sample size, study quality and type of intervention.

Bond 2012

Methods	To describe the frequency of industry involvement in ICS/LABA trials and explore associations among significant outcomes, type of industry involvement and type of primary outcome. RCTs up to February/March 2006.
Data	91 RCTs of drugs for asthma (drug vs drug), of which 71 had relevant data.
Comparisons	Industry, non-industry, mixed and not stated.
Outcomes	Study results.
Funding	Partly by Canadian Agency for Drugs and Technologies in Health.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two reviewers.
Comprehensive search?	Yes	Searches of electronic databases including BIOSIS Previews, Embase, MEDLINE, CENTRAL and Web of Science were conducted. References to studies included in other reviews.
Control for bias?	Unclear	Not reported.

Booth 2008

Methods	To describe trends in methodology and reporting of RCTs, in addition to sponsorship, outcomes, and authors' interpretation of results. All RCTs of systemic therapy in breast, colorectal cancer, and non-small-cell lung cancer published during three decades (1975 through 2004) in:*Journal of Clinical Oncology*, *Journal of the National Cancer Institute*, *Cancer Treatment/Chemotherapy Reports*, *New England Journal of Medicine*, *Lancet*, and *JAMA*.
Data	321 oncology drug RCTs (active comparators and placebo-controlled).
Comparisons	For-profit/mixed, non-profit and not known funding.
Outcomes	Study results, study conclusions and effect size.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description

Booth 2008 *(Continued)*

Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Database and handsearch.
Control for bias?	Yes	Multivariate logistic regression, final model controlled for time to event, effect size and P value.

Bourgeois 2010

Methods	To describe characteristics of drug trials listed in ClinicalTrials.gov and examine whether the funding source of these trials is associated with favorable published outcomes. Clinical trials registered from 2000 to 2006 and published up to 2010.
Data	546 clinical trials of cholesterol-lowering drugs, antidepressants, antipsychotics, proton-pump inhibitors and vasodilators (active or placebo-controlled) of which 345 had relevant data.
Comparisons	Industry, government and non-profit/non-federal (with or without industry contributions) funding.
Outcomes	Study results.
Funding	National Library of Medicine and National Institute of Child Health and Human Development, National Institutes of Health.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors independently carried out the literature search and disagreements were resolved by consensus.
Comprehensive search?	Yes	Four databases, trial registries and contact to investigators and companies.
Control for bias?	Yes	Post hoc multivariate logistic regression analysis to assess the association between funding source and trial outcome, while controlling for other trial characteristics (drug class, approval status of indication, study phase, multicenter status, anticipated sample size, age of study population, comparator type, and length of study).

Brown 2006

Methods	To evaluate the trends in the source of funding for gastrointestinal clinical research during the period from 1992 to 2002–2003; to determine whether the source of study funding predicted the likelihood that a study would publish results that favor the drug or device being tested; and to determine whether differences exist in the methodologic quality of the investigational study methods used in studies fund-

Brown 2006 *(Continued)*

	ed by private industry versus other sources. Clinical trials published in 4 gastrointestinal journals (*Gastroenterology*, *The American Journal of Gastroenterology*, *Hepatology*, and *Gastrointestinal Endoscopy*).
Data	450 clinical trials of drugs and devices in gastroenterology (active or placebo-controlled).
Comparisons	Private industry sponsored, federal/state government sponsored, national society/non-profit agency sponsored and not specified.
Outcomes	Study conclusions and risk of bias (Brown score, 0 to 5 point scale multiplied by 100).
Funding	Amos Scholars Program of the Robert Wood Johnson Foundation and the Center for Gastrointestinal Biology and Disease at the University of North Carolina at Chapel Hill.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearching of journals.
Control for bias?	No	No control for bias.

Buchkowsky 2004

Methods	To characterize clinical trial funding, reporting, and sources; investigate author-industry affiliation; and describe clinical outcome trends over time. Random papers from January 1981 to December 2000 from *Annals of Internal Medicine*, *BMJ*,*JAMA*,*Lancet* and *New England Journal of Medicine*.
Data	500 clinical drug trials (drug versus placebo, active comparator or non-drug comparator).
Comparisons	Industry, mixed, non-industry and not stated funding.
Outcomes	Study conclusions.
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.

Buchkowsky 2004 *(Continued)*

Comprehensive search?	Yes	Handsearching of journals.
Control for bias?	Unclear	Investigates choice of comparators over time, might have assessed other sources of bias.

Chard 2000

Methods	To assess the published research base for interventions for osteoarthritis of the knee, and to identify areas in need of further research. Studies from 1950 to 1998.
Data	930 studies of different interventions (various study designs with various comparators).
Comparisons	Commercial, government and not stated funding.
Outcomes	Study conclusions.
Funding	Medical Research Council—Health Services Research Collaboration.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	One assessor on all studies and one on 10% sample, but only 87% agreement indicating two needed for all studies.
Comprehensive search?	Yes	MEDLINE, Embase, BIDS, the Cochrane Library, previous reviews and experts contacted.
Control for bias?	No	No control for bias.

Cho 1996

Methods	To compare the quality, relevance, and structure of drug studies published in symposium proceedings that are sponsored by drug companies with 1) articles from symposia with other sponsors and 2) articles in the peer-reviewed parent journals of symposium proceedings; and to study the relation between drug company sponsorship and study outcome. Random selection of symposia from 625 symposia that had been identified for a previous study.
Data	127 drug studies (various study designs with various comparators).
Comparisons	Drug company support and no support.
Outcomes	Study conclusions and risk of bias (Cho scale, 0-1 point).
Funding	In part by the American Association for Retired Persons, the Cigarette and Tobacco Surtax Fund of the State of California through the Tobacco-Related Disease Research Program of the University of Califor-

Cho 1996 *(Continued)*

	nia (award 4RT0035), the Pew Charitable Trusts, and the Veterans Affairs Office of Academic Affairs and Health Services Research and Development Service Research Funds.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Unclear	Not clear enough to replicate how symposia were chosen and how matching papers were chosen.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Comprehensive search within their own database.
Control for bias?	Yes	Subgroup analysis of study design.

Clark 2002

Methods	To evaluate if erythropoietin (EPO) is effective in the treatment of cancer-related anemia, and if its effect remains unchanged when data are analyzed according to various clinical and methodological characteristics of the studies. RCTs from 1993 to 2001.
Data	30 EPO RCTs (drug vs placebo), only 19 RCTs for some outcomes.
Comparisons	Industry and academic.
Outcomes	Study results, study conclusions, effect size and risk of bias (Jadad scores, 0-5 point scale, randomization and blinding).
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Previous systematic review and updated search of MEDLINE, LILACS and CANCERLIT.
Control for bias?	Yes	Subgroup analysis and meta-regression.

Clifford 2002

Methods	To examine the relationship between funding source, trial outcome and reporting quality; 100 RCTs from *Annals of Internal Medicine*, *BMJ, JAMA*, *Lancet, New England Journal of Medicine*. From January 1999 to October 2000 with 20 RCTs/journal.
Data	100 drug RCTs (various comparators).
Comparisons	Entirely industry, entirely not-for-profit, mixed and not reported funding.
Outcomes	Study results, risk of bias (Jadad score, 0-5 point scale and concealment of allocation).
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearching of journals.
Control for bias?	No	No evidence of 'Risk of bias' assessment.

Corona 2014

Methods	To examine cardiovascular risk associated with testosterone-boosting medications. Search from January 1969 to January 2014.
Data	75 RCTs of testosterone supplementation (drug vs placebo).
Comparisons	Drug company supported and not supported.
Outcomes	Effect size and risk of bias (sequence generation, blinding-overall and follow-up).
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors included studies.

Corona 2014 *(Continued)*

Comprehensive search?	Yes	MEDLINE, Embase and the Cochrane Library, www.clinicaltrials.gov and hand-search.
Control for bias?	Yes	Meta-regression.

Corona 2014a

Methods	To examine the effect of testosterone supplementation on male sexual function and its synergism with the use of phosphodiesterase type 5 inhibitors. Search from January 1969 to June 2013.
Data	29 studies of testosterone supplementation (drug vs placebo).
Comparisons	Drug company supported and not supported.
Outcomes	Effect size.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	MEDLINE, Embase and the Cochrane Library, www.clinicaltrials.gov and hand-search.
Control for bias?	Yes	Meta-regression.

Crocetti 2010

Methods	To assess the risk of bias among pediatric RCTs reported in 8 high-impact journals (5 pediatric and 3 general medical) from July 2007 to June 2008.
Data	146 pediatric drug, behavioral/educational and nutritional RCTs (various comparators) of which 57 had relevant data.
Comparisons	Government, industry, internal hospital grant, multiple sources, none and private foundation funding.
Outcomes	Risk of bias (sequence generation; allocation concealment; masking of participants, personnel, and outcome assessors; incomplete outcome data reporting; selective outcome reporting; and other sources of bias).
Funding	Not reported.
Notes	

Crocetti 2010 *(Continued)*

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE search of selected journals.
Control for bias?	Yes	Multivariate logistic regression to test for an association between the presence of a high risk of bias according to domain and the independent variables of funding source, intervention type, author number, and trial registration status.

Davidson 1986

Methods	An analysis of the results of clinical trials according to funding source. Clinical trials from 1984 in *New England Journal of Medicine*, *Annals of Internal Medicine*,*the American Journal of Medicine*,*Archives of Internal Medicine*, and the *Lancet.*
Data	107 drug and non-drug clinical trials (various comparators).
Comparisons	Pharmaceutical support and general support.
Outcomes	Study conclusions.
Funding	In part by NIH grant.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Single assessor.
Comprehensive search?	Yes	Journals handsearched.
Control for bias?	No	Control for bias seems unlikely to have been done.

Davis 2008

Methods	The influence of several potentially biasing factors (e.g. industry support, extrapyramidal side effects) on efficacy of studies comparing second-generation antipsychotic with first-generation drugs. Dataset from previously published meta-analysis (search from 1953 to 2002).

Davis 2008 *(Continued)*

Data	124 RCTs of second-generation antipsychotics versus first-generation antipsychotics.
Comparisons	Industry and non-industry funding.
Outcomes	Effect size.
Funding	In part by National Institute of Mental Health Grant.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Comprehensive database search including search for unpublished data.
Control for bias?	Unclear	Carried out various sensitivity analysis, but not clear whether they assessed bias in relation to funding and effect size.

DeGeorge 2015

Methods	To examine the impact of financial relationships with industry sponsorship and conflicts of interest reporting on surgical outcomes of abdominal wall reconstruction with acellular dermal matrices (from January 2004 to December 2013).
Data	124 studies of abdominal wall reconstruction with acellular dermal matrices (type of comparison not stated).
Comparisons	Industry, federal or state government, national society or nonprofit organization and none.
Outcomes	Study conclusions.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Not objective inclusion criteria.
Adequate study inclusion process?	Unclear	Not reported.
Comprehensive search?	No	Searched only PubMed.

DeGeorge 2015 *(Continued)*

Control for bias?	No	No control for bias.

Djulbegovic 2000

Methods	To evaluate whether the uncertainty principle was upheld, comparison of the number of studies favoring experimental treatments over standard ones according to the source of funding. All RCTs for multiple myeloma from 1996 to 1998.
Data	136 multiple myeloma drug RCTs (various comparators).
Comparisons	Commercial and public funding.
Outcomes	Study conclusions and risk of bias (Jadad score, 0-5 point scale).
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Seems only one author involved in study inclusion.
Comprehensive search?	Yes	Using the Cochrane search strategy to identify trials.
Control for bias?	Yes	Controlled for types of comparator (active versus placebo/no treatment).

Djulbegovic 2013

Methods	To assess if commercially sponsored trials are associated with higher success rates than publicly-sponsored trials. RCTs from 1980 to 2010.
Data	96 published oncology RCTs (mixed comparisons) of which 85 comparisons had relevant data.
Comparisons	Industry and non-industry.
Outcomes	Study results, study conclusions and risk of bias (sequence generation, concealment of allocation, blinding and follow-up).
Funding	National Institutes of Health.
Notes	

Risk of bias

Item	Authors' judgement	Description

Djulbegovic 2013 *(Continued)*

Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two authors included studies.
Comprehensive search?	Yes	Clinical Trials Group provided list of non-industry trials. GSK clinical trial registry was searched for industry trials.
Control for bias?	Yes	Sensitivity analyses according to the methodological quality of trials (bias and random error), publication status, choice of control intervention as well as according to most important cancer outcomes and types of treatment.

Etter 2007

Methods	To assess whether source of funding affected the results of trials of nicotine replacement therapy for smoking cessation. RCTs from 1979 to 2003 identified from Cochrane review.
Data	105 RCTs of nicotine replacement therapy (gum or patch versus placebo or no treatment).
Comparisons	Industry/mixed and non-industry/not acknowledged funding.
Outcomes	Study results and effect size.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	From Cochrane review, seems more than one assessors was used.
Comprehensive search?	Yes	Identification via Cochrane review.
Control for bias?	Yes	Multivariate logistic regression with adjustment for sample size.

Finucane 2004

Methods	To evaluate the association between funding and findings of pharmaceutical research presented at an annual meeting of a clinically oriented US medical professional society.
Data	48 presentations of drug studies (observational studies, RCTs and other study designs).
Comparisons	Industry supported and not industry supported.
Outcomes	Study conclusions.

Finucane 2004 *(Continued)*

Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Unclear	Unclear what "any abstract that reported results about effectiveness or safety of drugs" means. Not clear which study designs and whether reviews were included.
Adequate study inclusion process?	Yes	Seems likely that two assessors were used.
Comprehensive search?	Yes	Comprehensive search within conference.
Control for bias?	Yes	Subgroup analysis of study design.

Flacco 2015

Methods	To map the current status of head-to-head comparative randomized evidence and to assess whether funding may impact on trial design and results. Random sample of PubMed RCTs indexed in 2011 with ≥ 100 participants.
Data	319 head-to-head drug RCTs.
Comparisons	Pharmaceutical companies, nonprofit and not reported.
Outcomes	Study results.
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Random sample of PubMed indexed RCTs.
Control for bias?	Yes	Logistic regression adjusting for sample size and study design (superiority vs non-inferiority). Affiliation, registration, impact factor, country, intervention type, conflict of interest) was significantly associated with favorable results in the final model, but none remained statistically significant when funding source and study design were adjusted for in the model.

Freemantle 2000

Methods	To assess whether specific pharmacological characteristics of alternative antidepressants resulted in altered efficacy compared to that of selective serotonin reuptake inhibitors (SSRI) in the treatment of major depression. All RCTs of SSRI versus alternative antidepressants (search from 1966 to 1997).
Data	105 SSRI versus alternative antidepressant RCTs.
Comparisons	Sponsor and not sponsor.
Outcomes	Effect size.
Funding	Study sponsored by an unrestricted grant from Wyeth Laboratories.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, Embase, references and reviews.
Control for bias?	No	No assessment of bias in relation to funding and effect size.

Gan 2012

Methods	To evaluate how reliably the expected benefit approximates the observed benefit in RCTs that evaluated cancer treatment. RCTs from January 2005 to December 2009 published in: *Annals of Oncology, Breast Cancer Research & Treatment, British Journal of Cancer, Cancer, European Journal of Cancer, Journal of Clinical Oncology, Journal of the National Cancer Institute, Lancet, Lancet Oncology,* and*New England Journal of Medicine*.
Data	253 oncology drug trials (mixed comparisons).
Comparisons	Any industry funding, no industry funding and unknown.
Outcomes	Study results.
Funding	Victorian Cancer Agency.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.

Gan 2012 *(Continued)*

Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Identified via MEDLINE search of journals.
Control for bias?	No	Subgroup analysis of various predictors, but not in relation to study result outcome.

Gartlehner 2010

Methods	The objective of this study was to determine the effect of industry bias in a systematically reviewed sample of head-to-head trials. Trials of SSRI head-to-head comparisons from 1993 to 2005.
Data	29 SSRI RCTs of head-to-head comparisons.
Comparisons	Sponsor and not sponsor.
Outcomes	Study results and effect size.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	MEDLINE, Embase, the Cochrane Library, the International Pharmaceutical Abstracts database, references and reviews and letters to the editor. In addition, the Center for Drug Evaluation and Research database to identify unpublished research submitted to the US Food and Drug Administration (FDA).
Control for bias?	Yes	Sensitivity analysis based on definition of funding.

Halpern 2005

Methods	To determine whether there is a difference in average statistical power between pharmacoepidemiologic studies of anti-retroviral adverse drug effects sponsored by for-profit versus non-profit organizations (drugs approved from 1987 to 1999 and published until 2002).
Data	48 pharmacoepidemiological studies of adverse effects of anti-retroviral drugs.
Comparisons	Non-profit, for-profit, charity/institution, none or unable to determine funding.
Outcomes	Study results (harms).

Halpern 2005 *(Continued)*

Funding	Agency for Healthcare Research and Quality (AHRQ) Centers for Education and Research on Therapeutics.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	One assessor only.
Comprehensive search?	Yes	MEDLINE, Embase and reference lists.
Control for bias?	No	No control for bias.

Heres 2006

Methods	To review the results of head-to-head studies of second-generation antipsychotics funded by pharmaceutical companies to determine if a relationship exists between the sponsor of the trial and the drug favored in the study's overall outcome. All head-to-head trials of second-generation antipsychotics from 1997 to 2005.
Data	42 head-to-head RCTs of second-generation antipsychotics.
Comparisons	Industry only (sponsor of test drug or comparator).
Outcomes	Study conclusions.
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	No	MEDLINE and screen of selected conference proceedings. Sample of conference proceedings limited to 1999 to 2004, which may introduce bias due to differences in approval dates for the different drugs.
Control for bias?	Yes	Sensitivity analysis of peer-reviewed trials only.

Jefferson 2009

Methods	To explore the relation between study concordance, take home message, funding, and dissemination of comparative studies assessing the effects of influenza vaccines. Studies of various designs from 1961 to 2006.
Data	274 studies of influenza vaccine versus placebo/no treatment.
Comparisons	Government/private/unfunded, industry/mixed and not stated funding.
Outcomes	Study conclusions, risk of bias (Cochrane risk of bias) and concordance between study results and conclusions.
Funding	ASL AL, Alessandria, Piemonte, Italy (regional health services).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	MEDLINE, Embase, the Cochrane Library, web, and likely references and previous reviews since it is based on Cochrane reviews.
Control for bias?	Yes	Sensitivity analysis based on definition of funding and regression analysis of various factors.

Jinapriya 2011

Methods	To determine whether sponsorship of prostaglandin analogue clinical trials results in investigator bias in outcomes when studying intraocular pressure. RCTs up to August 2008.
Data	43 RCTs of topical prostaglandin analogues (comparison not stated).
Comparisons	Parent company, competing company and non-industry.
Outcomes	Effect size.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.

Jinapriya 2011 *(Continued)*

Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	PubMed and reference lists were searched.
Control for bias?	Unclear	No control for bias.

Jones 2010

Methods	To compare the quality of publicly or privately funded randomized controlled trials. Trials included in Cochrane reviews on hypertension and preterm labour.
Data	105 drug trials (mixed comparisons).
Comparisons	Commercial, mixed and non-commercial.
Outcomes	Risk of bias (selection bias, performance bias, detection bias and attrition bias).
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Based on searches from Cochrane reviews.
Control for bias?	No	No control for bias.

Kelly 2006

Methods	To investigate the relationship between industry support and study outcome in the general psychiatric literature. Clinical studies from 1992 and 2002 in *American Journal of Psychiatry, Archives of General Psychiatry,* and *Journal of Clinical Psychopharmacology.*
Data	301 psychiatric drug studies (mixed comparisons).
Comparisons	Non-industry and industry (sponsor of test drug or comparator) funding.
Outcomes	Study results, study conclusions and concordance between study results and conclusions.
Funding	Not reported.
Notes	

Kelly 2006 *(Continued)*

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Sample of journals.
Control for bias?	Yes	Explanatory analysis of various mediating variables.

Kemmeren 2001

Methods	To evaluate quantitatively articles that compared effects of second- and third-generation oral contraceptives on risk of venous thrombosis. Cohort and case-control studies from 1995 to 2000.
Data	12 cohort and case control studies of second- versus third-generation oral contraceptives.
Comparisons	Industry and non-industry funding.
Outcomes	Study results and effect size.
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, reviews, relevant papers and experts.
Control for bias?	No	Multiple regression used, but not for the association between funding and results or effect size.

Khan 2012

Methods	To assess the association of industry funding with the characteristics, outcome, and reported quality of randomized controlled trials of drug therapy for rheumatoid arthritis. RCTs from 2002 to 2003 and 2006 to 2007.
Data	103 RCTs of drugs for rheumatoid arthritis (mixed comparisons).

Khan 2012 *(Continued)*

Comparisons	Industry, mixed, non-industry and not stated.
Outcomes	Study results and risk of bias (sequence generation, concealment of allocation and blinding).
Funding	Partly by NIH.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	No	PubMed and the Cochrane Central Register of Controlled Trials databases searched, but with very limited search terms used.
Control for bias?	Yes	Logistic regression adjusted for potential confounders (not stated).

Killin 2014

Methods	To investigate whether there is a difference in the treatment effect of donepezil on cognition in Alzheimer's disease between industry-funded and independent RCTs. Search for RCTs up to October 2012.
Data	14 RCTs of donezepil for Alzheimer's disease (mixed comparisons).
Comparisons	Industry and non-industry.
Outcomes	Effect size and risk of bias (sequence generation, concealment of allocation, performance bias, detection bias, attrition bias and reporting bias).
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Update of previous review using PubMed. Previous review with comprehensive search.
Control for bias?	No	No control for bias.

Kjaergard 2002

Methods	To assess the association between competing interests and authors' conclusions. RCTs published in *BMJ* 1997 to 2001.
Data	159 RCTs of mixed interventions (various comparators).
Comparisons	Profit, non-profit, non-profit and profit, non-profit and free drug, free drug only and no funding/not stated.
Outcomes	Study conclusions and risk of bias (sequence generation, concealment of allocation and blinding).
Funding	Danish Medical Research Council; 1991 Pharmacy Foundation, Denmark; Copenhagen Hospital Corporation, Medical Research Council; Danish Institute of Health Technology Assessments.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Only one assessor included studies.
Comprehensive search?	Yes	MEDLINE journal search.
Control for bias?	Yes	Regression analysis for potential confounders.

Lee 2012

Methods	To determine what proportion of studies on thromboprophylaxis after total joint arthroplasty were sponsored by industry and whether the assessments of thromboprophylaxis after total joint arthroplasty were associated with industry support. Studies published from 2004 to 2010.
Data	71 prospective studies of thromboprophylaxis after total joint arthroplasty (mixed comparisons and interventions).
Comparisons	Industry, non-industry and not stated.
Outcomes	Study conclusions.
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.

Lee 2012 *(Continued)*

Adequate study inclusion process?	No	Only one author included studies.
Comprehensive search?	No	PubMed in limited time period and limited to English language.
Control for bias?	No	No control for bias.

Liss 2006

Methods	To determine whether drug studies in the pulmonary/allergy literature also demonstrate a publication bias towards more favorable results when a pharmaceutical company funds the study. Primary research studies of drug interventions published in *Allergy, American Journal of Respiratory and Critical Care Medicine, Annals of Allergy Asthma and Immunology, Chest, European Respiratory Journal, Journal of Allergy and Clinical Immunology, Respiratory Medicine,* and *Thorax* in 2002 to 2003.
Data	Studies of nasal or oral inhaled corticosteroids, long- or short-acting bronchodilators, and leukotriene receptor antagonists (various designs and comparisons).
Comparisons	Pharmaceutically and not pharmaceutically funded.
Outcomes	Study conclusions.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Only one assessor included studies.
Comprehensive search?	Yes	Handsearch of journals indirectly described.
Control for bias?	No	No control for bias.

Lubowitz 2007

Methods	To compare outcomes (and levels of evidence) between published Autologous Chondrocyte Implantation outcome studies that were commercially funded and studies that were not commercially funded. Clinical studies from 1994 to 2005.
Data	23 studies of chondrocyte implantation (various designs and comparisons).
Comparisons	Commercially funded and not commercially funded.
Outcomes	Effect size.

Lubowitz 2007 *(Continued)*

Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	No	MEDLINE only, time period not stated and few search terms used.
Control for bias?	No	No control for bias.

Lynch 2007

Methods	To test the following hypotheses regarding orthopedic manuscripts submitted for review: (1) non-scientific variables, including receipt of commercial funding, affect the likelihood that a peer-reviewed submission will conclude with a report of a positive study outcome, and (2) positive outcomes and other, non-scientific variables are associated with acceptance for publication. Cohort of manuscripts submitted involving original research on the subject of adult hip or knee reconstruction to *The Journal of Bone and Joint Surgery* (American Volume) from January 2004 to June 2005.
Data	209 studies of knee or hip surgery (various designs, interventions and comparisons) of which 99 had relevant data.
Comparisons	Commercial, non-funded and non-commercial/philanthropic funding.
Outcomes	Study conclusions and risk of bias (Sackett scale, 0 to 100%).
Funding	University of Washington Friends of Orthopaedic Research and Education Foundation. Zimmer, Inc., Warsaw, Indiana, made an unrestricted gift to the University of Washington Friends of Orthopaedic Research and Education in 2002.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Sample of papers via journal submission system.
Control for bias?	No	No control for bias.

Ma 2014

Methods	To assess efficacy, acceptability, and safety of contemporary interventions in children and adolescents with major depressive disorder. RCTs from January 1988 to March 2013.
Data	21 RCTs of new-generation antidepressants and cognitive behavioural therapy depression in children and adolescents (mixed comparisons).
Comparisons	Industry and non-industry.
Outcomes	Effect size.
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two authors included studies.
Comprehensive search?	Yes	Search of the Cochrane Library, AMED, CINAHL, Embase, LILACS, MEDLINE, PsycINFO, PSYNDEX, and Journal of Medicine and Pharmacy. Additional search of reference lists, regulatory reports, scientific proceedings, clinical trial registries and contact with individual investigators.
Control for bias?	No	No control for bias.

Momeni 2009

Methods	To investigate if plastic surgical trials with industry-funding are more likely to be associated with statistically significant pro-industry findings. Trials in 4 plastic surgery journals (*Plastic and Reconstructive Surgery, British Journal of Plastic Surgery*, *Annals of Plastic Surgery,* and *Aesthetic Plastic Surgery*) from 1990 to 2005.
Data	346 RCTs and controlled clinical trials (various designs, interventions and comparisons).
Comparisons	Industry, public, university and not specified funding.
Outcomes	Study results.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description

Momeni 2009 *(Continued)*

Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearch of journals.
Control for bias?	No	No control for bias.

Moncrieff 2003

Methods	To re-evaluate the evidence comparing clozapine with conventional antipsychotics and to investigate sources of heterogeneity. RCTs from 1988 to 2001.
Data	9 RCTs of clozapine versus conventional antipsychotics.
Comparisons	Industry, other and not declared funding.
Outcomes	Study results and effect size.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Only one assessor included studies.
Comprehensive search?	Yes	MEDLINE, Embase and Cochrane review.
Control for bias?	No	Univariate controlled for various predictors in relation to effect size only.

Montgomery 2004

Methods	To analyze RCTs of second-generation antipsychotics in schizophrenia with respect to funding source (industry versus non-industry funding). RCTs from 1974 to 2002.
Data	86 RCTs of 2nd generation antipsychotics versus other types (various comparisons).
Comparisons	Industry and non-industry.
Outcomes	Study conclusions and risk of bias (Jadad score, 0-5 point scale).
Funding	No funding provided.

Montgomery 2004 *(Continued)*

Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, PsycINFO and references.
Control for bias?	No	No control for bias.

Naci 2014

Methods	To explore the risk of industry sponsorship bias in a systematically identified set of placebo-controlled and active comparator trials of statins. RCTs from January 1985 to March 2013.
Data	183 RCTs of statins (mixed comparisons).
Comparisons	Industry and non-industry.
Outcomes	Effect size and risk of bias (sequence generation, concealment of allocation, blinding, attrition bias and selective outcome reporting).
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two authors included studies.
Comprehensive search?	Yes	MEDLINE, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials and reference lists from published trials and review articles.
Control for bias?	No	Meta-regressions seem only to include covariates of dosage.

Nieto 2007

Methods	To evaluate differences between studies funded by the pharmaceutical manufacturer of the drug and those with no pharmaceutical funding regarding the findings and interpretation of adverse effects of inhaled corticosteroids. Studies from 1993 to 2002.
Data	504 studies of inhaled corticosteroids (various study designs with various comparators).
Comparisons	Pharmaceutical funded and not pharmaceutical funded.
Outcomes	Study results (harms), study conclusions (harms) and concordance between study results and conclusions (harms).
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Sample of journals were identified by MEDLINE.
Control for bias?	Yes	Controlled for confounders using multivariate model.

Pengel 2009

Methods	To examine the quality of reporting of RCTs in solid organ transplantation that were published from 2004 to 2006.
Data	332 trials in solid organ transplantation (mixed interventions and comparisons).
Comparisons	Commercial, non-profit, mixed, no funding and not described.
Outcomes	Risk of bias (concealment of allocation and Jadad score, 0-5 point scale).
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.

Pengel 2009 *(Continued)*

Comprehensive search?	Yes	MEDLINE, Embase and the Cochrane Library.
Control for bias?	No	No control for bias.

Peppercorn 2007

Methods	To evaluate the correlations between pharmaceutical company involvement, study design, and study outcome and to explore changes in these areas over time. Breast cancer trials of medical therapies that were published in the years 1993, 1998, and 2003 in 10 select English-language medical journals.
Data	140 breast cancer drug trials (single-arm studies and RCTs).
Comparisons	Pharmaceutical studies versus non-pharmaceutical studies.
Outcomes	Study conclusions.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearch and MEDLINE used.
Control for bias?	No	Only assessment of differences in study design in relation to funding.

Perlis 2005a

Methods	To determine the extent and impact of industry sponsorship conflicts of interest in dermatology research. Drug trials from *Journal of Investigative Dermatology, Archives of Dermatology, British Journal of Dermatology,* and *Journal of the American Academy of Dermatology* from 2000 to 2003.
Data	179 RCTs of dermatological drugs (various comparators).
Comparisons	Industry and non-industry funding.
Outcomes	Study conclusions and risk of bias(blinding and Jadad score, 0-5 point scale).
Funding	No funding provided.
Notes	

Risk of bias

Perlis 2005a *(Continued)*

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Sample of journals.
Control for bias?	Yes	Multivariate regression analysis adjusted for conflict of interest, Jadad score, and sample size.

Perlis 2005b

Methods	To study the extent and implications of industry sponsorship and financial conflicts of interest in psychiatric trials. Drug trials from the *American Journal of Psychiatry, Archives of General Psychiatry, Journal of Clinical Psychiatry, and Journal of Clinical Psychopharmacology* from 2001 to 2003.
Data	397 psychiatric clinical drug trials (various comparators).
Comparisons	Industry and non-industry funding.
Outcomes	Study results.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Not sure if 3 assessors extracting data were involved in including studies.
Comprehensive search?	Yes	MEDLINE and handsearch of journals.
Control for bias?	Yes	Logistic regression adjusted for confounders.

Popelut 2010

Methods	To examine financial sponsorship of dental implant trials, and to evaluate whether research funding sources affects the annual failure rate. Clinical trials from 1988 to 2005.
Data	41 clinical trials of dental implants (single arm and active control).
Comparisons	Industry, non-industry and unknown funding.

Popelut 2010 *(Continued)*

Outcomes	Effect size.
Funding	Grant from the University Paris Diderot, U.F.R. of Odontologie (Paris, France).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	No	Inclusion criteria reported, but not possible to decipher and seems subjective.
Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	MEDLINE and handsearch.
Control for bias?	Yes	Controlled for confounders using multivariate analysis.

Printz 2013

Methods	Whether the qualitative conclusions by the authors about the therapeutic effects of the hyaluronic acid drug were associated with either industry sponsorship or the financial conflicts of interest of the authors. RCTs from January 2010 to April 2012.
Data	48 RCTs of hyaluronic acid injections for osteoarthritis (drug vs placebo).
Comparisons	Industry and non-industry sponsorship.
Outcomes	Study conclusions.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Only one assessor included studies.
Comprehensive search?	Yes	PubMed, Embase, Scopus, Web of Science and other sources searched.
Control for bias?	No	No control for bias.

Rasmussen 2009

Methods	To compare the prevalence of favorable results and conclusions among published reports of registered and unregistered RCTs of new oncology drugs. Cohort of trials from 25 drugs granted first-time Food and Drug Administration (FDA) approval for oncology indications from 2000 to 2005 and published from 1996 to 2008.
Data	137 RCTs of oncology drugs (placebo or active control).
Comparisons	Industry sponsor and other funding.
Outcomes	Study results, study conclusions, risk of bias (blinding) and concordance between study results and conclusions.
Funding	National Center for Research Resources (a component of the National Institutes of Health) and the Australian Research Council.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE and the Cochrane Library.
Control for bias?	Yes	Logistic regression adjusted for confounders.

Rattinger 2009

Methods	To examine the association between research funding source, study design characteristics aimed at reducing bias, and other factors with the results and conclusions of RCTs of thiazolidinediones compared to other oral hypoglycemic agents (search from 1996 to 2006).
Data	61 RCTs of thiazolidinediones (active or placebo control).
Comparisons	Test drug company, other drug company, all others and not declared funding.
Outcomes	Study results, study conclusions, risk of bias (sequence generation and allocation concealment, blinding and follow-up) and concordance between study results and conclusions.
Funding	California Tobacco-Related Disease Research Program. The statistical analysis was funded by a Pathway Project Grant from the UCSF School of Pharmacy Vince Isnardi Opportunity Fund.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.

Rattinger 2009 *(Continued)*

Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, the Cochrane Library, references and reviews.
Control for bias?	Yes	Intended multivariate analysis, but due to few associations only univariate performed.

Ridker 2006

Methods	To determine in contemporary randomized cardiovascular trials the association between funding source and the likelihood of reporting positive findings. Cardiovascular RCTs published in *JAMA*, *Lancet*, and the *New England Journal of Medicine* from 2000 to 2005.
Data	349 RCTs (mixed interventions and comparators).
Comparisons	For profit, mixed and not for profit funding.
Outcomes	Study conclusions.
Funding	Not reported.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Sample of journals identified via MEDLINE.
Control for bias?	No	No control for bias.

Rios 2008

Methods	To assess the reporting quality of RCTs in general endocrinology and to identify predictors for better reporting quality. RCTs published in the *Journal of Clinical Endocrinology* and *Metabolism, Clinical Endocrinology,* and the *European Journal of Endocrinology* from 2005 to 2006.
Data	89 endocrinology drug RCTs (various comparators).
Comparisons	Industry, mixed, non-industry and not stated funding.
Outcomes	Risk of bias (concealment of allocation and blinding).
Funding	Not reported.

Rios 2008 *(Continued)*

Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	Handsearch of journals.
Control for bias?	Yes	Controlled for confounders using multivariate analysis.

Rochon 1994

Methods	To study the relation between reported drug performance in published trials and support of the trials by the manufacturer of the drug under evaluation. All non-steroidal anti-inflammatory (NSAID) RCTs from September 1987 to May 1990.
Data	56 NSAID RCTs (placebo and head-to-head comparisons).
Comparisons	Manufacturer associated only.
Outcomes	Study results (efficacy and harms), study conclusions (efficacy and harms) and risk of bias (Chalmers' scale, 0-100 points).
Funding	Agency for Health Care Policty and Research, Public Health Service, Department of Health and Humar Resources; research fellowship at Brockton/West Roxbury Division if the Boston (Mass) area Geriatric Research Education and Clinical Center (Dr Rochon); clinical Investigators award from the National Institute of Aging, National Institutes of Helath, Bethesda, MD (Dr Gurwittz); and Le Fonds de la Recherche en Sante du Quebec and Arthritis Society of Canada (Toronto, Ontario) (Dr Fortin).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE searched.
Control for bias?	No	Control for bias seems unlikely to have been done.

Roper 2014

Methods	To examine whether industry funding with collaboration was associated with certain trial design features and outcomes. RCTs from December 2011 to November 2012 in 10 high impact biomedical journals.
Data	219 drug and device RCTs (placebo and active comparators) of which 216 had relevant data.
Comparisons	Industry with collaboration, industry without collaboration and neither industry or collaboration.
Outcomes	Study results and risk of bias (concealment of allocation and blinding).
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	No	Does not describe selection criteria.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Unclear	Does not describe search strategy.
Control for bias?	No	No control for bias.

Rösner 2010

Methods	To determine the effectiveness and tolerability of acamprosate in comparison to placebo and other pharmacological agents. RCTs from 1966 to January 2009.
Data	24 RCTs of acamprosate for alcohol dependence (mixed comparisons).
Comparisons	Industry, mixed and non-industry.
Outcomes	Effect size.
Funding	Internal sources (Ludwig Maximilian University of Munich and Technical University of Munich provided infrastructure and related services). External sources (Federal Ministry of Education and Research in Germany provided financial support / salary).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Only one author included studies.

Rösner 2010 *(Continued)*

Comprehensive search?	Yes	Cochrane Central Register of Controlled Trials, MEDLINE, Embase and CINAHL. Other sources were: Trial registries, investigators, experts, public sponsors and drug manufacturer(Merck Serono) and reference lists of included trials and reviews.
Control for bias?	No	No control for bias.

Rösner 2010a

Methods	To determine the effectiveness and tolerability of opioid antagonists in the treatment of alcohol dependence. RCTs from 1966 to January 2010.
Data	50 RCTs of opioid antagonists for alcohol dependence (mixed comparisons).
Comparisons	Industry and non-industry.
Outcomes	Effect size.
Funding	Internal sources (Ludwig Maximilian University of Munich (Germany), Technical University of Munich (Germany), Chiang Mai University (Thailand) provided infrastructure and related services). External sources (Federal Ministry of Education and Research in Germany provided financial support / salary).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Only one author included studies.
Comprehensive search?	Yes	Cochrane Central Register of Controlled Trials, MEDLINE, Embase and CINAHL. Other sources were: trial registries, investigators, experts, public sponsors and drug manufacturers and reference lists of included trials and reviews.
Control for bias?	No	No control for bias.

Sinyor 2012

Methods	This study aims to determine the relationship between sponsorship and antidepressant dosing and efficacy in RCTs for major depressive disorder. RCTs from 1996 to June 2010.
Data	58 RCTs of antidepressants for major depressive disorder (drug vs drug).
Comparisons	Sponsor vs non-sponsor company.
Outcomes	Effect size.
Funding	No funding provided.

Sinyor 2012 *(Continued)*

Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE and PsycINFO. Pharmaceutical websites were searched for unpublished RCTs.
Control for bias?	No	No control for bias.

Spanemberg 2012

Methods	To carry out a qualitative analysis of RCT methodology in the treatment of bipolar depression. RCTs from 1990 to June 2010.
Data	30 drug RCTs for bipolar depression (mixed comparisons).
Comparisons	Industry, non-industry and not stated.
Outcomes	Study results and risk of bias (follow-up).
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two authors included studies.
Comprehensive search?	No	Only PubMed searched.
Control for bias?	No	No control for bias.

Sung 2013

Methods	To determine as to what proportion of prospectively designed comparative studies on botulinum toxin A injections in patients with cerebral palsy was industry sponsored and whether the qualitative conclusions by the study authors about the use of the botulinum toxin A injection was associated with the financial sponsorship of the studies. Search from January 1991 to November 2011.

Sung 2013 *(Continued)*

Data	66 prospective comparative studies of botulinum toxin A injections in cerebral palsy (mixed comparisons).
Comparisons	Industry, non-industry and not stated.
Outcomes	Study results, study conclusions and risk of bias (PEDro score, 0-10 point scale).
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Only one assessor included studies.
Comprehensive search?	No	PubMed.
Control for bias?	No	No control for bias.

Tulikangas 2006

Methods	To determine if there is a significant difference in outcomes of clinical trials funded by industry or not of antimuscarinic medications used to treat overactive bladder symptoms and detrusor overactivity. RCTs from 1980 to 2002.
Data	24 RCTs of antimuscarinic drugs (various comparators).
Comparisons	Industry funded and public funded.
Outcomes	Study results.
Funding	Not reported.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE and references.
Control for bias?	No	No control for bias.

Tungaraza 2007

Methods	To compare drug trials reported in three major psychiatric journals to investigate whether treatments are more likely to report favorable outcomes when they are funded by the pharmaceutical industry. Studies published in the *British Journal of Psychiatry*, *American Journal of Psychiatry* and *Archives of General Psychiatry* from 2000 to 2004.
Data	198 psychiatric drug trials (various designs and comparators).
Comparisons	Industry sponsored, industry authored and independent.
Outcomes	Study conclusions.
Funding	No funding provided.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearch of journals.
Control for bias?	No	No control for bias.

van Lent 2014

Methods	To evaluate whether submitted manuscripts onRCTs with drugs are more likely to be accepted if they report positive results. Manuscripts of drug trials submitted from January 2010 through April 2012 to one general medical journal (BMJ) and seven specialty journals (*Annals of the Rheumatic Diseases, British Journal of Ophthalmology, Gut, Heart, Thorax, Diabetologia,* and *Journal of Hepatology*).
Data	Sample of 472 drug RCTs (mixed comparisons) of which 98 had relevant data.
Comparisons	Industry, industry-supported and non-industry.
Outcomes	Study results.
Funding	Unrestricted educational grant from MSD.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.

van Lent 2014 *(Continued)*

Adequate study inclusion process?	No	Only one assessor included studies.
Comprehensive search?	Yes	Access to manuscripts provided by journal editors.
Control for bias?	No	No control for bias.

Vlad 2007

Methods	To identify factors that explain heterogeneity in trials of glucosamine. RCTs of glucosamine from 1980 to 2006.
Data	15 RCTs of glucosamine versus placebo for osteoarthritis.
Comparisons	Industry funding, industry participation, industry author and independent.
Outcomes	Study results, effect size and risk of bias (concealment of allocation and Jadad score, 0-5 point scale).
Funding	NIH.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, the Cochrane Library, conference abstracts, references and reviews.
Control for bias?	Yes	Exploration of heterogeneity.

Xu 2013

Methods	To examine the overall risk of cardiovascular-related events associated with testosterone therapy. RCTs from up to December 2012.
Data	27 RCTs of testosterone therapy for men (drug vs placebo).
Comparisons	Industry and non-industry.
Outcomes	Effect size and risk of bias (concealment of allocation, detection bias and performance bias).
Funding	No funding provided.
Notes	

Risk of bias

Xu 2013 *(Continued)*

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	PubMed, WHO Trial Registry, reference lists and reviews.
Control for bias?	No	No control for bias.

Zhang 2013

Methods	To compare second-generation vs first-generation antipsychotics in first-episode psychosis. RCTs up to December 2010.
Data	RCTs of second-generation vs first-generation antipsychotics in first-episode psychosis (drug vs drug).
Comparisons	Industry and government.
Outcomes	Effect size.
Funding	Supported in part by The Zucker Hillside Hospital Advanced Center for Intervention and Services Research for the Study of Schizophrenia and Center for Intervention Development and Applied Research from the National Institute of Mental Health.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	PubMed and Web of Science. Additional sources were reference lists of RCTs and reviews, conference abstracts and contact to manufacturers.
Control for bias?	No	No control for bias.

RCT: Randomized controlled trial

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

Study	Reason for exclusion
Adams 2013	No industry versus non-industry comparison.
Adams 2014	No industry versus non-industry comparison.

Study	Reason for exclusion
Afshari 2011	No industry versus non-industry comparison.
Alves 2013	No industry versus non-industry comparison.
Amiri 2014	No separate drug or device data.
Aneja 2013	No separate drug or device data.
Apler 2011	No industry versus non-industry comparison.
Auerbach 2013	No industry versus non-industry comparison.
Baethge 2013	No relevant outcomes.
Bailey 2011	No relevant outcomes.
Baker 2013	No industry versus non-industry comparison.
Bala 2013	No relevant outcomes.
Balevi 2011	No quantitative data.
Barbui 2011	No industry versus non-industry comparison.
Batalla 2011	No relevant outcomes.
Bennett 2010	Includes non human studies.
Bourgeois 2012	No relevant outcomes.
Brignardello-Petersen 2013	No industry versus non-industry comparison.
Buesching 2012	No industry versus non-industry comparison.
Califf 2012	No industry versus non-industry comparison.
Catala-Lopez 2013	No relevant outcomes.
Chaturvedi 2014	No industry versus non-industry comparison.
Chen 2012	No industry versus non-industry comparison.
Chowers 2009	No relevant outcomes.
Cipriani 2012	No industry versus non-industry comparison.
Cipriani 2012a	No industry versus non-industry comparison.
Conen 2008	No relevant outcomes.
Cordoba 2010	No industry versus non-industry comparison.
Cosgrove 2011	No industry versus non-industry comparison.
Cunningham 2007	No separate drug or device data.

Study	Reason for exclusion
Deb 2014	No industry versus non-industry comparison.
Demicheli 2014	No industry versus non-industry comparison.
Do 2015	No industry versus non-industry comparison.
Dufka 2014	No industry versus non-industry comparison.
Dunn 2012	No industry versus non-industry comparison.
Dunn 2014	Includes systematic reviews.
Faggion 2014	Includes systematic reviews.
Finnerup 2015	No industry versus non-industry comparison.
Fleurence 2010	No relevant outcomes.
Friedman 2004	Conflicts of interest, not funding.
Fu 2013	No industry versus non-industry comparison.
Fukunaga 2014	No industry versus non-industry comparison.
Furuse 2011	No industry versus non-industry comparison.
Garattini 2010	No relevant outcomes.
Garrison 2010	No industry versus non-industry comparison.
Gasparyan 2013	No quantitative data.
Gerrald 2010	No industry versus non-industry comparison.
Gewandter 2014	No relevant outcomes.
Glick 2006	No relevant outcomes.
Glujovsky 2012	No industry versus non-industry comparison.
Goswami 2014	No relevant outcomes.
Graham 2012	No industry versus non-industry comparison.
Grillo-Ardila 2014	No industry versus non-industry comparison.
Guaiana 2013	No industry versus non-industry comparison.
Guo 2013	No industry versus non-industry comparison.
Guo 2014	No relevant outcomes.
Hall 2007	No relevant outcomes.
Hartling 2011	No relevant outcomes.

Study	Reason for exclusion
Hartung 2014	No industry versus non-industry comparison.
Hashmi 2014	No quantitative data.
Hill 2007	No relevant outcomes (not methodological quality, but reporting quality).
Hodgson 2014	No relevant outcomes.
Hughes 2014	No industry versus non-industry comparison.
Ioannidis 2013	No relevant outcomes.
Ipser 2015	No relevant outcomes.
Jagsi 2009	No separate drug or device data.
Jang 2010	Includes economic analyses.
Jefferson 2012	No industry versus non-industry comparison.
Jefferson 2014	No relevant outcomes.
Jones 2013	No relevant outcomes.
Kaiser 2012	No relevant outcomes.
Khan 2008	No separate drug or device data.
Kjaergard 1999	No separate drug or device data.
Komossa 2011	No relevant outcomes.
Krauth 2014	Includes non human studies.
Krzyzanowska 2003	No relevant outcomes.
Kulier 2004	No quantitative data.
Kulkarni 2007	No relevant outcomes.
Lai 2006	No separate drug or device data.
Lawrie 2011	No relevant outcomes.
Leopold 2003	No separate drug or device data.
Lethaby 2013	No relevant outcomes.
Leucht 2009a	No relevant outcomes.
Leucht 2009b	No relevant outcomes.
Li 2013	No relevant outcomes.
Lopez 2014	Conflicts of interest, not funding.

Study	Reason for exclusion
Lundh 2012	No industry versus non-industry comparison.
Lunn 2014	No relevant outcomes.
Magni 2013	No relevant outcomes.
Manzoli 2011	No relevant outcomes.
Manzoli 2014	No relevant outcomes.
McIlvennan 2014	No relevant outcomes.
McLennan 2008	No relevant outcomes.
Montedori 2011	No separate drug or device data.
Montori 2005	No relevant outcomes.
Moteshafi 2012	No industry versus non-industry comparison.
Nkansah 2009	Calcium supplementation, not a drug.
Okike 2007	Conflicts of interest, not funding.
Okike 2008	No relevant outcomes.
Peura 2012	Includes economic analyses.
Phillips 2012	No quantitative data.
Polyzos 2011	Includes economic analyses.
Probst 2014	Study protocol.
Procyshyn 2004	No relevant data for non-industry studies.
Purgato 2014	No relevant outcomes.
Radecki 2011	No relevant outcomes.
Ramagopalan 2014	No relevant outcomes.
Rattehalli 2010	No relevant outcomes.
Roach 2008	No separate drug or device data.
Sanossian 2006	No relevant outcomes.
Sawata 2011	No separate drug or device data.
Schott 2010	No quantitative data.
Schott 2010a	No relevant outcomes.
Schott 2013	No relevant outcomes.

Study	Reason for exclusion
Shah 2005	No separate drug or device data.
Shamliyan 2012	No relevant outcomes.
Shen 2014	No relevant outcomes.
Stamatakis 2013	No quantitative data.
Strupp 2010	No quantitative data.
Sun 2011	No relevant outcomes.
Sun 2013	No separate drug or device data.
Thirugnanam 2012	Includes economic analyses.
Thomas 2008	No relevant outcomes (not methodological quality, but reporting quality).
Thomson 2010	No separate drug or device data.
Valachis 2012	Includes economic analyses.
van Lent 2013	No quantitative data.
Wang 2010	Conflicts of interest, not funding.
Watanabe 2010	No relevant outcomes.
Yao 2007	No separate drug or device data.
Yaphe 2001	No separate drug or device data.
Yuan 2011	No relevant outcomes.
Yue 2013	No separate drug or device data.
Zani 2011	No relevant outcomes.
Zulman 2011	No relevant outcomes.

DATA AND ANALYSES

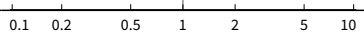
Comparison 1. Results: Industry sponsored versus non-industry sponsored studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable efficacy results	25	2923	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.17, 1.37]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of studies with favorable harms results	4	826	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.64, 2.93]

Analysis 1.1. Comparison 1 Results: Industry sponsored versus non-industry sponsored studies, Outcome 1 Number of studies with favorable efficacy results.

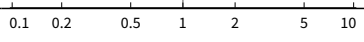
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alasbali 2009	7/29	2/10		0.34%	1.21[0.3,4.88]
Bariani 2013	32/56	25/49		4.02%	1.12[0.78,1.6]
Bero 2007	65/94	48/97		6.79%	1.4[1.1,1.78]
Bond 2012	56/67	2/4		0.66%	1.67[0.62,4.48]
Booth 2008	49/120	50/165		4.79%	1.35[0.98,1.85]
Bourgeois 2010	222/260	48/85		8.65%	1.51[1.25,1.83]
Clark 2002	8/16	1/3		0.24%	1.5[0.28,8]
Clifford 2002	46/66	21/34		4.96%	1.13[0.83,1.54]
Djulbegovic 2013	19/33	17/52		2.42%	1.76[1.08,2.87]
Etter 2007	25/49	9/41		1.5%	2.32[1.23,4.4]
Flacco 2015	152/182	86/137		10.99%	1.33[1.15,1.54]
Gan 2012	70/162	25/91		3.67%	1.57[1.08,2.29]
Kelly 2006	12/13	4/8		1.23%	1.85[0.91,3.76]
Khan 2012	39/54	24/32		6.24%	0.96[0.74,1.25]
Momeni 2009	20/24	69/85		8.11%	1.03[0.84,1.26]
Moncrieff 2003	2/2	2/7		0.5%	2.67[0.85,8.39]
Perlis 2005b	93/113	37/49		9.19%	1.09[0.91,1.31]
Rasmussen 2009	66/109	14/28		3.35%	1.21[0.81,1.81]
Rattinger 2009	26/36	18/25		4.76%	1[0.73,1.38]
Roper 2014	91/152	34/64		6.09%	1.13[0.87,1.47]
Spanemberg 2012	10/14	6/16		1.22%	1.9[0.93,3.89]
Sung 2013	22/28	13/25		3.06%	1.51[0.99,2.31]
Tulikangas 2006	15/15	7/9		3.81%	1.29[0.89,1.87]
van Lent 2014	46/71	14/27		3.33%	1.25[0.84,1.87]
Vlad 2007	5/11	0/4		0.09%	4.58[0.31,68.24]
Total (95% CI)	**1776**	**1147**		**100%**	**1.27[1.17,1.37]**
Total events: 1198 (Industry), 576 (Non-industry)					
Heterogeneity: Tau^2=0.01; Chi^2=33.55, df=24(P=0.09); I^2=28.47%					
Test for overall effect: Z=5.63(P<0.0001)					



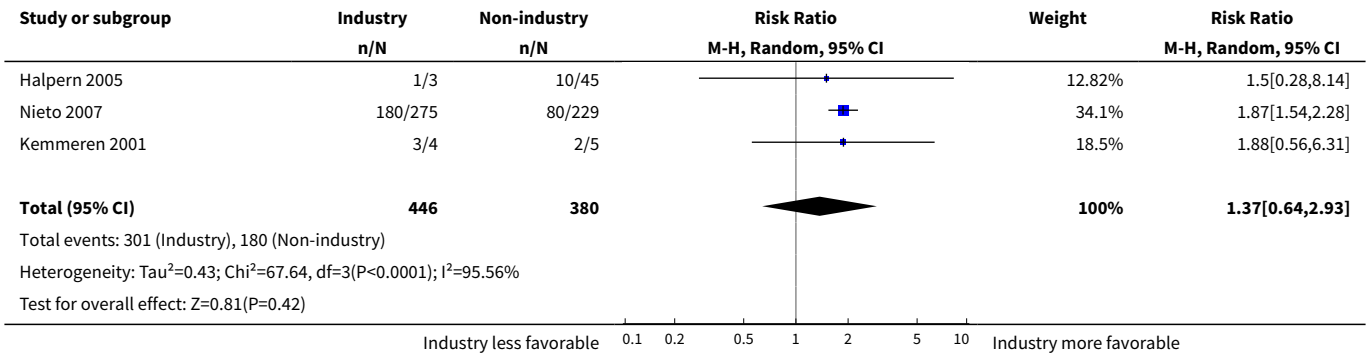
Industry less favorable — Industry more favorable

Analysis 1.2. Comparison 1 Results: Industry sponsored versus non-industry sponsored studies, Outcome 2 Number of studies with favorable harms results.

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
Als-Nielsen 2003	117/164	88/101		34.58%	0.82[0.72,0.93]



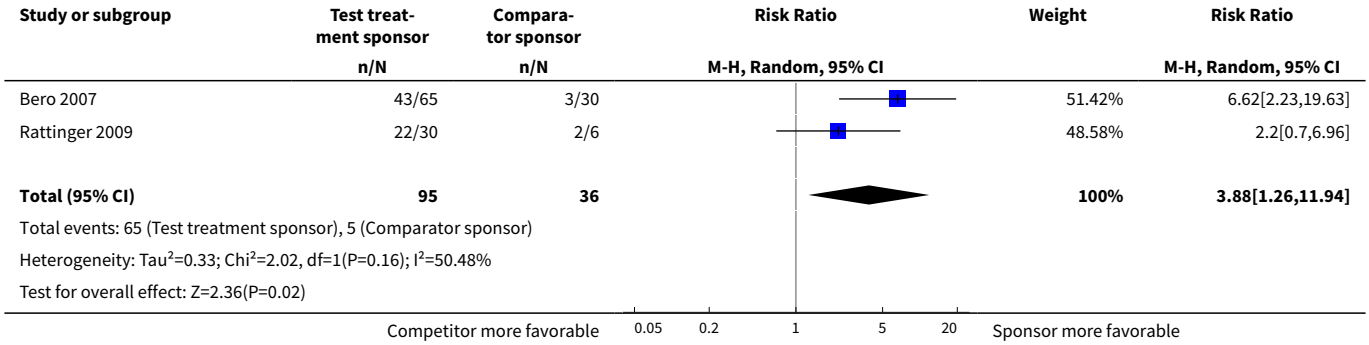
Industry less favorable — Industry more favorable



Comparison 2. Results: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable test treatment efficacy results	2	131	Risk Ratio (M-H, Random, 95% CI)	3.88 [1.26, 11.94]

Analysis 2.1. Comparison 2 Results: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company, Outcome 1 Number of studies with favorable test treatment efficacy results.

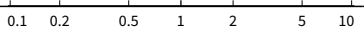


Comparison 3. Conclusions: industry sponsored versus non-industry sponsored studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable conclusions	29	4583	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.19, 1.51]

Analysis 3.1. Comparison 3 Conclusions: industry sponsored versus non-industry sponsored studies, Outcome 1 Number of studies with favorable 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
Ahmer 2005	125/138	39/50		4.28%	1.16[0.99,1.36]
Alasbali 2009	26/29	2/10		0.78%	4.48[1.29,15.58]
Als-Nielsen 2003	92/197	43/173		3.59%	1.88[1.39,2.53]
Bariani 2013	39/56	39/49		3.98%	0.88[0.7,1.09]
Bartels 2012	28/31	76/129		4.16%	1.53[1.27,1.84]
Bero 2007	66/94	39/97		3.71%	1.75[1.32,2.3]
Booth 2008	66/118	55/153		3.77%	1.56[1.19,2.03]
Buchkowsky 2004	138/181	224/319		4.44%	1.09[0.97,1.21]
Chard 2000	106/108	373/383		4.6%	1.01[0.98,1.04]
Cho 1996	39/40	89/112		4.45%	1.23[1.1,1.36]
Clark 2002	21/23	5/7		2.64%	1.28[0.79,2.08]
Davidson 1986	32/36	31/49		3.88%	1.41[1.1,1.79]
DeGeorge 2015	18/18	77/106		4.35%	1.34[1.17,1.54]
Djulbegovic 2000	26/35	50/95		3.73%	1.41[1.07,1.85]
Djulbegovic 2013	29/32	29/52		3.76%	1.63[1.24,2.12]
Finucane 2004	30/30	12/18		3.44%	1.5[1.08,2.07]
Jefferson 2009	64/76	131/194		4.35%	1.25[1.09,1.43]
Kjaergard 2002	28/38	16/22		3.49%	1.01[0.74,1.39]
Lee 2012	15/43	4/10		1.37%	0.87[0.37,2.06]
Liss 2006	62/63	12/37		2.73%	3.03[1.9,4.84]
Lynch 2007	26/34	49/65		3.93%	1.01[0.8,1.28]
Peppercorn 2007	52/67	48/73		4.05%	1.18[0.96,1.46]
Perlis 2005a	87/102	47/77		4.11%	1.4[1.15,1.7]
Printz 2013	12/30	1/3		0.47%	1.2[0.23,6.31]
Rasmussen 2009	83/109	15/28		3.26%	1.42[0.99,2.04]
Rattinger 2009	31/36	21/25		4.02%	1.03[0.83,1.27]
Ridker 2006	121/189	21/51		3.35%	1.55[1.1,2.2]
Sung 2013	15/28	5/25		1.39%	2.68[1.14,6.31]
Tungaraza 2007	124/146	28/44		3.93%	1.33[1.06,1.69]
Total (95% CI)	**2127**	**2456**		**100%**	**1.34[1.19,1.51]**
Total events: 1601 (Industry), 1581 (Non-industry)					
Heterogeneity: Tau^2=0.08; Chi^2=336.13, df=28(P<0.0001); I^2=91.67%					
Test for overall effect: Z=4.77(P<0.0001)					

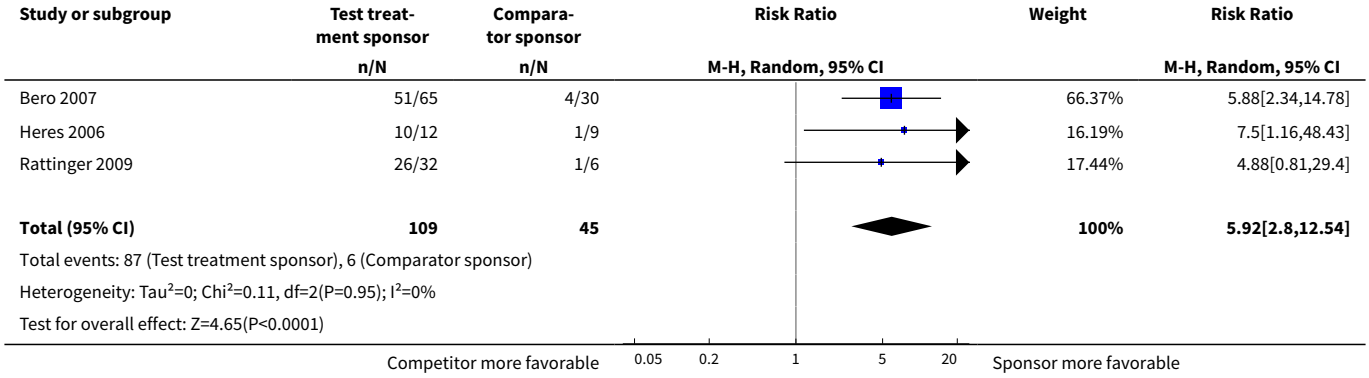


Industry less favorable — Industry more favorable

Comparison 4. Conclusions: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable test treatment conclusions	3	154	Risk Ratio (M-H, Random, 95% CI)	5.92 [2.80, 12.54]

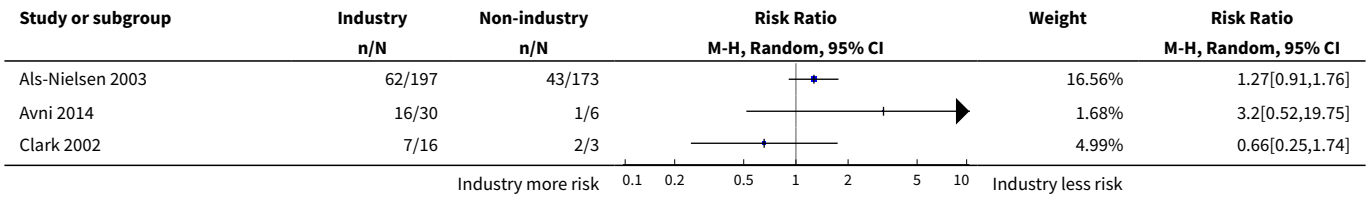
Analysis 4.1. Comparison 4 Conclusions: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company, Outcome 1 Number of studies with favorable test treatment conclusions.

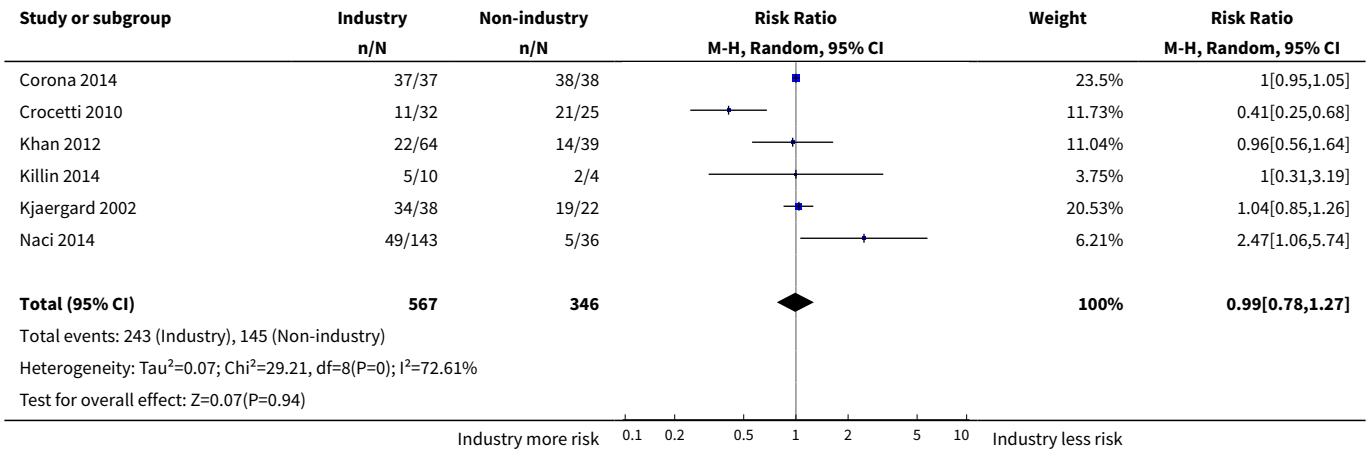


Comparison 5. Risk of bias: industry sponsored versus non-industry sponsored studies

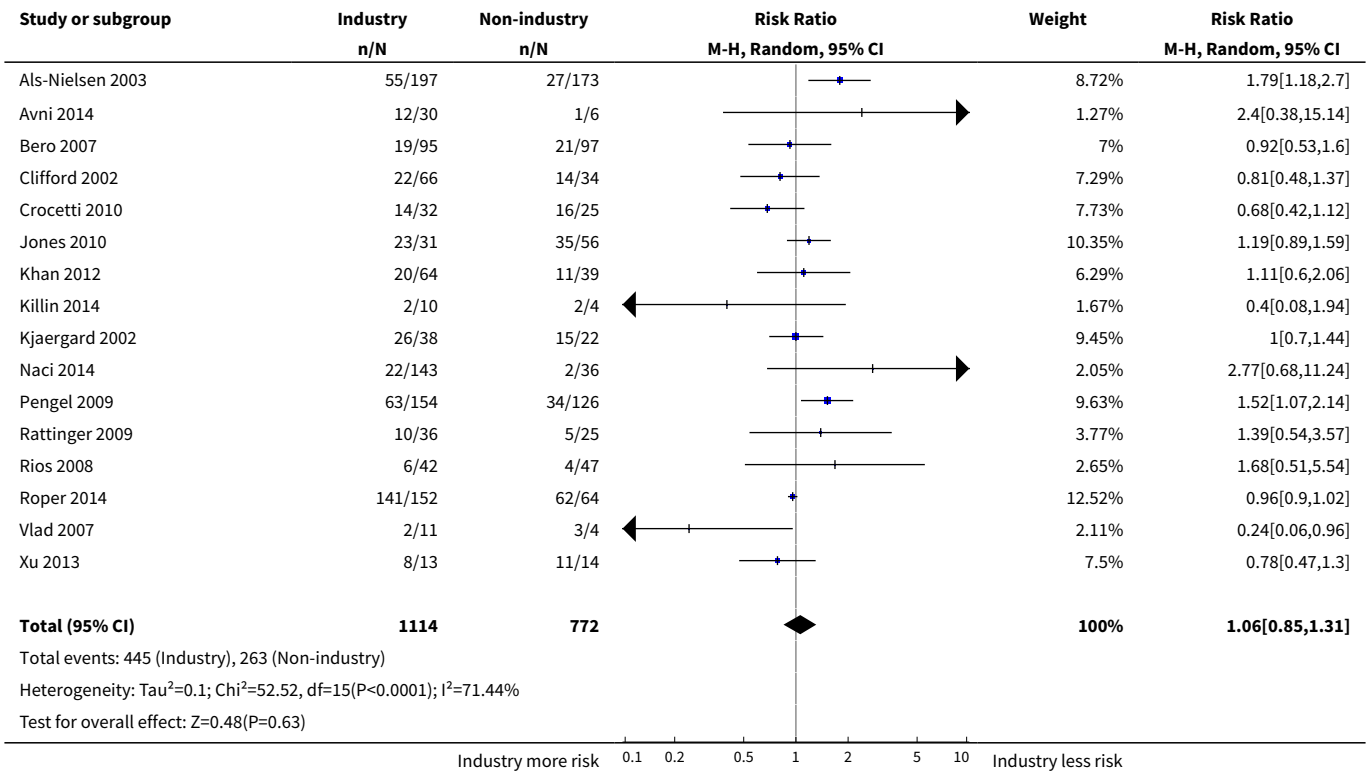
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with low risk of bias from sequence generation	9	913	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.78, 1.27]
2 Number of studies with low risk of bias from concealment of allocation	16	1886	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.85, 1.31]
3 Number of studies with low risk of bias from blinding-overall	13	1578	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.05, 1.50]
4 Number of studies with low risk from blinding-performance bias	3	128	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.60, 2.62]
5 Number of studies with low risk from blinding-detection bias	4	307	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.02, 2.12]
6 Number of studies with low risk of bias from loss to follow-up	6	416	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.92, 1.18]
7 Number of studies with low risk of bias from selective outcome reporting	2	193	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.61, 3.60]

Analysis 5.1. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 1 Number of studies with low risk of bias from sequence generation.

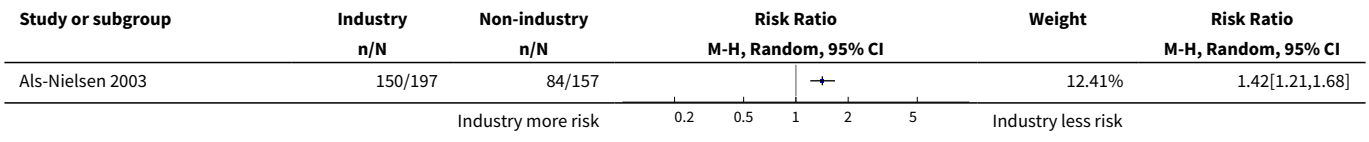




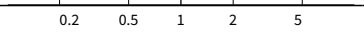
Analysis 5.2. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 2 Number of studies with low risk of bias from concealment of allocation.



Analysis 5.3. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 3 Number of studies with low risk of bias from blinding-overall.



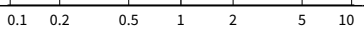
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Avni 2014	16/30	1/6		0.92%	3.2[0.52,19.75]
Bero 2007	53/95	36/97		9.76%	1.5[1.1,2.06]
Clark 2002	6/16	1/3		1.02%	1.13[0.2,6.29]
Corona 2014	32/37	32/38		12.06%	1.03[0.85,1.24]
Crocetti 2010	28/32	23/25		12.27%	0.95[0.8,1.13]
Khan 2012	55/64	20/39		9.64%	1.68[1.21,2.31]
Kjaergard 2002	26/38	13/22		8.11%	1.16[0.77,1.74]
Perlis 2005a	71/102	27/77		9.48%	1.99[1.43,2.76]
Rasmussen 2009	33/109	3/28		2.24%	2.83[0.93,8.54]
Rattinger 2009	20/36	15/25		7.72%	0.93[0.6,1.43]
Rios 2008	7/42	13/47		3.61%	0.6[0.27,1.37]
Roper 2014	89/152	35/64		10.77%	1.07[0.83,1.39]
Total (95% CI)	**950**	**628**		**100%**	**1.25[1.05,1.5]**
Total events: 586 (Industry), 303 (Non-industry)					
Heterogeneity: Tau^2=0.06; Chi^2=43.06, df=12(P<0.0001); I^2=72.13%					
Test for overall effect: Z=2.44(P=0.01)					



Industry more risk | Industry less risk

Analysis 5.4. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 4 Number of studies with low risk from blinding-performance bias.

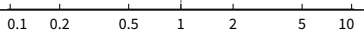
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Jones 2010	16/31	14/56		38.99%	2.06[1.17,3.64]
Killin 2014	4/10	3/4		27.55%	0.53[0.21,1.37]
Xu 2013	8/13	6/14		33.46%	1.44[0.68,3.02]
Total (95% CI)	**54**	**74**		**100%**	**1.26[0.6,2.62]**
Total events: 28 (Industry), 23 (Non-industry)					
Heterogeneity: Tau^2=0.28; Chi^2=5.91, df=2(P=0.05); I^2=66.17%					
Test for overall effect: Z=0.62(P=0.54)					



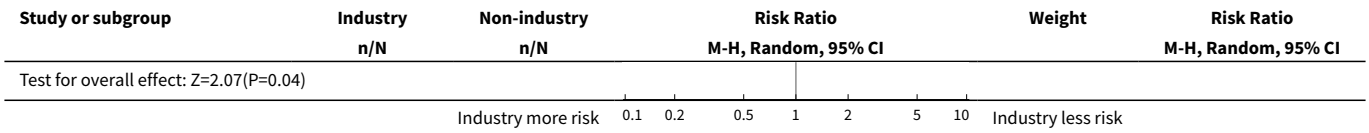
Industry more risk | Industry less risk

Analysis 5.5. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 5 Number of studies with low risk from blinding-detection bias.

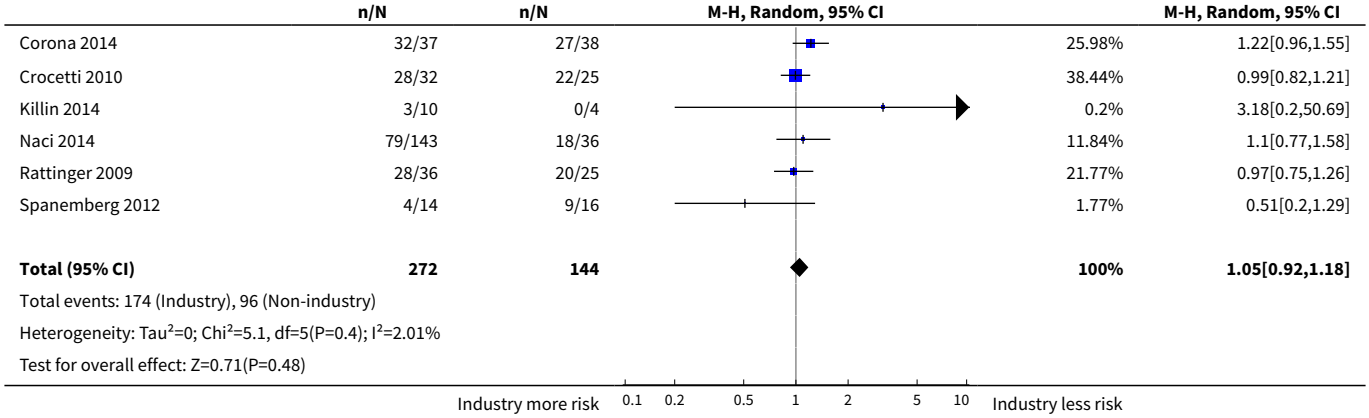
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Jones 2010	15/31	15/56		41.8%	1.81[1.03,3.18]
Killin 2014	5/10	2/4		9.94%	1[0.31,3.19]
Naci 2014	60/143	10/36		42.48%	1.51[0.86,2.65]
Xu 2013	2/13	4/14		5.78%	0.54[0.12,2.46]
Total (95% CI)	**197**	**110**		**100%**	**1.47[1.02,2.12]**
Total events: 82 (Industry), 31 (Non-industry)					
Heterogeneity: Tau^2=0; Chi^2=2.63, df=3(P=0.45); I^2=0%					



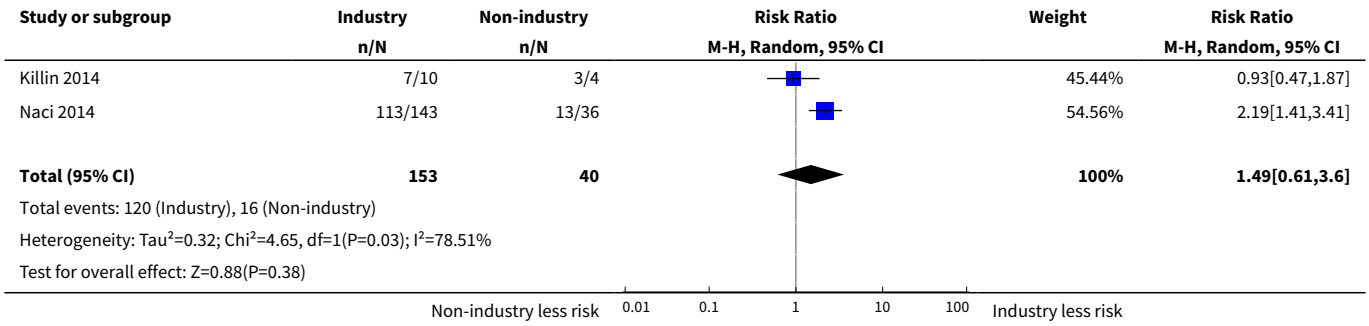
Industry more risk | Industry less risk



Analysis 5.6. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 6 Number of studies with low risk of bias from loss to follow-up.



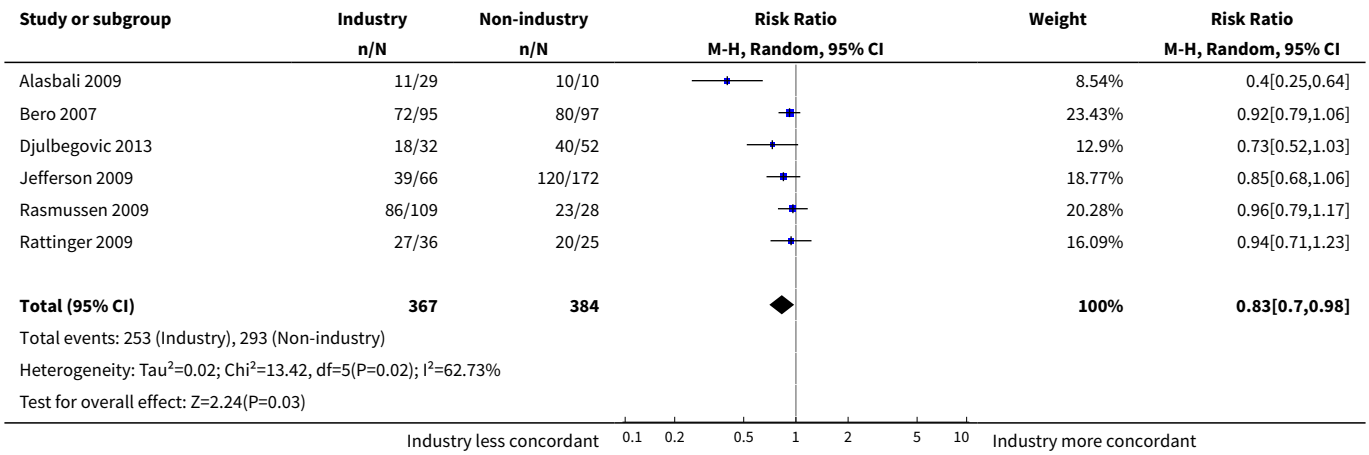
Analysis 5.7. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 7 Number of studies with low risk of bias from selective outcome reporting.



Comparison 6. Concordance between study results and conclusions: industry sponsored versus non-industry sponsored studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with concordant study results and conclusions	6	751	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.70, 0.98]

Analysis 6.1. Comparison 6 Concordance between study results and conclusions: industry sponsored versus non-industry sponsored studies, Outcome 1 Number of studies with concordant study results and conclusions.



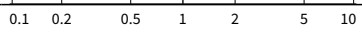
Comparison 7. Subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable efficacy results, stratified by risk of bias	25	2923	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.17, 1.37]
1.1 High risk of bias	20	2107	Risk Ratio (M-H, Random, 95% CI)	1.20 [1.11, 1.30]
1.2 Low risk of bias	5	816	Risk Ratio (M-H, Random, 95% CI)	1.46 [1.25, 1.71]
2 Number of studies with favorable harms results, stratified by risk of bias	4	826	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.64, 2.93]
2.1 High risk of bias	3	561	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.54, 2.27]
2.2 Low risk of bias	1	265	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.72, 0.93]
3 Number of studies with favorable conclusions, stratified by risk of bias	29	4583	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.19, 1.51]
3.1 High risk of bias	23	3515	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.15, 1.50]
3.2 Low risk of bias	6	1068	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.12, 1.79]
4 Number of studies with favorable efficacy results, stratified by type of intervention	25	2923	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.15, 1.38]
4.1 Drug studies	25	2904	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.17, 1.38]
4.2 Device studies	1	19	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.26, 0.97]

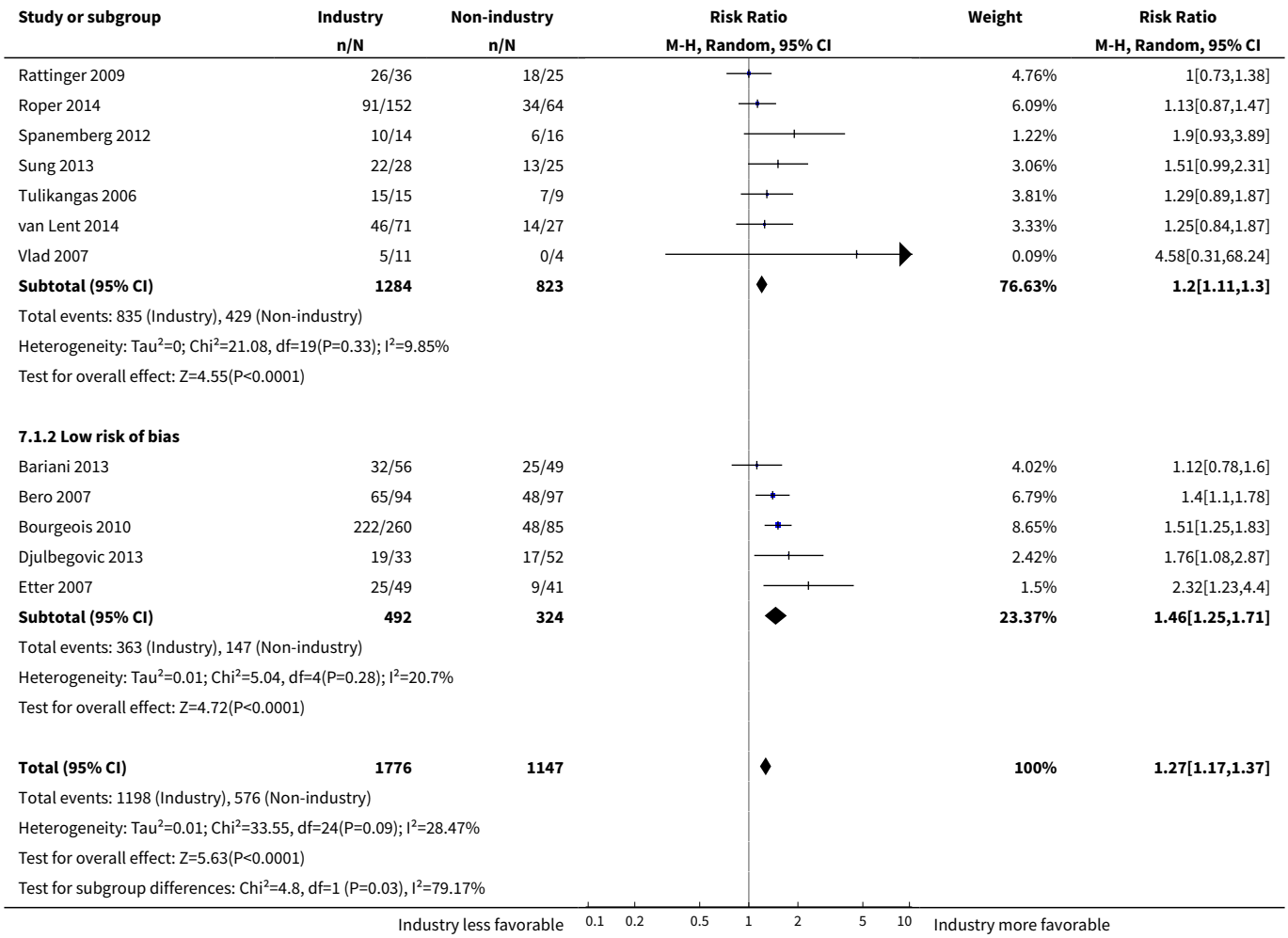
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Number of studies with favorable conclusions, stratified by type of intervention	29	4583	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.18, 1.49]
5.1 Drug studies	27	4179	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.17, 1.52]
5.2 Device studies	4	404	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.13, 1.57]
6 Number of studies with favorable efficacy results, stratified by type of domain	25	2923	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.17, 1.37]
6.1 Specific treatments or diseases	20	1845	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.13, 1.42]
6.2 Mixed domain	5	1078	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.18, 1.46]
7 Number of studies with favorable harms results, stratified by type of domain	4	826	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.64, 2.93]
7.1 Specific treatments or diseases	3	561	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.54, 2.27]
7.2 Mixed study domain	1	265	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.72, 0.93]
8 Number of studies with favorable conclusions, stratified by type of domain	29	4583	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.19, 1.51]
8.1 Specific treatments or diseases	24	3416	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.17, 1.61]
8.2 Mixed study domain	5	1167	Risk Ratio (M-H, Random, 95% CI)	1.26 [1.07, 1.49]

Analysis 7.1. Comparison 7 Subgroup analysis, Outcome 1 Number of studies with favorable efficacy results, stratified by risk of bias.

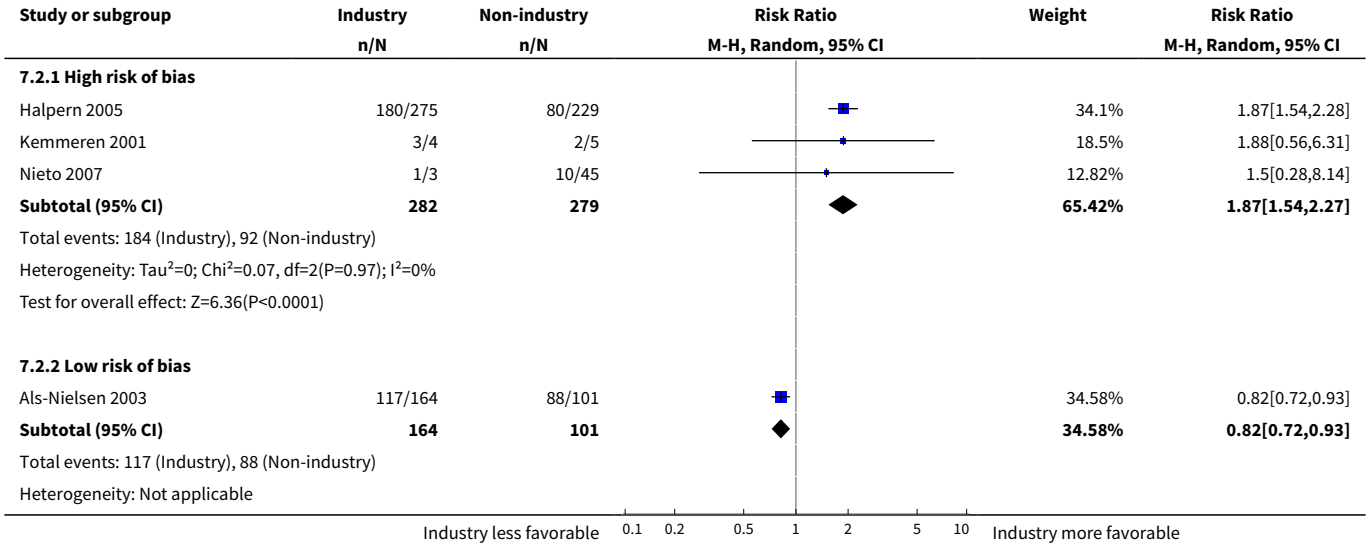
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 High risk of bias					
Alasbali 2009	7/29	2/10		0.34%	1.21[0.3,4.88]
Bond 2012	56/67	2/4		0.66%	1.67[0.62,4.48]
Booth 2008	49/120	50/165		4.79%	1.35[0.98,1.85]
Clark 2002	8/16	1/3		0.24%	1.5[0.28,8]
Clifford 2002	46/66	21/34		4.96%	1.13[0.83,1.54]
Flacco 2015	152/182	86/137		10.99%	1.33[1.15,1.54]
Gan 2012	70/162	25/91		3.67%	1.57[1.08,2.29]
Kelly 2006	12/13	4/8		1.23%	1.85[0.91,3.76]
Khan 2012	39/54	24/32		6.24%	0.96[0.74,1.25]
Momeni 2009	20/24	69/85		8.11%	1.03[0.84,1.26]
Moncrieff 2003	2/2	2/7		0.5%	2.67[0.85,8.39]
Perlis 2005b	93/113	37/49		9.19%	1.09[0.91,1.31]
Rasmussen 2009	66/109	14/28		3.35%	1.21[0.81,1.81]



Industry less favorable — Industry more favorable



Analysis 7.2. Comparison 7 Subgroup analysis, Outcome 2 Number of studies with favorable harms results, stratified by risk of bias.

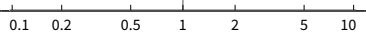


Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=3.2(P=0)					
Total (95% CI)	**446**	**380**		**100%**	**1.37[0.64,2.93]**
Total events: 301 (Industry), 180 (Non-industry)					
Heterogeneity: Tau^2=0.43; Chi^2=67.64, df=3(P<0.0001); I^2=95.56%					
Test for overall effect: Z=0.81(P=0.42)					
Test for subgroup differences: Chi^2=50.11, df=1 (P<0.0001), I^2=98%					

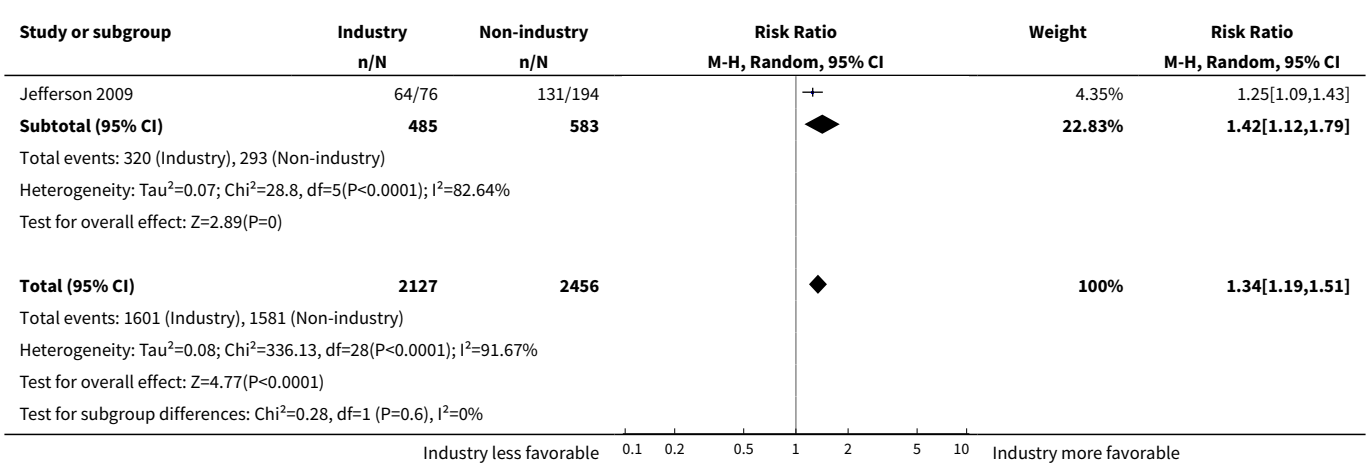
Industry less favorable — Industry more favorable

Analysis 7.3. Comparison 7 Subgroup analysis, Outcome 3 Number of studies with favorable conclusions, stratified by risk of bias.

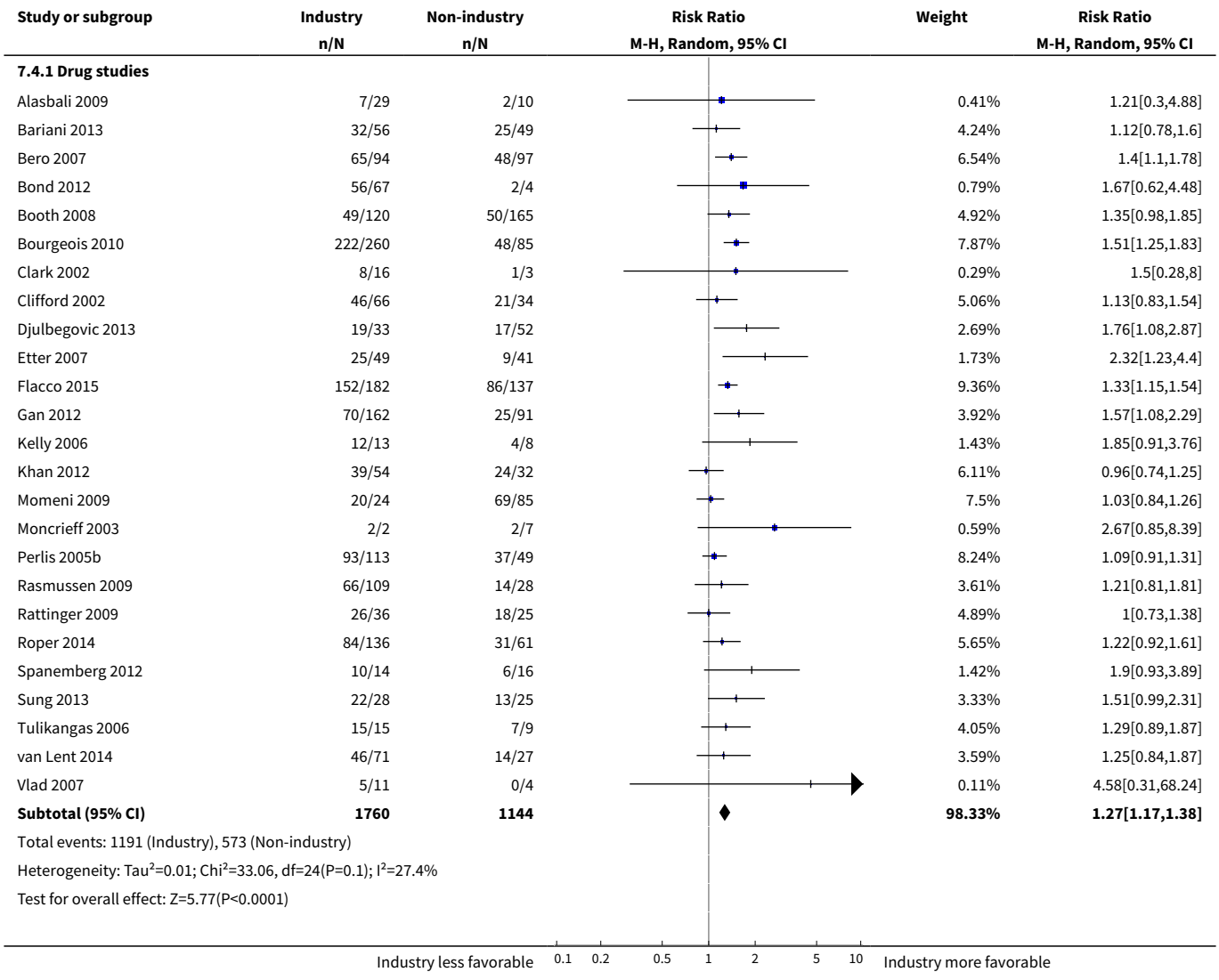
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.3.1 High risk of bias					
Ahmer 2005	125/138	39/50		4.28%	1.16[0.99,1.36]
Alasbali 2009	26/29	2/10		0.78%	4.48[1.29,15.58]
Bartels 2012	28/31	76/129		4.16%	1.53[1.27,1.84]
Booth 2008	66/118	55/153		3.77%	1.56[1.19,2.03]
Buchkowsky 2004	138/181	224/319		4.44%	1.09[0.97,1.21]
Chard 2000	106/108	373/383		4.6%	1.01[0.98,1.04]
Cho 1996	39/40	89/112		4.45%	1.23[1.1,1.36]
Clark 2002	21/23	5/7		2.64%	1.28[0.79,2.08]
Davidson 1986	32/36	31/49		3.88%	1.41[1.1,1.79]
DeGeorge 2015	18/18	77/106		4.35%	1.34[1.17,1.54]
Djulbegovic 2000	26/35	50/95		3.73%	1.41[1.07,1.85]
Kjaergard 2002	28/38	16/22		3.49%	1.01[0.74,1.39]
Lee 2012	15/43	4/10		1.37%	0.87[0.37,2.06]
Liss 2006	62/63	12/37		2.73%	3.03[1.9,4.84]
Lynch 2007	26/34	49/65		3.93%	1.01[0.8,1.28]
Peppercorn 2007	52/67	48/73		4.05%	1.18[0.96,1.46]
Perlis 2005a	87/102	47/77		4.11%	1.4[1.15,1.7]
Printz 2013	12/30	1/3		0.47%	1.2[0.23,6.31]
Rasmussen 2009	83/109	15/28		3.26%	1.42[0.99,2.04]
Rattinger 2009	31/36	21/25		4.02%	1.03[0.83,1.27]
Ridker 2006	121/189	21/51		3.35%	1.55[1.1,2.2]
Sung 2013	15/28	5/25		1.39%	2.68[1.14,6.31]
Tungaraza 2007	124/146	28/44		3.93%	1.33[1.06,1.69]
Subtotal (95% CI)	**1642**	**1873**		**77.17%**	**1.32[1.15,1.5]**
Total events: 1281 (Industry), 1288 (Non-industry)					
Heterogeneity: Tau^2=0.07; Chi^2=251.86, df=22(P<0.0001); I^2=91.26%					
Test for overall effect: Z=4.09(P<0.0001)					
7.3.2 Low risk of bias					
Als-Nielsen 2003	92/197	43/173		3.59%	1.88[1.39,2.53]
Bariani 2013	39/56	39/49		3.98%	0.88[0.7,1.09]
Bero 2007	66/94	39/97		3.71%	1.75[1.32,2.3]
Djulbegovic 2013	29/32	29/52		3.76%	1.63[1.24,2.12]
Finucane 2004	30/30	12/18		3.44%	1.5[1.08,2.07]



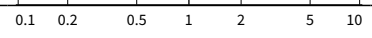
Industry less favorable — Industry more favorable



Analysis 7.4. Comparison 7 Subgroup analysis, Outcome 4 Number of studies with favorable efficacy results, stratified by type of intervention.

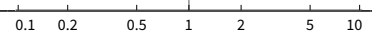


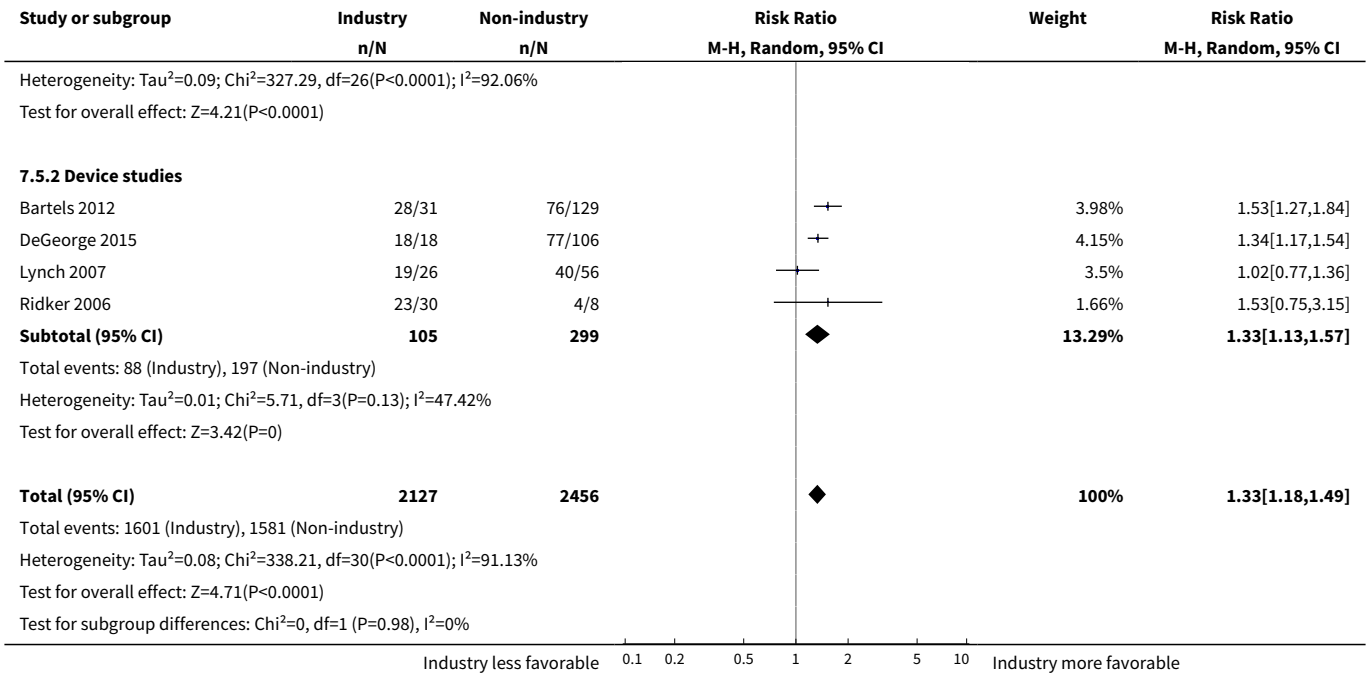
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.4.2 Device studies					
Roper 2014	7/16	3/3		1.67%	0.5[0.26,0.97]
Subtotal (95% CI)	**16**	**3**		**1.67%**	**0.5[0.26,0.97]**
Total events: 7 (Industry), 3 (Non-industry)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.06(P=0.04)					
Total (95% CI)	**1776**	**1147**		**100%**	**1.26[1.15,1.38]**
Total events: 1198 (Industry), 576 (Non-industry)					
Heterogeneity: Tau^2=0.02; Chi^2=40.88, df=25(P=0.02); I^2=38.85%					
Test for overall effect: Z=5(P<0.0001)					
Test for subgroup differences: Chi^2=7.64, df=1 (P=0.01), I^2=86.91%					



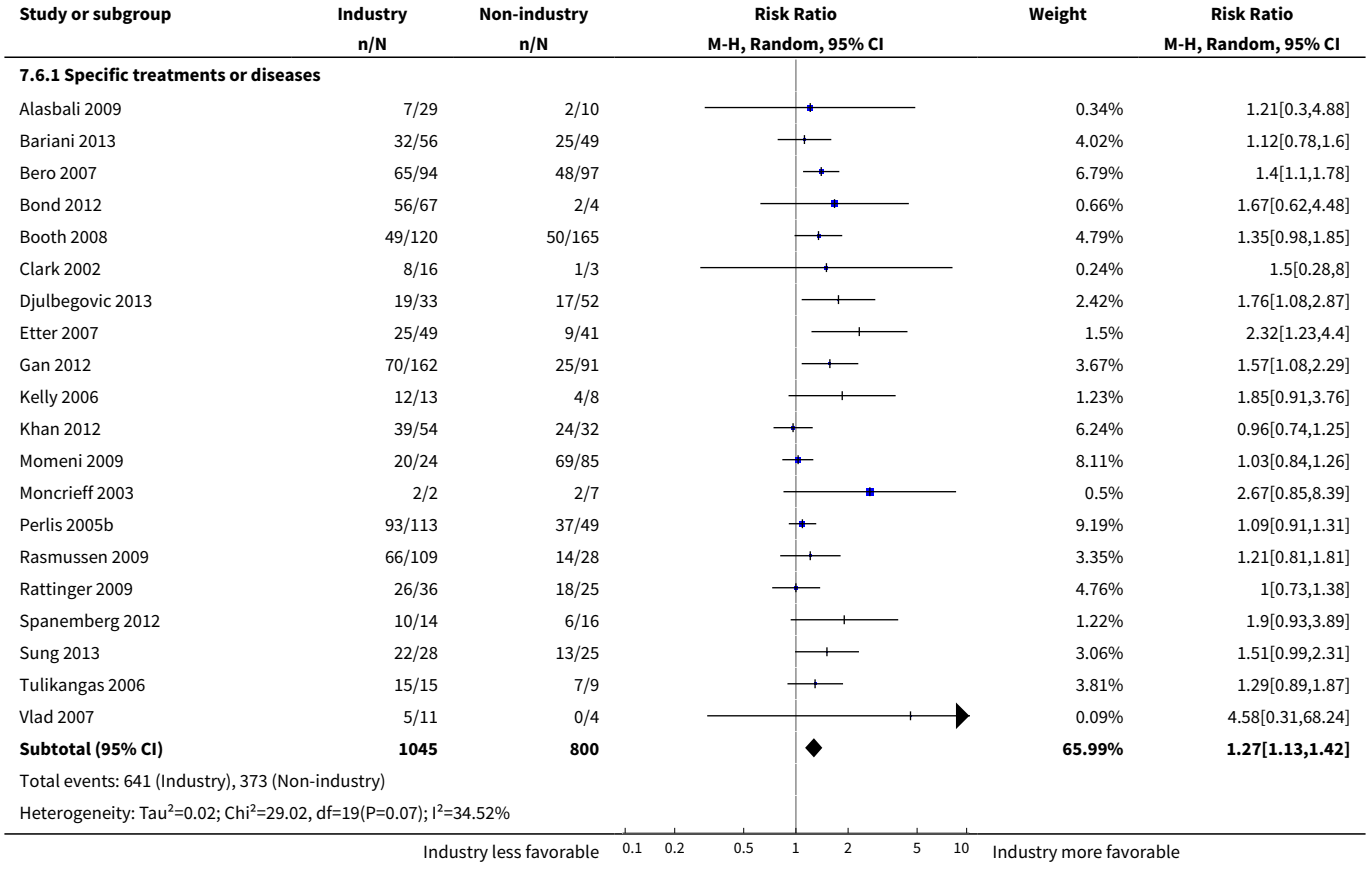
Analysis 7.5. Comparison 7 Subgroup analysis, Outcome 5 Number of studies with favorable conclusions, stratified by type of intervention.

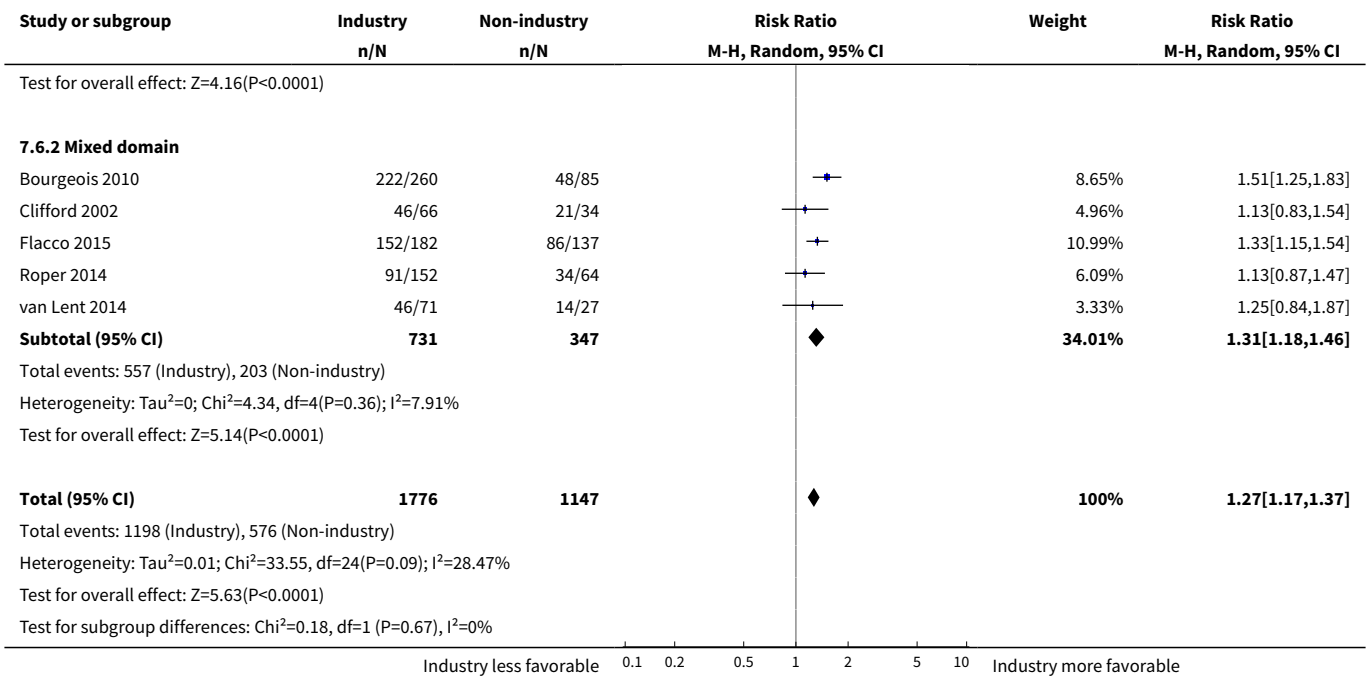
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
7.5.1 Drug studies					
Ahmer 2005	125/138	39/50		4.09%	1.16[0.99,1.36]
Alasbali 2009	26/29	2/10		0.74%	4.48[1.29,15.58]
Als-Nielsen 2003	92/197	43/173		3.43%	1.88[1.39,2.53]
Bariani 2013	39/56	39/49		3.8%	0.88[0.7,1.09]
Bero 2007	66/94	39/97		3.55%	1.75[1.32,2.3]
Booth 2008	66/118	55/153		3.6%	1.56[1.19,2.03]
Buchkowsky 2004	138/181	224/319		4.25%	1.09[0.97,1.21]
Chard 2000	106/108	373/383		4.39%	1.01[0.98,1.04]
Cho 1996	39/40	89/112		4.25%	1.23[1.1,1.36]
Clark 2002	21/23	5/7		2.52%	1.28[0.79,2.08]
Davidson 1986	32/36	31/49		3.71%	1.41[1.1,1.79]
Djulbegovic 2000	26/35	50/95		3.56%	1.41[1.07,1.85]
Djulbegovic 2013	29/32	29/52		3.59%	1.63[1.24,2.12]
Finucane 2004	30/30	12/18		3.29%	1.5[1.08,2.07]
Jefferson 2009	64/76	131/194		4.16%	1.25[1.09,1.43]
Kjaergard 2002	28/38	16/22		3.33%	1.01[0.74,1.39]
Lee 2012	15/43	4/10		1.31%	0.87[0.37,2.06]
Liss 2006	62/63	12/37		2.6%	3.03[1.9,4.84]
Lynch 2007	7/8	9/9		3.3%	0.88[0.63,1.21]
Peppercorn 2007	52/67	48/73		3.87%	1.18[0.96,1.46]
Perlis 2005a	87/102	47/77		3.93%	1.4[1.15,1.7]
Printz 2013	12/30	1/3		0.45%	1.2[0.23,6.31]
Rasmussen 2009	83/109	15/28		3.12%	1.42[0.99,2.04]
Rattinger 2009	31/36	21/25		3.84%	1.03[0.83,1.27]
Ridker 2006	98/159	17/43		2.97%	1.56[1.06,2.3]
Sung 2013	15/28	5/25		1.32%	2.68[1.14,6.31]
Tungaraza 2007	124/146	28/44		3.75%	1.33[1.06,1.69]
Subtotal (95% CI)	**2022**	**2157**		**86.71%**	**1.33[1.17,1.52]**
Total events: 1513 (Industry), 1384 (Non-industry)					



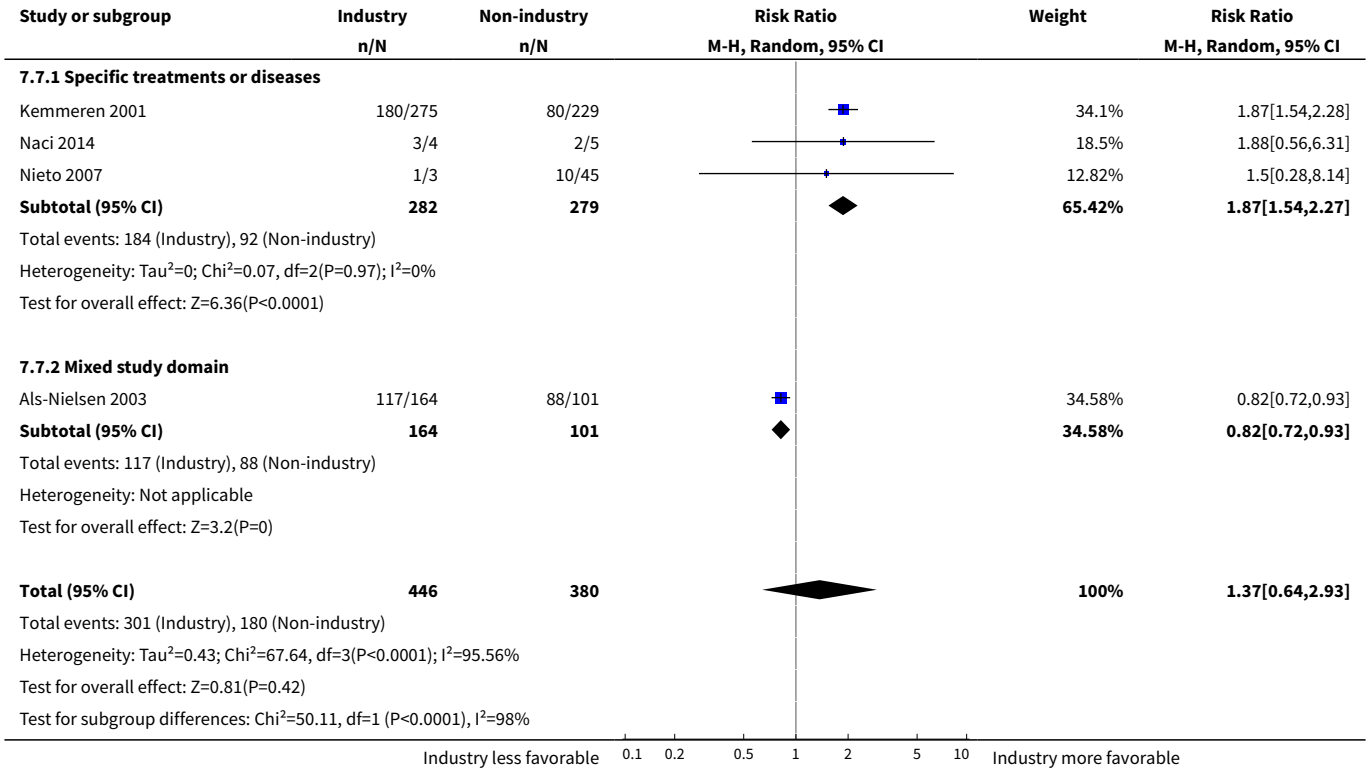


Analysis 7.6. Comparison 7 Subgroup analysis, Outcome 6 Number of studies with favorable efficacy results, stratified by type of domain.



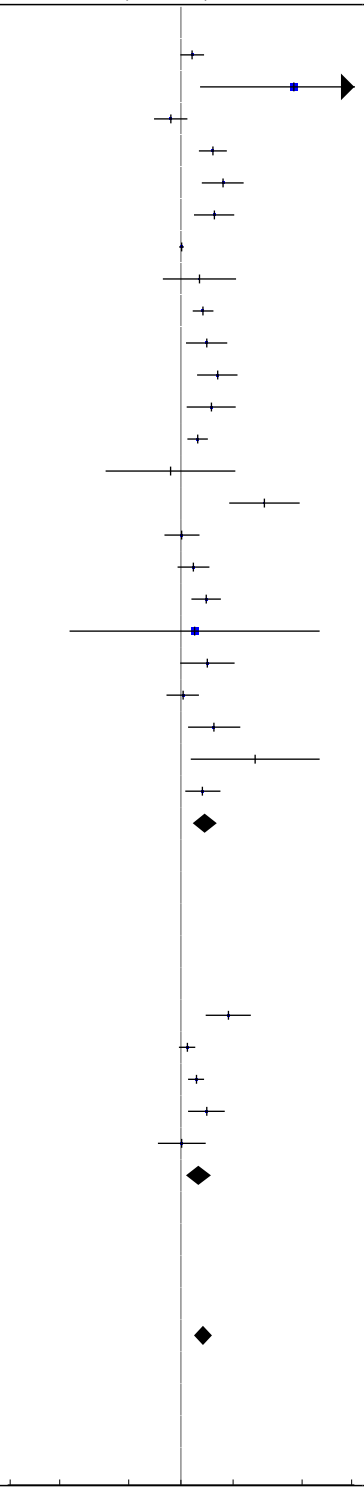


Analysis 7.7. Comparison 7 Subgroup analysis, Outcome 7 Number of studies with favorable harms results, stratified by type of domain.



Analysis 7.8. Comparison 7 Subgroup analysis, Outcome 8 Number of studies with favorable conclusions, stratified by type of domain.

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
7.8.1 Specific treatments or diseases					
Ahmer 2005	125/138	39/50		4.28%	1.16[0.99,1.36]
Alasbali 2009	26/29	2/10		0.78%	4.48[1.29,15.58]
Bariani 2013	39/56	39/49		3.98%	0.88[0.7,1.09]
Bartels 2012	28/31	76/129		4.16%	1.53[1.27,1.84]
Bero 2007	66/94	39/97		3.71%	1.75[1.32,2.3]
Booth 2008	66/118	55/153		3.77%	1.56[1.19,2.03]
Chard 2000	106/108	373/383		4.6%	1.01[0.98,1.04]
Clark 2002	21/23	5/7		2.64%	1.28[0.79,2.08]
DeGeorge 2015	18/18	77/106		4.35%	1.34[1.17,1.54]
Djulbegovic 2000	26/35	50/95		3.73%	1.41[1.07,1.85]
Djulbegovic 2013	29/32	29/52		3.76%	1.63[1.24,2.12]
Finucane 2004	30/30	12/18		3.44%	1.5[1.08,2.07]
Jefferson 2009	64/76	131/194		4.35%	1.25[1.09,1.43]
Lee 2012	15/43	4/10		1.37%	0.87[0.37,2.06]
Liss 2006	62/63	12/37		2.73%	3.03[1.9,4.84]
Lynch 2007	26/34	49/65		3.93%	1.01[0.8,1.28]
Peppercorn 2007	52/67	48/73		4.05%	1.18[0.96,1.46]
Perlis 2005a	87/102	47/77		4.11%	1.4[1.15,1.7]
Printz 2013	12/30	1/3		0.47%	1.2[0.23,6.31]
Rasmussen 2009	83/109	15/28		3.26%	1.42[0.99,2.04]
Rattinger 2009	31/36	21/25		4.02%	1.03[0.83,1.27]
Ridker 2006	121/189	21/51		3.35%	1.55[1.1,2.2]
Sung 2013	15/28	5/25		1.39%	2.68[1.14,6.31]
Tungaraza 2007	124/146	28/44		3.93%	1.33[1.06,1.69]
Subtotal (95% CI)	**1635**	**1781**		**80.14%**	**1.37[1.17,1.61]**
Total events: 1272 (Industry), 1178 (Non-industry)					
Heterogeneity: Tau^2=0.12; Chi^2=341.62, df=23(P<0.0001); I^2=93.27%					
Test for overall effect: Z=3.87(P=0)					
7.8.2 Mixed study domain					
Als-Nielsen 2003	92/197	43/173		3.59%	1.88[1.39,2.53]
Buchkowsky 2004	138/181	224/319		4.44%	1.09[0.97,1.21]
Cho 1996	39/40	89/112		4.45%	1.23[1.1,1.36]
Davidson 1986	32/36	31/49		3.88%	1.41[1.1,1.79]
Kjaergard 2002	28/38	16/22		3.49%	1.01[0.74,1.39]
Subtotal (95% CI)	**492**	**675**		**19.86%**	**1.26[1.07,1.49]**
Total events: 329 (Industry), 403 (Non-industry)					
Heterogeneity: Tau^2=0.02; Chi^2=16.38, df=4(P=0); I^2=75.59%					
Test for overall effect: Z=2.8(P=0.01)					
Total (95% CI)	**2127**	**2456**		**100%**	**1.34[1.19,1.51]**
Total events: 1601 (Industry), 1581 (Non-industry)					
Heterogeneity: Tau^2=0.08; Chi^2=336.13, df=28(P<0.0001); I^2=91.67%					
Test for overall effect: Z=4.77(P<0.0001)					
Test for subgroup differences: Chi^2=0.48, df=1 (P=0.49), I^2=0%					



Comparison 8. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable efficacy results, sponsorship recoded	8	726	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.18, 1.55]
2 Number of studies with favorable harms results, sponsorship recoded	3	501	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.31, 6.50]
3 Number of studies with favorable conclusions, sponsorship recoded	8	1029	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.04, 1.47]
4 Number of studies with favorable efficacy results, analysis adjusted for confounders	3		Odds Ratio (Random, 95% CI)	3.15 [2.07, 4.80]
5 Number of studies with favorable conclusions, analysis adjusted for confounders	4		Odds Ratio (Random, 95% CI)	3.13 [1.66, 5.93]
6 Number of studies with favorable efficacy results, fixed-effect model	25	2923	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.23, 1.40]
7 Number of studies with favorable harms results, fixed-effect model	4	826	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.15, 1.46]
8 Number of studies with favorable test treatment efficacy results, fixed-effect model	2	131	Risk Ratio (M-H, Fixed, 95% CI)	4.64 [2.08, 10.32]
9 Number of studies with favorable conclusions, fixed-effect model	29	4583	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.24, 1.35]
10 Number of studies with favorable test treatment conclusions, fixed-effect model	3	154	Risk Ratio (M-H, Fixed, 95% CI)	5.90 [2.79, 12.49]
11 Number of studies with favorable conclusions, papers with unpublished studies excluded	27	4436	Risk Ratio (M-H, Random, 95% CI)	1.35 [1.19, 1.54]
12 Number of studies with favorable efficacy results, restricted to specific domains	13	797	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.07, 1.51]
13 Number of studies with favorable harms results, restricted to specific domains	3	561	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.54, 2.27]
14 Number of studies with favorable test treatment efficacy results, restricted to specific domains	2	131	Risk Ratio (M-H, Random, 95% CI)	3.88 [1.26, 11.94]
15 Number of studies with favorable conclusions, restricted to specific domains	15	1803	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.25, 1.61]
16 Number of studies with favorable test treatment conclusions, restricted to specific domains	3	154	Risk Ratio (M-H, Random, 95% CI)	5.92 [2.80, 12.54]

Analysis 8.1. Comparison 8 Sensitivity analysis, Outcome 1 Number of studies with favorable efficacy results, sponsorship recoded.

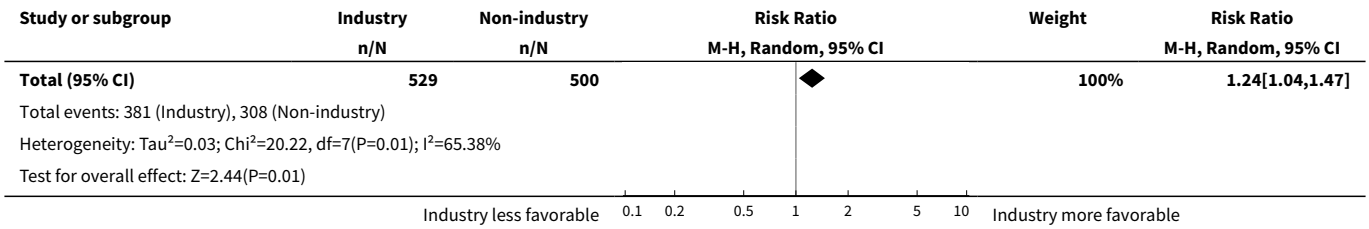
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bariani 2013	24/35	23/43		14.02%	1.28[0.9,1.83]
Bero 2007	54/76	10/23		7.7%	1.63[1,2.66]
Bond 2012	53/64	2/2		6.83%	0.99[0.59,1.66]
Bourgeois 2010	188/220	48/85		43.18%	1.51[1.25,1.84]
Clifford 2002	30/44	15/28		11.33%	1.27[0.85,1.9]
Khan 2012	37/49	11/16		13.36%	1.1[0.76,1.59]
Moncrieff 2003	2/2	1/6		0.82%	3.89[0.86,17.54]
Rattinger 2009	25/32	1/1		2.75%	1.03[0.45,2.34]
Total (95% CI)	**522**	**204**		**100%**	**1.35[1.18,1.55]**
Total events: 413 (Industry), 111 (Non-industry)					
Heterogeneity: Tau^2=0; Chi^2=7.24, df=7(P=0.4); I^2=3.26%					
Test for overall effect: Z=4.33(P<0.0001)					

Analysis 8.2. Comparison 8 Sensitivity analysis, Outcome 2 Number of studies with favorable harms results, sponsorship recoded.

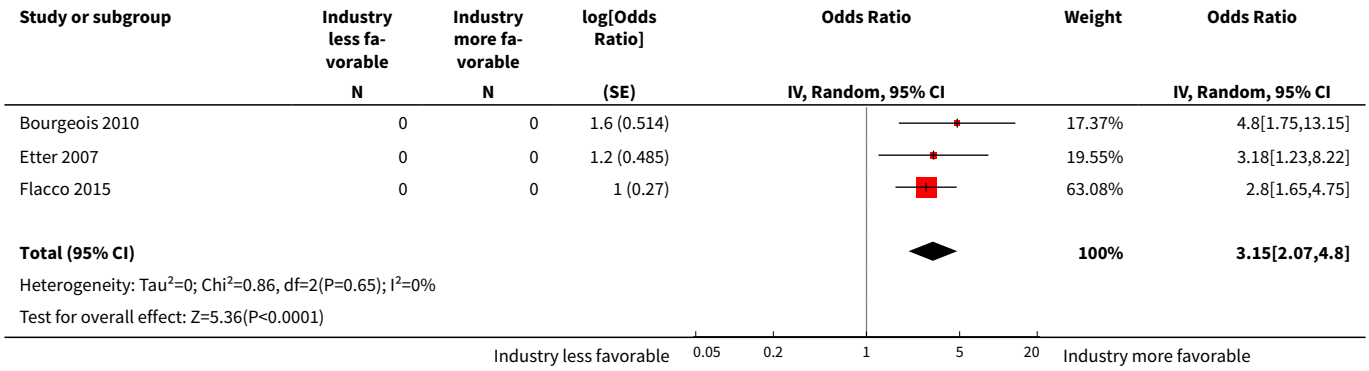
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Als-Nielsen 2003	95/128	29/32		37.52%	0.82[0.7,0.95]
Halpern 2005	1/3	10/38		25.7%	1.27[0.23,6.84]
Nieto 2007	166/226	20/74		36.78%	2.72[1.85,3.98]
Total (95% CI)	**357**	**144**		**100%**	**1.42[0.31,6.5]**
Total events: 262 (Industry), 59 (Non-industry)					
Heterogeneity: Tau^2=1.59; Chi^2=78.09, df=2(P<0.0001); I^2=97.44%					
Test for overall effect: Z=0.46(P=0.65)					

Analysis 8.3. Comparison 8 Sensitivity analysis, Outcome 3 Number of studies with favorable conclusions, sponsorship recoded.

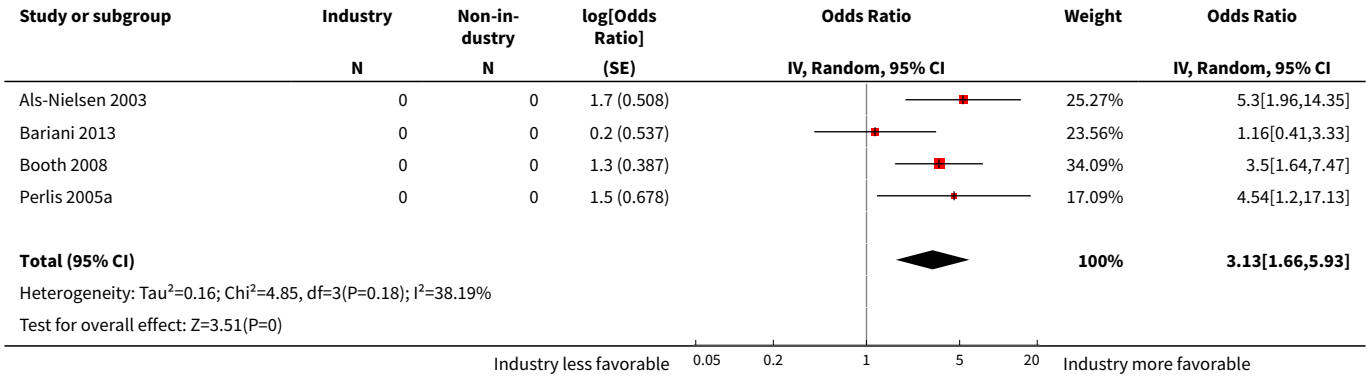
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ahmer 2005	75/84	34/43		18.47%	1.13[0.95,1.34]
Als-Nielsen 2003	74/146	11/67		6.53%	3.09[1.76,5.42]
Bariani 2013	27/35	32/43		15.19%	1.04[0.81,1.33]
Bero 2007	57/76	10/23		8.04%	1.73[1.06,2.8]
Buchkowsky 2004	76/104	121/180		19.09%	1.09[0.93,1.27]
Jefferson 2009	23/29	89/130		16.48%	1.16[0.93,1.44]
Kjaergard 2002	21/23	10/13		12.5%	1.19[0.86,1.64]
Rattinger 2009	28/32	1/1		3.7%	1.15[0.51,2.59]



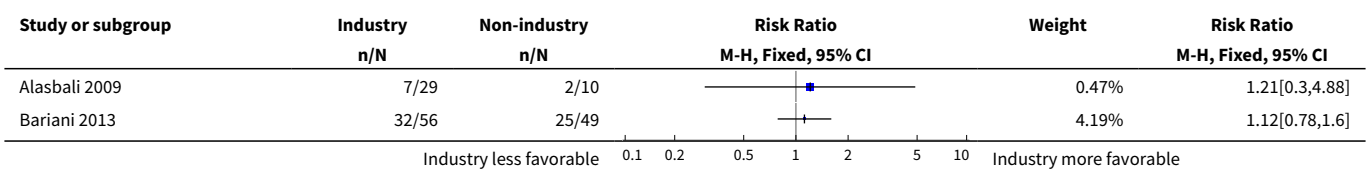
Analysis 8.4. Comparison 8 Sensitivity analysis, Outcome 4 Number of studies with favorable efficacy results, analysis adjusted for confounders.

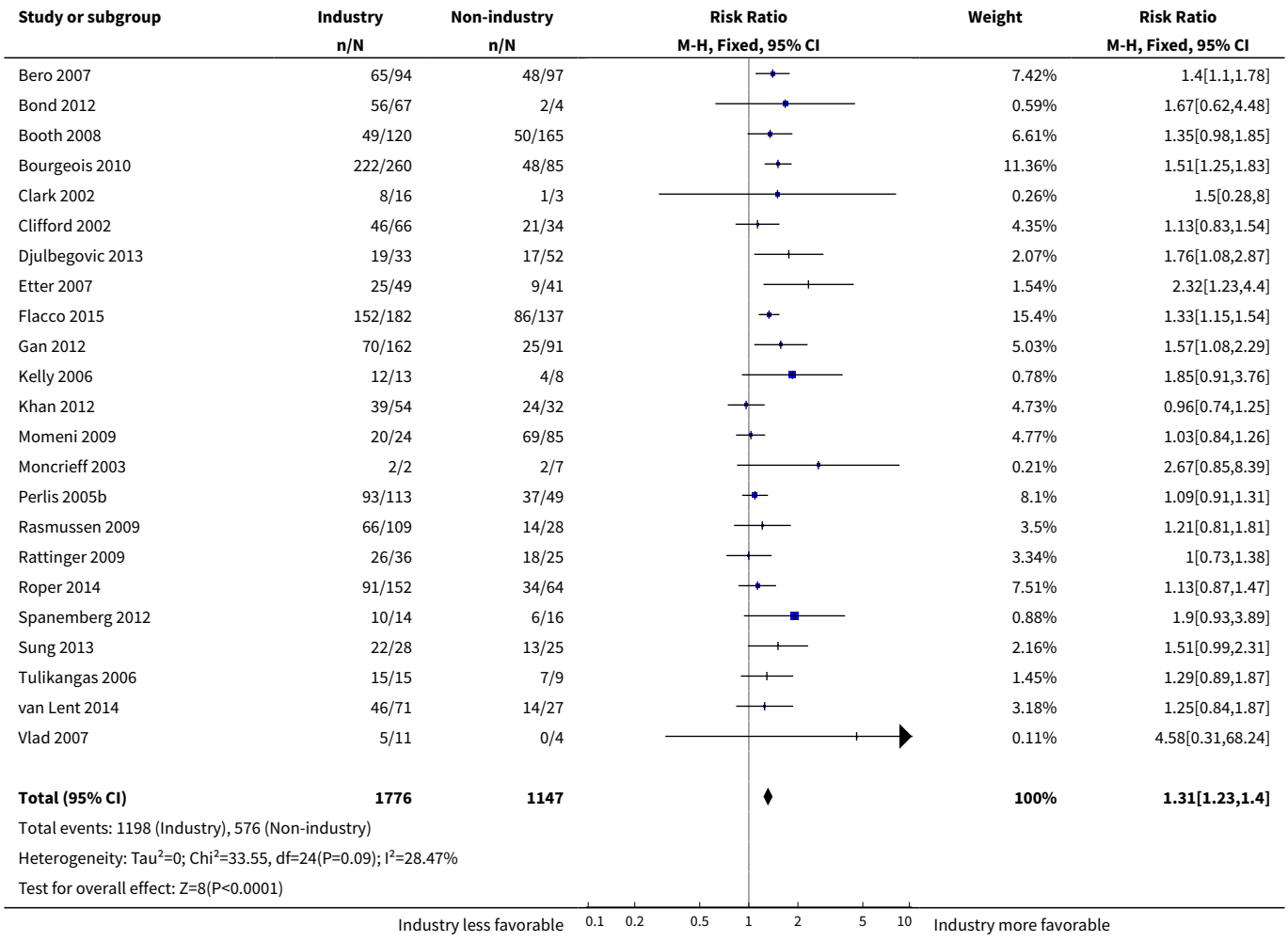


Analysis 8.5. Comparison 8 Sensitivity analysis, Outcome 5 Number of studies with favorable conclusions, analysis adjusted for confounders.

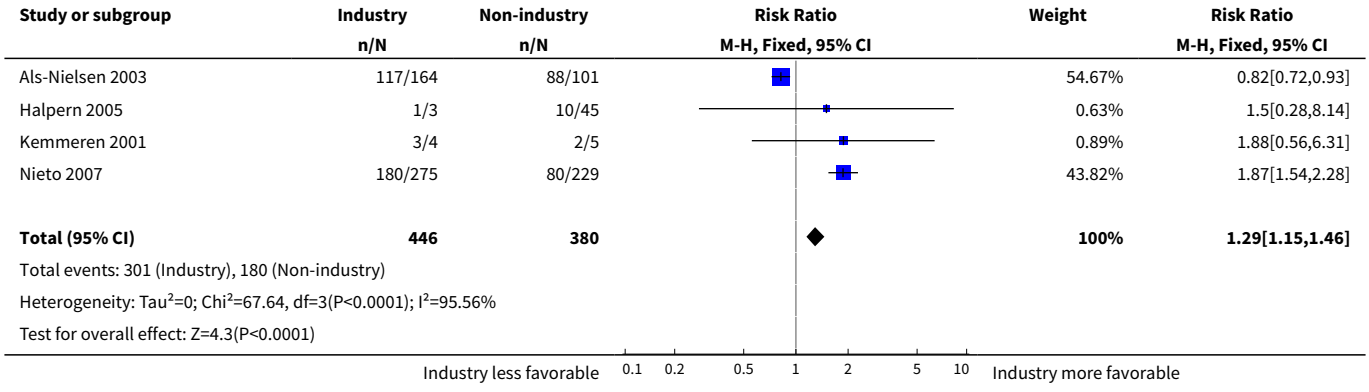


Analysis 8.6. Comparison 8 Sensitivity analysis, Outcome 6 Number of studies with favorable efficacy results, fixed-effect model.



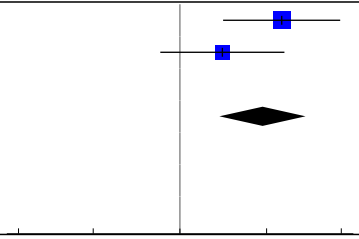


Analysis 8.7. Comparison 8 Sensitivity analysis, Outcome 7 Number of studies with favorable harms results, fixed-effect model.



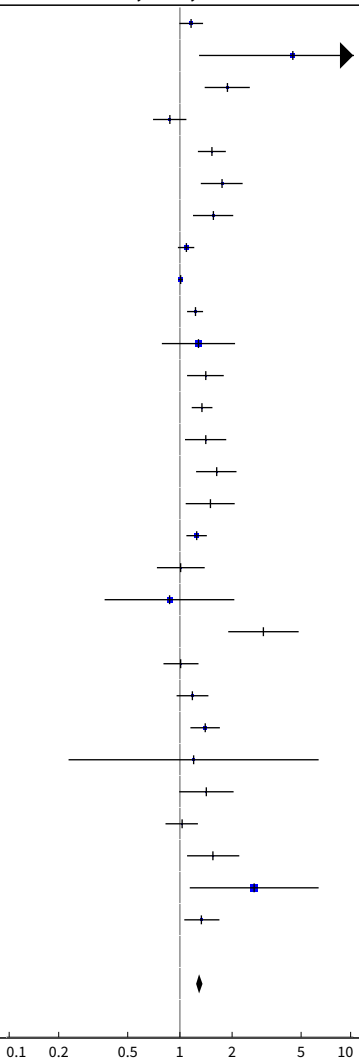
Analysis 8.8. Comparison 8 Sensitivity analysis, Outcome 8 Number of studies with favorable test treatment efficacy results, fixed-effect model.

Study or subgroup	Test treatment sponsor n/N	Comparator treatm sponsor n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bero 2007	43/65	3/30		55.19%	6.62[2.23,19.63]
Rattinger 2009	22/30	2/6		44.81%	2.2[0.7,6.96]
Total (95% CI)	**95**	**36**		**100%**	**4.64[2.08,10.32]**
Total events: 65 (Test treatment sponsor), 5 (Comparator treatm sponsor)					
Heterogeneity: Tau^2=0; Chi^2=2.02, df=1(P=0.16); I^2=50.48%					
Test for overall effect: Z=3.76(P=0)					

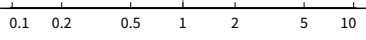


Analysis 8.9. Comparison 8 Sensitivity analysis, Outcome 9 Number of studies with favorable conclusions, fixed-effect model.

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmer 2005	125/138	39/50		5.03%	1.16[0.99,1.36]
Alasbali 2009	26/29	2/10		0.26%	4.48[1.29,15.58]
Als-Nielsen 2003	92/197	43/173		4.02%	1.88[1.39,2.53]
Bariani 2013	39/56	39/49		3.65%	0.88[0.7,1.09]
Bartels 2012	28/31	76/129		2.59%	1.53[1.27,1.84]
Bero 2007	66/94	39/97		3.37%	1.75[1.32,2.3]
Booth 2008	66/118	55/153		4.21%	1.56[1.19,2.03]
Buchkowsky 2004	138/181	224/319		14.24%	1.09[0.97,1.21]
Chard 2000	106/108	373/383		14.41%	1.01[0.98,1.04]
Cho 1996	39/40	89/112		4.11%	1.23[1.1,1.36]
Clark 2002	21/23	5/7		0.67%	1.28[0.79,2.08]
Davidson 1986	32/36	31/49		2.31%	1.41[1.1,1.79]
DeGeorge 2015	18/18	77/106		2.05%	1.34[1.17,1.54]
Djulbegovic 2000	26/35	50/95		2.36%	1.41[1.07,1.85]
Djulbegovic 2013	29/32	29/52		1.94%	1.63[1.24,2.12]
Finucane 2004	30/30	12/18		1.36%	1.5[1.08,2.07]
Jefferson 2009	64/76	131/194		6.48%	1.25[1.09,1.43]
Kjaergard 2002	28/38	16/22		1.78%	1.01[0.74,1.39]
Lee 2012	15/43	4/10		0.57%	0.87[0.37,2.06]
Liss 2006	62/63	12/37		1.33%	3.03[1.9,4.84]
Lynch 2007	26/34	49/65		2.96%	1.01[0.8,1.28]
Peppercorn 2007	52/67	48/73		4.03%	1.18[0.96,1.46]
Perlis 2005a	87/102	47/77		4.7%	1.4[1.15,1.7]
Printz 2013	12/30	1/3		0.16%	1.2[0.23,6.31]
Rasmussen 2009	83/109	15/28		2.1%	1.42[0.99,2.04]
Rattinger 2009	31/36	21/25		2.18%	1.03[0.83,1.27]
Ridker 2006	121/189	21/51		2.9%	1.55[1.1,2.2]
Sung 2013	15/28	5/25		0.46%	2.68[1.14,6.31]
Tungaraza 2007	124/146	28/44		3.78%	1.33[1.06,1.69]
Total (95% CI)	**2127**	**2456**		**100%**	**1.29[1.24,1.35]**
Total events: 1601 (Industry), 1581 (Non-industry)					



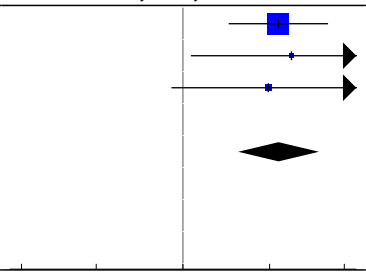
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=336.13, df=28(P<0.0001); I²=91.67%					
Test for overall effect: Z=12.11(P<0.0001)					



Industry less favorable — Industry more favorable

Analysis 8.10. Comparison 8 Sensitivity analysis, Outcome 10 Number of studies with favorable test treatment conclusions, fixed-effect model.

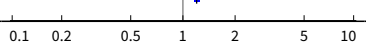
Study or subgroup	Test treatment sponsor n/N	Comparator treatm sponsor n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bero 2007	51/65	4/30		65.94%	5.88[2.34,14.78]
Heres 2006	10/12	1/9		13.77%	7.5[1.16,48.43]
Rattinger 2009	26/32	1/6		20.29%	4.88[0.81,29.4]
Total (95% CI)	**109**	**45**		**100%**	**5.9[2.79,12.49]**
Total events: 87 (Test treatment sponsor), 6 (Comparator treatm sponsor)					
Heterogeneity: Tau²=0; Chi²=0.11, df=2(P=0.95); I²=0%					
Test for overall effect: Z=4.64(P<0.0001)					



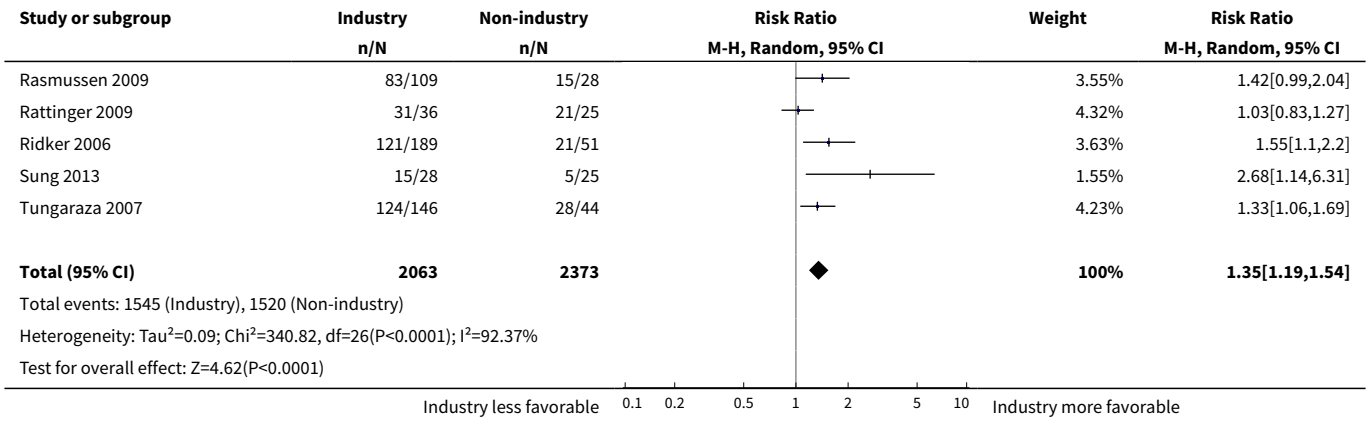
Competitor more favorable — Sponsor more favorable

Analysis 8.11. Comparison 8 Sensitivity analysis, Outcome 11 Number of studies with favorable conclusions, papers with unpublished studies excluded.

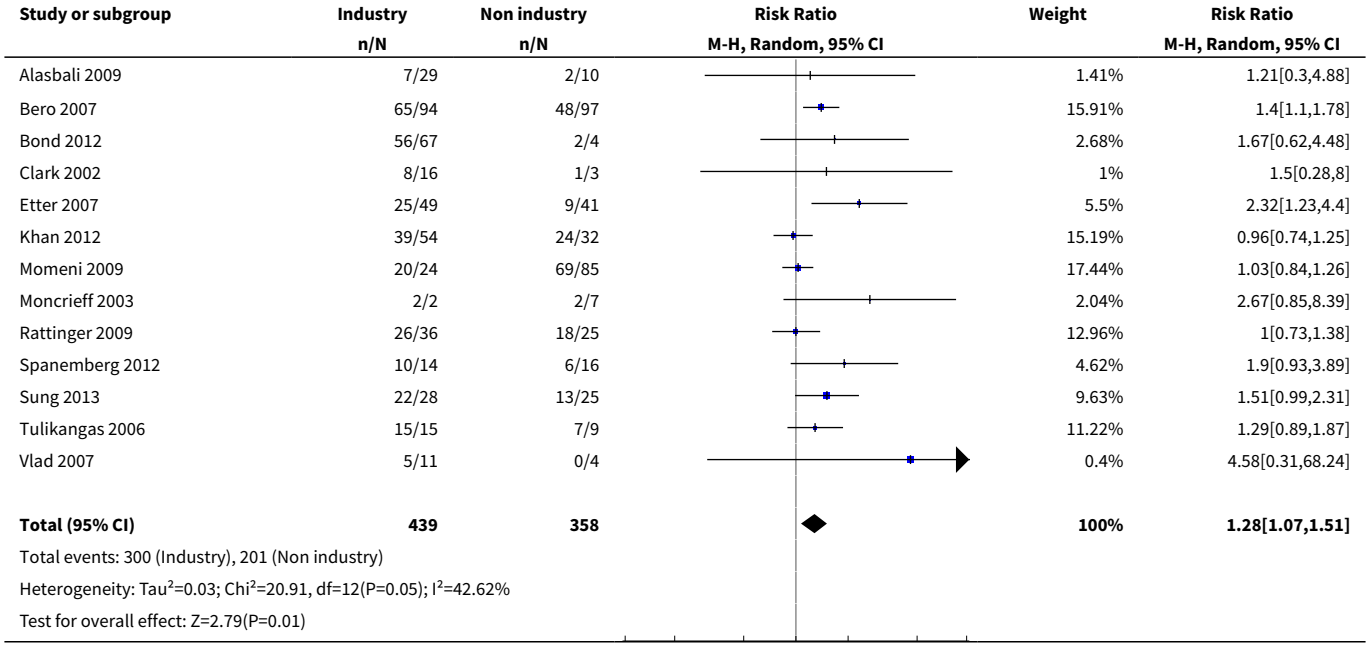
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ahmer 2005	125/138	39/50		4.59%	1.16[0.99,1.36]
Alasbali 2009	26/29	2/10		0.88%	4.48[1.29,15.58]
Als-Nielsen 2003	92/197	43/173		3.89%	1.88[1.39,2.53]
Bariani 2013	39/56	39/49		4.28%	0.88[0.7,1.09]
Bartels 2012	28/31	76/129		4.47%	1.53[1.27,1.84]
Bero 2007	66/94	39/97		4.01%	1.75[1.32,2.3]
Booth 2008	66/118	55/153		4.07%	1.56[1.19,2.03]
Buchkowsky 2004	138/181	224/319		4.76%	1.09[0.97,1.21]
Chard 2000	106/108	373/383		4.91%	1.01[0.98,1.04]
Cho 1996	39/40	89/112		4.76%	1.23[1.1,1.36]
Clark 2002	21/23	5/7		2.89%	1.28[0.79,2.08]
Davidson 1986	32/36	31/49		4.19%	1.41[1.1,1.79]
DeGeorge 2015	18/18	77/106		4.66%	1.34[1.17,1.54]
Djulbegovic 2000	26/35	50/95		4.03%	1.41[1.07,1.85]
Djulbegovic 2013	29/32	29/52		4.06%	1.63[1.24,2.12]
Jefferson 2009	64/76	131/194		4.66%	1.25[1.09,1.43]
Kjaergard 2002	28/38	16/22		3.78%	1.01[0.74,1.39]
Lee 2012	15/43	4/10		1.53%	0.87[0.37,2.06]
Liss 2006	62/63	12/37		2.99%	3.03[1.9,4.84]
Peppercorn 2007	52/67	48/73		4.35%	1.18[0.96,1.46]
Perlis 2005a	87/102	47/77		4.42%	1.4[1.15,1.7]
Printz 2013	12/30	1/3		0.54%	1.2[0.23,6.31]



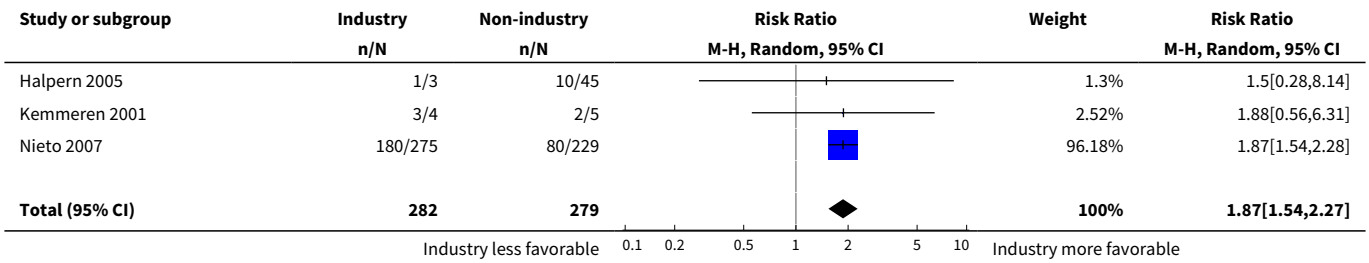
Industry less favorable — Industry more favorable

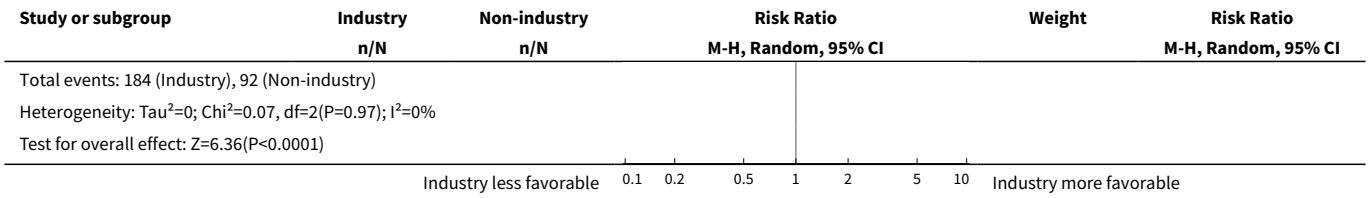


Analysis 8.12. Comparison 8 Sensitivity analysis, Outcome 12 Number of studies with favorable efficacy results, restricted to specific domains.

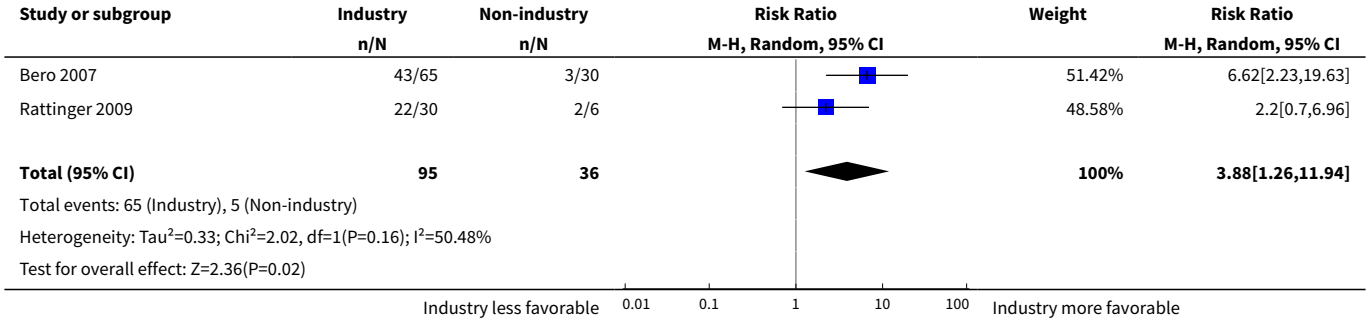


Analysis 8.13. Comparison 8 Sensitivity analysis, Outcome 13 Number of studies with favorable harms results, restricted to specific domains.

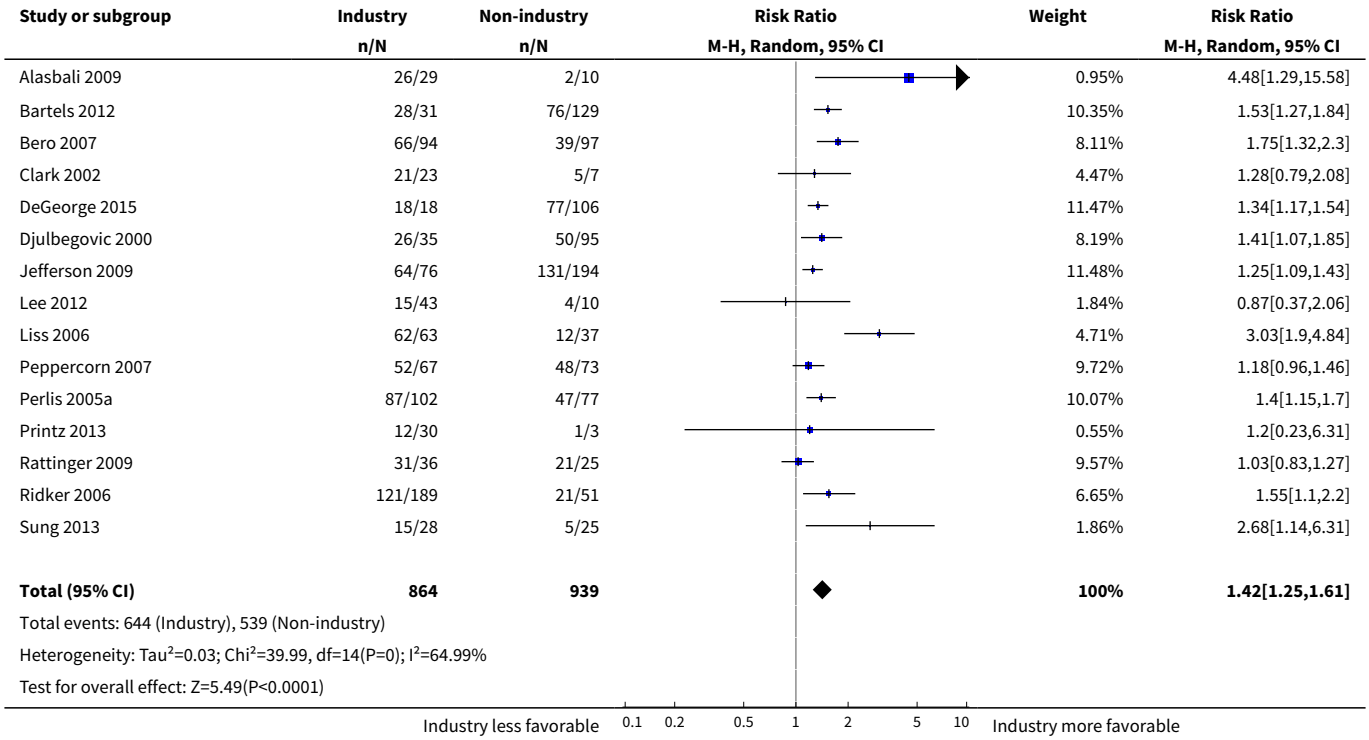




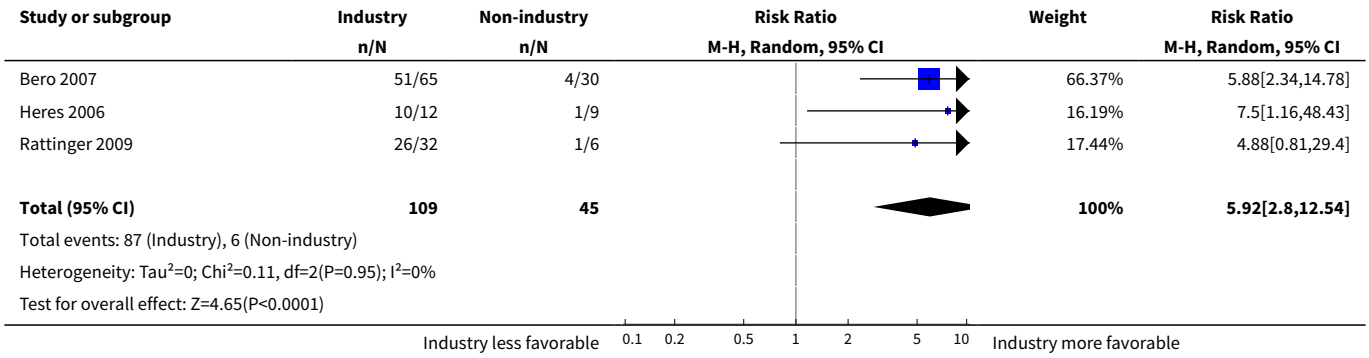
Analysis 8.14. Comparison 8 Sensitivity analysis, Outcome 14 Number of studies with favorable test treatment efficacy results, restricted to specific domains.



Analysis 8.15. Comparison 8 Sensitivity analysis, Outcome 15 Number of studies with favorable conclusions, restricted to specific domains.



Analysis 8.16. Comparison 8 Sensitivity analysis, Outcome 16 Number of studies with favorable test treatment conclusions, restricted to specific domains.



APPENDICES

Appendix 1. Search strategy

MEDLINE via OvidSP (2010 – February 2015)

1. Drug Industry/

2. ((drug$ or pharmaceutical or device$ or for-profit or commercial$) adj2 (industr$ or company or companies or manufacturer$ or organi#ation$ or agency or agencies or source$ or party or parties)).ti,ab.

3. private industr$.ti,ab.

4. (industr$ or nonindustr$ or non-industr$).ti,ab.

5. or/1-4

6. "Conflict of Interest"/

7. Financial Support/

8. Research Support as Topic/

9. (influenc$ or funded or funding or sponsor$ or support$ or financ$ or involvement).ti,ab.

10. competing interest$.ti,ab.

11. or/6-10

12. and/5,11

13. Publication Bias/

14. "bias (epidemiology)"/

15. bias$.ti,ab.

16. or/13-15

17. and/12,16

18. Treatment Outcome/

19. "Outcome Assessment (Health Care)"/

20. (outcome$ or finding$).ti,ab.

21. or/18-20

22. (favo?r$ or positive or significan$ or beneficial or benefit$ or effective or effectual or efficacious).ti,ab.

23. (insignifican$ or nonsignifican$ or negative or adverse or ineffectiv$ or ineffectual or unfavo?rabl$ or detrimental).ti,ab.

24. or/22-23

25. and/21,24

26. and/12,25

27. ((favo?r$ or positive or significan$ or insignifican$ or nonsignifican$ or negative or unfavo?rabl$ or detrimental) adj2 (event$ or result $ or outcome$ or conclusion$)).ti,ab.

28. and/12,27

29. or/17,26,28

WHAT'S NEW

Date	Event	Description
7 February 2017	New search has been performed	Updated version of review from Issue 12 in 2012. Including updated search (February 2015) and inclusion of 27 new papers (now total of 75 papers).
7 February 2017	New citation required but conclusions have not changed	Addition of new papers did not change conclusions.

CONTRIBUTIONS OF AUTHORS

Development of protocol (AL, BM, JL, JS and LB); study inclusion (BM, JL, JS and LB); data extraction (AL, BM, JL and JS); data analysis and interpretation of results (all authors); writing of manuscript (all authors).

DECLARATIONS OF INTEREST

Andreas Lundh, Joel Lexchin and Lisa Bero are authors of the some of the previous reviews and included studies.

In 2015 to 2016, Joel Lexchin received payment from non-profit entities for being a consultant on two projects, one looking at indications-based prescribing and a second looking at which drugs should be provided free of charge by general practitioners. He received payment from a for-profit company for being on a panel that discussed expanding drug coverage in Canada. He is on the Foundation Board of Health Action International.

In 2014, Barbara Mintzes was retained as an expert witness by the law firm representing the plaintiffs in a Canadian class action on hormone replacement therapy and breast cancer, and in 2015 to 2016 in an application for a Canadian class action on cardiovascular risks of testosterone supplements. She was a member of the Health Action International – Europe Association Board from 2012 to 2015.

The review authors have no other relevant interests.

SOURCES OF SUPPORT

Internal sources

- Center for Evidence-Based Medicine, Odense, Denmark.

  The author was personally salaried by his institution during some period of the review.
- The Nordic Cochrane Centre, Copenhagen, Denmark.

  The author was externally affiliated with The Nordic Cochrane Centre for this work and received no financial support during the period of the review.

- University of Sydney, Sydney, Australia.

  The authors were personally salaried by their institution during the period of the review.
- York University, Toronto, Canada.

  The author was personally salaried by his institutions during the period of the review.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this update, we decided to analyze data with the random-effects model due to heterogeneity of data encountered in our previous review. In addition, we included four new sensitivity analysis in this update: 1) fixed-effect model; 2) excluding papers including unpublished studies: 3) restricting analyses restricted to papers on specific treatments or diseases: and 4) including unstructured letters and conference abstracts. All decisions were made prior to data analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

*Conflict of Interest; *Equipment and Supplies; *Industry; Data Interpretation, Statistical; Drug Industry; Publication Bias; Research Report [*standards]; Research Support as Topic [*standards]; Treatment Outcome