Industry funding of patient and health consumer organisations: Systematic review with meta-analysis

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Industry Funding of Patient and Health Consumer Organisations: Systematic Review with Meta-analysis

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Abstract

Objective: To investigate pharmaceutical or medical device industry funding of patient groups.

Design: Systematic review with meta-analysis.

Data sources: Medline, Embase, Web of Science, Scopus and Google Scholar up to January 2018, reference lists of eligible studies and experts in the field.

Study selection: Observational studies including cross-sectional, cohort, case-control, interrupted time series, and before-after studies of patient groups reporting at least one of the following outcomes: prevalence of industry funding; proportion of industry funded patient groups which disclosed information about this funding; association between industry funding and organisational positions on health and policy issues. Studies were included irrespective of language or publication type.

Review methods: Reviewers carried out duplicate independent data extraction and assessments of study quality. An amended version of the Checklist for Prevalence Studies developed by the Joanna Briggs Institute was used to assess study quality. For meta-analyses of prevalence, a DerSimonian-Laird estimate of single proportions with Freeman-Tukey arcsine transformation was used. GRADE was used to assess the quality of the evidence per outcome.

Results: Twenty-six cross-sectional studies met the inclusion criteria. Fifteen studies estimated the prevalence of industry funding and their prevalence estimates ranged from 20% to 83%. Among patient organisations having received industry funding, 27% (95% CI: 24 to 31%) disclosed this information on their websites. In submissions to consultations, two studies showed very different disclosure rates (0% and 91%, respectively), appearing to reflect differences in the relevant government agency's disclosure requirements. Estimates of prevalence of organisational policies governing corporate sponsorship ranged from 2% to 64%. Four studies analysed the relationship between industry funding and organisational positions on a range of highly controversial issues; industry-funded groups generally supported sponsors' interests.

Conclusion: In general, industry funding of patient groups is common with prevalence estimates ranging from 20% to 83%. Few patient groups have policies governing corporate sponsorship. Transparency concerning corporate funding is also inadequate. Among the few studies examining funding status versus organisational position, industry sponsored groups tend to have positions that are favourable to the sponsor. Considering the important role that patient groups play in advocacy, education, and research, strategies to prevent biases that may favour sponsors' interests above those of the public are urgently needed.

Systematic review registration: PROSPERO CRD42017079265

What is already known on this topic

- Patient groups play an important role in health care, including education of consumers, funding of medical research, and contributing to decisions on approval and public coverage of medicines and treatments.
- Patient groups often rely on multiple sources of financial support, including the pharmaceutical and medical device industries.
- Concerns have been raised about the financial relationships between industry and patient groups, because of conflicts of interest and potential threats to groups' integrity and independence.

What this study adds

- This systematic review shows that pharmaceutical industry funding of patient groups is common in many higher income countries and clinical areas and documents the extent of existing research on this topic. The extent of industry funding of patient groups in low and middle income countries is unknown, as only one study included data from South Africa, an upper middle income country.
- Few patient groups have policies governing corporate sponsorship. Transparency concerning corporate funding is also inadequate.

- Among the few studies examining funding status versus organisational position, industry sponsored groups tend to have positions that are favourable to the sponsor.
- The conclusions that could be drawn are limited by the low quality and variability of the available data.

Introduction

Patient and health consumer groups are non-profit organisations that aim to focus on the needs and interests of patients and communities affected by a specific disease/condition, or of health service users more generally.(1) Their size can also widely vary from small organisations run by volunteers to big national organisations with salaried staff and thousands of members. Patient and health consumer groups carry out many activities, such as: providing direct support, services, and education to patients and health consumers, funding of and participating in medical research, contributing to guideline development, and advocating for policies related to health services and/or health products. The latter may include lobbying for patient access and/or government subsidy for medicines and devices. In some fields (e.g. HIV) patient groups were also instrumental in lowering the price of drugs, taking positions that did not align with manufacturers of HIV/AIDS drugs.(2)

Patient and health consumer organisations (referred to below as "patient groups") often rely on multiple sources of financial support, including the pharmaceutical and medical device industries. Concerns have been raised in recent years about financial relationships between patient groups and the pharmaceutical/medical device industries, because of conflicts of interest and potential threats to groups' integrity, credibility, and independence.(3, 4)

Although in some areas such as access and subsidy for drugs, the interests of the two parties might align, industry funding does put patient groups in a conflict of interest situation. The primary interest of pharmaceutical and device companies to maximize profits can conflict with the mission of patient groups to protect the welfare of the people they represent.(5) Industry funded groups may, consciously or unconsciously, undertake advocacy, education, training and research activities

that echo their sponsors' interests.(6) Industry funding may also work more subtly, nudging the sector towards a particular emphasis: assuming that industries will target groups and activities that further their interests, a culture of industry funding within a diverse patient group sector may selectively enhance the patient group voices that align with industry priorities.(3) These concerns raise a number of questions about the extent and impact of industry funding of patient groups.

In recent years there has been increasing attention to these interactions as demonstrated by the development of educational programs,(7) codes and guidelines.(8-11) These documents have been usually co-developed by representatives of patient groups and of the pharmaceutical industry, and list principles for collaborations such as transparency, respect for independence, confidentiality, and accountability.

There is also growing research evidence on the nature and frequency of pharmaceutical industry sponsorship of patient groups.(12-15) However, until now, no systematic review has been carried out in this research area. The aim of this review was to investigate industry funding of patient groups. In particular, we sought to answer the following questions:

- *Prevalence of industry funding:* percent of patient groups that accept industry funding, percent of patient groups' funding that is from industry, and number of funders per group;
- *Transparency:* proportion of industry funded patient groups that report the source of their funding on their websites and during governmental consultations;
- *Positions:* association between industry funding and organisational positions on health and policy issues.

Methods

Protocol

The protocol was published in PROSPERO prior to carrying out this review, and includes additional details about pre-specified methods. (PROSPERO CRD42017079265)

Search strategy

We searched the following databases (from inception to January 20th 2018): Ovid MEDLINE, Embase, Web of Science, Scopus, and Google Scholar. Supplementary File 1 describes the search strategy for each database. We also hand searched the reference lists of included studies and contacted experts in the field to identify additional studies.

Study selection

The eligibility criteria for studies included in this review were:

- *Study design:* observational studies with the following designs: cross-sectional, cohort, case-control, interrupted time series, and before-after studies;
- *Population:* patient groups, including both non-profit patient organisations that aim to represent the interests of patients at risk or affected by a specific disease/condition or set of conditions, and non-profit consumer organisations that advocate for the health rights of people and/or the interests of health services users;
- *Exposure:* pharmaceutical and/or medical device (i.e. industry) funding; pharmaceutical companies included producers of medicines, biologics as well as small molecule drugs (e.g. biotech industry)
- *Comparison groups:* non-industry funded patient groups (if present);
- *Outcome measures,* at least one of the following measures was reported:
    - *Prevalence:* percent of patient groups that accept industry funding, percent of patient groups' funding that is from industry, and number of funders per group;
    - *Transparency:* proportion of industry funded patient groups that report the source of their funding on their websites and during governmental consultations;
    - *Positions:* association between industry funding and organisational positions on health and policy issues and/or organisational policies on conflict of interest.

We excluded the following types of studies:

- Editorials, commentaries, systematic reviews, narrative reviews, studies that only used qualitative methodologies;

- Studies focusing on multiple types of organisations (e.g. patient groups and professional organisations) without a separate analysis for patient groups, for which a breakdown could not be obtained from the study authors;
- Studies analysing non pharmaceutical or medical device industry funding, or studies of mixed funding sources, for which pharmaceutical or medical device industry funding was not reported separately, and a breakdown could not be obtained from the study authors.

We did not exclude studies based on language, publication date, or study setting. Four pairs of assessors independently screened the titles and abstracts of all retrieved records for obvious exclusions and then applied our inclusion criteria to the full text of the remaining papers. Agreement was reached on any discrepancies by consensus between the two investigators. Reasons for exclusion of potentially eligible papers are described in the "List of excluded studies" table. (Supplementary File 2) If multiple reports of a study were identified, we considered the most comprehensive report to be the primary data source.

Data extraction

Four pairs of assessors independently extracted the following data: general study information (author, year of publication, funding source and authors' conflicts of interest); study design and study population details (location, sample size, response rate - if applicable, disease area of the included patient groups); year and methods of data collection; and outcomes as listed above. Discrepancies in data extraction were resolved by consensus between the two assessors. If agreement could not be reached, a third assessor adjudicated the outcome. If reporting in published articles was unclear, or if data on primary outcome measures were not provided separately for patient groups, we contacted the authors for clarifications and to request access to the raw data. We stored all extracted data from the included studies in REDcap, a secure web-based application for the collection and management of data.(16) We contacted the authors of eight papers to obtain extra information or clarifications, and all responded (1, 14, 17-22)

Quality Assessment

As all the included studies were cross-sectional, we used and adapted the Checklist for Prevalence Studies developed by the Joanna Briggs Institute to measure their quality.(23) The checklist

assesses the quality of a study across nine domains. We amended this tool to reflect the focus on a policy issue versus a clinical condition (Supplementary File 3) and pilot tested it on two studies to achieve agreement between reviewers. We changed the possible answers for each domain from Yes/No/Unclear/Not applicable to High quality/Low quality/Unclear/Not applicable. The quality assessment is presented in tables by item and individual study. For the assessment, we considered an entire study to be of low quality if: more than one domain was judged as "low quality"; if one domain was of "low quality" and any others were "unclear"; or if more than two domains were judged as "unclear".

To assess the quality of evidence, we used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) for the following outcomes: prevalence of industry funding, proportion of industry funded patient groups which disclosed information about industry funding on their websites and during governmental consultations; prevalence of patient groups' policies governing corporate sponsorship; proportion of groups (industry funded versus non-industry funded) with policy positions in sponsors' interests; comprehensiveness of information on harms provided by industry funded and non-industry funded groups. GRADE assesses the evidence as high, moderate, low, or very low quality based on the following criteria: risk of bias, directness, consistency, precision, and reporting bias.(24) Observational studies usually start as low quality evidence, but can be upgraded or downgraded according to the GRADE Recommendations. Two reviewers independently assessed certainty of the evidence for each outcome, and then consulted if discrepancies were found until consensus was reached.

Statistical analysis

We undertook an initial descriptive analysis of the studies, including study characteristics and setting. We present the populations, outcomes and other characteristics of the studies in tables. For assessed quantitative outcomes, we conducted a meta-analysis of single proportions (random effects meta-analysis using the DerSimonian-Laird estimate (25) of single proportions with prevalence estimates that had been transformed using the Freeman-Tukey Double arcsine transformation).(26) Confidence intervals for individual studies were calculated using the Clopper-Pearson method.(27)

Heterogeneity between estimates was assessed using the I^2 statistic, and reasons for heterogeneity were explored using subgroup analyses. We interpreted the I^2 index as representing low, moderate or high heterogeneity at thresholds of 25%, 50% and 75%, respectively.(28) We pre-specified the following types of subgroup analyses in the protocol if sufficient data were available: setting (low/middle vs. high income country according to World Bank classification), disease group (multiple diseases versus condition-specific studies), funding source (pharmaceutical versus medical device industry), proportion of industry funding, and service provision versus advocacy-only organisations (namely, groups that provide direct support to patients versus groups that advocate for policies related to health services or health products). Additional post hoc subgroup analyses were conducted to explore heterogeneity including: sample size (above or below the median), timing (pre-2010, the midpoint for included studies, or 2010 onwards). We also undertook a subgroup analysis of study quality considering a study to be of high quality if ≤ 2 domains were judged as "unclear" or ≤ 1 as "low quality". To assess potential publication bias, we tested for funnel plot asymmetry using the Peter test,(29) as it may be more accurate than funnel plots based on the Begg or Egger tests when assessing publication bias for meta-analyses of proportion studies.(29, 30) We also conducted sensitivity analyses for publication bias using trim-and-fill funnel plots.(Supplementary File 4, Figure 6 and 7). Statistical analyses were conducted in R (version 3.5.1) using the "metaprop" or "metabin" (for the meta-analyses) and "metabias" (for publication bias) functions of the "meta" package (version 4.9-3). All data and analysis codes are included in the article or uploaded as supplementary files.

Patient involvement

Two of the study authors (PM and BM) have been involved for many years with women's health and consumer groups and maintain strong community engagement. Additionally, one representative of a Canadian patient group was involved in commenting on the findings of the review. Systematic review results will be disseminated to patient groups through publicly accessible conferences, workshops and the media.

Results

Description of included studies

As shown in Figure 1, 5309 references were identified for screening and 26 studies (included in 27 reports) met the inclusion criteria. Supplementary file 2 contains the 'List of Excluded Studies' and reasons for exclusion at the full text screening stage. The most common reason was study design (not research, e.g. commentaries or editorials; n=43), followed by a lack of inclusion of any outcomes of interest (n=14).

Table 1 summarises the characteristics of the included studies. The 26 studies were published between 2003 and 2017 and were all cross-sectional.(1, 5, 12-15, 17-22, 31-43) Most of the studies included patient groups from multiple disease areas and were conducted in high income countries, primarily the United States and Europe. Several studies used data collected from multiple sources such as questionnaire surveys, websites or documents analysis; others relied only on a single data source. Survey response rates ranged from 39% to 87%. Sample sizes per study also varied greatly, from 8 to 1215. (22, 36)

Table 2 shows findings for all outcomes. We meta-analysed the following outcomes: prevalence of industry funding, proportion of industry funded patient groups which disclosed information about industry funding on their websites, and prevalence of patient group policies governing corporate sponsorship. We could not conduct the following subgroup analyses due to lack of adequate data: setting (low/middle versus high income country), funding source (pharmaceutical versus medical device industry), proportion of industry funding, and service provision versus advocacy-only organisations. Due to the high level of unexplained heterogeneity, we cannot meaningfully present summary estimates for prevalence of industry funding and prevalence of organisational policies. For the sake of transparency, all the analyses we conducted are available in Supplementary File 4.

Quality of included studies

Figure 2 shows the quality assessment for each included study. Nine studies were assessed at high quality for all the domains and six studies were considered of high quality for all the domains apart

from one that was judged unclear. For one domain, selection of statistical techniques, all included studies were considered to have high quality as most of the analyses presented only descriptive statistics. The domain with the most studies (n=7/26) judged to be of low quality relates to the provision of baseline information on study subjects and setting (Q4). Overall, 17 (65%) studies were judged to be of high quality and 9 (35%) of low quality. Supplementary File 3 contains the reviewers' judgement on the domains judged as low quality or unclear.

Prevalence of industry funding of patient groups

Fifteen studies looked at prevalence of industry funding of patient groups. As Figure 3 shows, we grouped the studies in three categories. Eleven studies looked at prevalence within a population-based sample: eight focused on multiple disease with prevalence estimate ranging from 43% to 83%, three focused on a specific condition with prevalence estimates ranging from 20% to 75%. Four studies focused on a selected population of patient groups (e.g. respondents to consultations or patient groups that interact with regulatory agencies); prevalence ranged from 34% to 75%. Industry funding among patient groups varied greatly, from a few percent of the total budget to almost its entirety.(Table 3)

As shown in Supplementary File 4, the eleven studies that looked at prevalence within a population-based sample were included a meta-analysis. We found a high-level of heterogeneity that was not explained by any of the pre-specified and post-hoc subgroup analyses. Results of the Peter test suggest that there is not enough evidence to reject the null hypothesis of funnel plot symmetry (p = 0.5657), meaning that publication bias has not been detected.

Numbers of industry sponsors and frequency of contact

Four studies reported on the numbers of industry sponsors per patient group. One study found a median of 7 (range 1-19);(32) and another study found a median of 1 (range 0-21) industry sponsors reported on patient group websites. The latter increased to a median of 6 industry sponsors (range 0-38) in information provided in annual reports.(5) A UK study found that 140/246 (57%) patient groups received funding from only one company (14) whereas in a Dutch study, 29/41 (71%) patient groups were funded by two or more companies.(33)

Frequency of industry contacts (e.g. number of meetings, phone calls) was reported in four studies. In two UK studies, 55/123 (45%) (41) and 43/122 (35%) of groups reported at least quarterly contact with the pharmaceutical industry.(34) A Dutch study reported that in a response to a query on how often they were contacted by companies in the last two years, 38% (36/96) of groups were contacted, on average 3.4 times. Reported reasons for communication included company requests to distribute an article on a medicine, requests to promote a medicine, and offers to produce information materials or fund awareness-raising activities. The study reported also that 38% (36/96) patient groups had requested support from pharmaceutical companies in the last two years.(33) A Finnish study asked groups about changes of cooperation with drug manufacturers over the last five years: 22/55 (40%) reported no change, 18/55 (33%) an increase and 5/55 (9%) a decrease.(13)

Proportion of industry-funded patient groups which disclose information about this funding

Table 4 describes the proportion of industry funded patient groups which disclosed information about industry funding on their websites or in public consultations. Four studies (from Australia, Italy, UK and US) analysed patient groups' websites and found that one quarter to one third of the groups disclosed industry funding.(12, 14, 30, 39). When we meta-analysed these four studies, the overall pooled proportion of groups that disclosed industry funding was 27% (95% CI: 24% to 31%, I^2=0%; Figure 4). However, the four studies were published between 2008 and 2012, and there may have been additional shifts in disclosure of financial relationships with industry since 2012. Two studies of submissions to consultations in the US had the highest and lowest disclosure rates. Abola et al. analysed whether Food and Drug Administration (FDA) speakers at advisory committee meetings disclosed and found a 91% disclosure rate;(32) whereas Lin et al. found zero

disclosures in submissions to a Center for Disease Control (CDC) consultation on opioid guidelines.(19) Finally, the amount, use or the proportion of income derived from industry funding was rarely disclosed.(Table 4)

Relationship between industry funding and organisational positions

Four studies analysed the association between organisational positions and industry funding: three were on organisational positions versus industry funding, two of which included comparisons between industry-funded and non-funded groups. One study examined information quality among industry-funded vs. non-funded groups.

Perehudoff surveyed patient and consumer organisations in official relations with the European Medicines Agency on their opinions on a controversial European legislative proposal on industry-provided patient information.(20) Specific elements of this proposal were interpreted as partial introduction of direct-to-consumer advertising in Europe, whereas others were less controversial. (44, 45) Legislative change to increase the industry's role was supported by 6/6 (100%) of industry-sponsored versus 0/5 (0%) of non-sponsored groups. For two other outcomes, support for broadcast advertising and mention of brands in disease-awareness advertising, there was little difference between industry-funded and non-funded groups: 17% vs. 20% support for broadcast advertising, and 33% vs. 20% for mention of brands.

The second study by Lin et al. analysed links between funding from opioid manufacturers and statements of professional organisations and patient groups when consulting during guideline development aiming to minimise harms of opioid use developed by the US Centers for Disease Control and Prevention.(19) According to supplementary data provided by the authors, most non-industry funded groups (15/17, 88%) supported the guidelines recommendations; in contrast less than half of the opioid manufacturer-funded patient groups (4/9, 44%) were supportive and the majority (5/9, 56%) were unsupportive.(19)

The third study examined prevalence of industry funding among patient groups opposing a proposal aimed to reduce Medicare Part B drug costs.(35) This proposal included changes to reimbursement to minimize financial incentives to prescribe more expensive drugs, and introduction of value-based purchasing tools tying drug prices to patient health outcomes.(46) In total, 110/147 (75%) of the patient groups that sided with pharmaceutical companies and opposed the proposal received industry funding.(35)

Finally, one study explored the association between industry funding and information quality.(18) The authors analysed the information about mammographic screening on websites of 16 consumer advocacy groups. They measured the comprehensiveness of information on potential harms of mammography, including risks of false positives and overdiagnosis, using a checklist of 17 information items.(18) The mean number of information items was 3.7 (SD=3.66) for industry funded groups and 10 (SD=4.24) for the non-industry funded ones. We compared the number of information items provided with a Mann-Whitney test and the result was not statistically significant (p=0.100).

Policies governing corporate sponsorship

None of the included studies compared organisational policies (e.g. code of conduct) of industry funded versus non-industry funded groups. As comparative data were unavailable, we are reporting instead on a related outcome, namely prevalence of organisational policies governing corporate sponsorship. Estimates of prevalence of organisational policies ranged from 2% to 64%. (Figure 5) Six (60%) of the studies had a prevalence below 10%. Among studies of high quality, the highest prevalence of policies was reported in two 2017 US studies,(1, 15) possibly reflecting recent shifts in disclosure of financial relationship with industry. The meta-analysis found a high level of heterogeneity that was not explained by the subgroup analysis.(See Supplementary File 4) The test of funnel plot asymmetry was not statistically significant (p = 0.6973), indicating a lack of observed publication bias.

Financial conflicts of interest among governing and advisory bodies

One of the primary outcomes in our protocol was a comparison between industry funded and non-industry funded groups in terms of how often industry employees or people with financial links to companies were present on governing and advisory boards. Comparative data were unavailable. However, two studies reported on a related outcome, the proportion of patient groups with industry employees or people with financial conflicts of interest on the governing or advisory board. A German study found that 5/8 groups had a scientific advisory board with listed members; of these, 100% (5/5) had members with financial ties with pharmaceutical companies.(22) A recent US study reported that 37/104 (36%) patient groups had at least one drug, device, or biotechnology company executive on the board.(1)

Presence of industry logos and advertising

Three articles reported on the prevalence of industry logos on patient groups' websites.(12) (5) (33) Company logos were displayed on 26/157 (17%) of Italian patient groups' websites (12), in 23/69 (33%) of the websites of major national and international patient groups (5), and in 21/41 (51%) of Dutch patient groups.(33) Three studies reported on the prevalence of banner advertisements and/or links to industry websites; all found they were present to some extent, although frequencies differed, ranging from 11% to 30% of the websites analysed.(5, 12, 13) A German study analysed magazines for members and found that 6/7 (86%) had direct advertisements such as industry logos or links to industry websites; the analysis of patient groups' websites showed that 4/8 (50%) had logos or hyperlinks to industry websites.(22)

Discussion

Key findings

Of the 26 studies included in this systematic review, 11 included estimates of the prevalence of industry funding within a population-based sample, which ranged from 20% to 83%. Four studies focused on a selected population of patient groups (e.g. respondents to consultations or patient groups that interact with regulatory agencies); prevalence ranged from 34% to 75%. Most of the included studies did not provide data on the amount and proportion of funding that came from industry. Among patient organisations having received industry funding, 27% (95% CI: 24 to 31%) disclosed this information on their websites. However, the four studies were published between 2008 and 2012, and there may have been additional shifts in disclosure of financial relationships with industry since 2012. In submissions to governmental consultations, two studies showed very different disclosure rates (0% and 91% respectively), appearing to reflect differences in the relevant government agency's disclosure policies. Few patient groups had formal policies governing corporate sponsorship. Four studies analysed the relationship between organisational positions and industry funding. These studies addressed a range of highly controversial issues: overdiagnosis, pharmaceutical advertising, harm from opioid use, and high drug costs. All four represent situations in which a conflict existed between the interests of commercial sponsors and the interests of patients and/or the public. For example, the study by Claypool focused on groups who opposed a proposal aimed at decreasing the prescription of high cost drugs when less expensive and equally effective medicines are available.(35) Access to equally effective but less costly medicines is in patients' interests as it improves affordability. The data available from the four studies points to positions reflective of sponsors' interests. However, this finding should be interpreted with caution as three of these studies had small sample sizes and all focused on a single policy or health issue. Additionally, this association of sponsored groups' and sponsors' positions does not necessarily reflect an influence by sponsors on a group's agenda. It is also possible that sponsors selectively funded groups with positions that were closely aligned with their interests.

Strengths and limitations of study

This is the first systematic review that summarises published data on industry funding of patient groups. We registered our protocol prior to conducting the review, undertook a comprehensive

search of multiple databases with no restrictions based on language or publication type, and contacted experts in the field to identify additional studies for inclusion.

Our review has several limitations. First, all the studies were conducted in high-income countries (apart from one study that included data from South Africa, an upper middle-income country), thus our findings may not be generalisable to middle- or low income settings. Second, although most included studies relied on more than one data source, these were mainly publicly disclosed data and self-reported information, which could underestimate the true prevalence of industry funding. Third, we relied on how the included studies defined pharmaceutical and medical device companies. In many cases these industries were defined quite broadly and this might have brought in some inconsistencies. Moreover, the focus of this systematic review was specifically on relationships between patient groups and the pharmaceutical and device companies and it is possible that other conflicts are also relevant for specific groups within this sector, such as relationships with the food industry or with private health insurance providers. Fourth, for two outcomes (prevalence of industry funding and prevalence of policies) we could not present summary estimates due to the high level of heterogeneity that was not explained by any of the subgroup analyses. Heterogeneity could be due the fact that the included studies differed considerably in data collection methods. For example, some relied only on a single source of information (e.g. the groups' websites) to assess prevalence rates, while others used multiple sources of data, including websites of patient groups and pharmaceutical companies, questionnaires and tax records. Survey response rates ranged from 39% to 87%. Another limitation is that the "Checklist for Prevalence Studies" that we used to asses study quality includes items relevant to broader study quality, to reporting quality, and to assessing risk of bias. This might have impacted on our ability to measure the methodological quality of the included studies. Finally, not all the included studies were peer-reviewed.

Implications for research

We found limited research on the association between industry funding and organisational policy positions. Considering the important role that patient groups play in education, health policy and advocacy, more research on the potential impact of industry funding on the groups' activities is needed. Moreover, future research should use multiple sources of information in order to better estimate the prevalence of industry funding. Due to the inadequate financial transparency, studies

relying only on self-reported information could underestimate the extent of the phenomenon. Increased requirements of pharmaceutical companies for transparency about funding relationships (47) may lead to more accurate estimates. In this regard, legislations similar to the US Sunshine Act should be implemented also in other jurisdictions and expanded to cover industry payments to patient groups.(48) Moreover, our systematic review shows a research gap on this topic in the context of low- and middle-income countries. Industry funding and influence may be even greater in jurisdictions with fewer local resources, so these settings could be an important area for future research.

Implications for policy and practice

Our systematic review showed that pharmaceutical industry funding of patient groups is common in a variety of high-income countries. We recognise that industry funding might be the only source of income for some groups; however, there is increasing evidence that industry sponsorship can create bias in medical research and clinical practice,(49, 50) and patient groups may be subject to the same concerns. The pharmaceutical industry is likely to prioritise funding of groups whose views are aligned to its interests.(3) Patient groups are powerful advocates with influence over health policy. If industry-funded patient groups are more likely to flourish and to have the most influence over the health sector, this could lead to widespread commercial biases in the representation of patients' interests, with misalignment between the public's health priorities and advocacy-driven health policy. Alternative funding mechanisms could be explored. Consideration could also be given to whether there is a greater need for mechanisms for public financing of patient groups, for example provision of small grants allowing community organisations without corporate subsidies to participate in advocacy.

We found few studies that assessed links between funding status of patient groups and their health and policy positions,(18-20, 35) but the limited data available points to positions reflective of sponsors' interests. Moreover, a recent analysis of patient groups that contributed to health technology assessments at England's National Institute for Clinical Excellence (NICE) found that 72% had received funding by companies with products under consideration or their competitors, raising concerns about the role these conflicts of interest may play in approval of new health technologies in the UK. NICE was rarely aware of these financial relationships, and in nearly two thirds of cases, NICE's disclosure policy did not require declaration of these undisclosed conflicts

of interest.(51) Governmental agencies should therefore develop robust guidelines to ensure financial transparency from patient groups they interact with, including monitoring procedures and strategies to manage the disclosed conflicts of interest, as well as ensuring inclusion of patient groups without industry funding when obtaining input into decisions. Disclosure of groups' financial associations would assist those who listen to patient group voices (e.g., patients, health professionals, and policy makers) in the critical evaluation of those groups' practices. Disclosure might also have an important effect on the groups themselves, increasing their accountability in managing conflicts of interests and encouraging them to seek other sources of funding in order to maintain the public's trust.(52) Two studies examining disclosure in patient group submissions to consultations with US governmental agencies reported very different disclosure rates: 0%, in submissions to the CDC (19) and 91% in submission to the FDA.(32) This suggests that the agencies' policies exert a strong influence on disclosure rates. Finally, we examined industry funding of patient groups in this review because of the limited attention to conflicts of interest in this sector. However, financial conflicts of interest are a systemic challenge facing healthcare today and they can have an impact on many other stakeholders such as researchers, health professionals, and medical societies.(53, 54)

Conclusion

This systematic review shows that pharmaceutical industry funding of patient groups is common in many high income countries and clinical areas. The extent of industry funding of patient groups in low to middle income countries is unknown, as only one study included data from South Africa, an upper middle income country. Few groups have policies governing corporate sponsorship. Transparency concerning corporate funding is also inadequate. The few studies that assessed the link between policy positions and funding status raise concerns about industry influence. In conclusion, we encourage patient groups to critically evaluate the role of industry funding on their operations. Greater transparency in reporting of industry funding, and policy development to govern corporate sponsorship are steps that are clearly needed and easy to implement. In the long term, we would recommend a broader discussion around the role of industry funding in the patient group sector, both amongst patient groups themselves, and in the wider society, and exploration of alternate funding mechanisms.

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Conflicts of interest: All authors have completed the ICMJE uniform disclosure form. Paola Mosconi and Cinzia Colombo report an unconditional grant from the Smith Kline Foundation, outside the submitted work. Paola Mosconi and Cinzia Colombo are authors of some of the studies included in the review and were not involved in extracting data from or in assessing the quality of their own studies. Paola Mosconi is a member of the Board of Europa Donna, the European Breast Cancer Coalition. Barbara Mintzes is a member of the European network of Health Action International (HAI-Europe). Given this relationship with HAI-Europe, Barbara Mintzes was not involved in extracting data from or in assessing the quality of the two studies published by HAI-Europe (20, 43). Barbara Mintzes acted as an expert witness on behalf of plaintiffs in a Canadian class action suit on cardiovascular risks of testosterone. All the other authors declare: no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Ethical approval: Not required.

Data sharing: All data relevant to the study are included in the article or uploaded as supplementary information.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Contributors: AF, CC, PM, EL, BM conceived the study idea. DS conducted the literature search. AF, LP, CC, PM, EL, PF, GB, BM screened abstracts and full texts and acquired the data. CMK and CL analysed the data. AF wrote the first draft of the manuscript. All authors edited drafts of this article and approved the final version.

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Table 1. Characteristics of studies included in systematic review of industry funding of patient groups

Study*	Location of study sample	Number of patient groups** (Response rate, if applicable)	Disease focus	Year of data collection	Key data collection methods***	Publication type	Funding source	Author conflicts of interest (only with pharmaceutical or device industries)
Abola, 2016a	US	68	Cancer	2015-2016	Websites	Peer reviewed journal	Not reported	Not reported
Abola, 2016b	US	58	Cancer	2015	FDA meeting transcripts	Peer reviewed journal	Not reported	No
Anonymous, 2003	UK	125	Multiple	Not reported	Websites	Lay press	Non-profit	Not reported
Baggott, 2005	UK	123/186 (66%)	Multiple	1999	Questionnaires	Academic book	Government	Not reported
Baggott, 2014♦	UK	122/312 (39%)	Multiple	2010	Questionnaires	Peer reviewed journal	Not reported	Not reported
Ball, 2006	Various (USA, UK, Australia, Canada and South Africa)	69	Multiple	2005	Websites	Peer reviewed journal	No funding received	No
Claypool, 2016	US	147	Multiple	2016	Websites (patient groups and pharmaceutical companies); transparency databases	Report	Not reported	Not reported
Colombo, 2012	Italy	157	Multiple	2010	Websites (patient groups and pharmaceutical companies)	Peer reviewed journal	Non profit	No
Garcia Sempere, 2005	Spain	21/38 (55%)	Multiple	2003-2004	Questionnaires	Peer reviewed journal	Government	Not reported

Hemminki, 2010	Finland	Questionnaires: 55/85 (65%) Websites: 13	Multiple	2003	Questionnaires, websites	Peer reviewed journal	Government	No
Jones, 2008	UK	246	Multiple	2007	Websites (patient groups and pharmaceutical companies)	Peer reviewed journal	Government	Not reported
Jorgensen, 2004	Various (Australia, Canada, Denmark, New Zealand, Norway, Sweden, UK, US)	16 (n=13 advocacy groups, n=3 consumer groups)	Breast cancer	2002 (websites; funding information); 1998 (pamphlets; some positions)	Websites; follow-up queries to patient groups; patient information pamphlets	Peer reviewed journal	No funding received	No
Kopp, 2018	US	1215	Multiple	2015	Websites (patient groups and pharmaceutical companies); tax records	Report	Non-profit	No
Lin, 2017	US	30 Questionnaire: 26/30 (87%)	Multiple	2016	Websites; tax records; questionnaires; annual reports	Peer reviewed journal	Not reported	No
Marshall, 2006	US	29	Multiple	2006	Websites; tax records; questionnaires	Lay press	Media (New Scientist)	Not reported
McCoy, 2017	US	104	Multiple	2016	Tax records; websites	Peer reviewed journal	Not reported	Yes
Mosconi, 2003	Italy	67	Breast cancer	1998-1999	Questionnaires	Peer reviewed journal	Non profit	No

O'Donovan, 2007◊	Ireland	112/167 (67%)	Multiple	2004	Questionnaires	Peer reviewed journal	Non profit	Not reported
Perehudoff, 2010	Europe	23	Multiple	2010	Websites (patient groups and pharmaceutical companies); Google searches; direct email communication with patient groups	Report	Government and non profit	No
Perehudoff, 2011	Europe	Questionnaire: 12/22 (55%); Policy analysis: 14/22 (64%)	Multiple	2009-2010	Websites (patient groups and pharmaceutical companies); questionnaires; published policies	Report	Government and non profit	No
Pinto, 2016	Australia	61/114 (54%)	Rare Diseases	2013-2014	Questionnaires	Peer reviewed journal	No funding received	No
Rose, 2017	US	289/439 (66%)	Multiple	2013-2014	Questionnaires	Peer reviewed journal	Non profit	Yes
Rothman, 2011	US	161	Multiple	2007-2009	Websites; pharmaceutical company's grant registry	Peer reviewed journal	Non profit	Not reported
Schubert, 2006	Germany	8	Multiple	Not reported	Websites; questionnaires and interviews; magazines from patient	Report	Not reported	Not reported

					groups			
van Rijn van Alkmade, 2005	The Netherlands	96/219 (44%)	Multiple	2004	Questionnaires; annual reports	Report	Government	Not reported
Vitry, 2011	Australia	135	Multiple	2011	Websites (patient groups and pharmaceutical companies)	Conference presentation	Not profit	Not reported

*Study design: all cross sectional
** This refers to the number of patient groups included in our analysis; some studies included several samples.
***Some studies used several data collection methods (e.g. websites analyses, questionnaires, interviews): only those used to collect data included in this systematic review are reported. If not further specified, websites and questionnaires refer to patient groups as a data source.
♦ Baggott 2014 describes two studies, one of which is described in greater detail in Baggott 2005 (see row above); the listing for Baggott 2014 in this table covers only the second study.
◊We also identified a less comprehensive version of the same study conducted in 2005.
^ The term 'multiple disease' is used for studies that focused on patient groups that work on a range of clinical areas.

Table 2. GRADE summary of findings: Industry funding of patient groups

Outcomes	Prevalence	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Prevalence measures				
Industry funding	Population sample-multiple disease: range from 43% to 83% Population sample-specific condition: range from 20% to 75% Consultation: range from 34% to 75%	2150 (15 studies)	⨁⨁⊖⊖ **low**	Downgraded due to inconsistency
Transparency of funding on websites	27 per 100 (95% CI 24 to 31)	642 (4 studies)	⨁⨁⨁⊖ **moderate**	No inconsistency; 3 of 4 studies of high quality; studies in four countries.
Transparency of funding during consultations	0 per 100 (US CDC) 91 per 100 (US FDA)	31 (2 studies)	⨁⊖⊖⊖ **very low**	Downgraded due to imprecision; divergent results mirror policies of agency holding consultation.
Organisational policies governing sponsorship	Range from 2% to 64%	1294 (10 studies)	⨁⊖⊖⊖ **very low**	Downgraded due to inconsistency; data collection & definitions differ.
Comparative analyses				
Organisational positions versus industry funding		**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**

Positions consistent with sponsors' interests	Industry-funded groups generally supported sponsors' interests more often than non-funded groups	37 (2)	⊕⊖⊖⊖ **very low**	Downgraded for imprecision; 1 of 2 studies of low quality
Comprehensiveness of information on harm; (mean # harms, max=17)	x =10 items (SD 4.2) for non-industry funded x = 3.7 items (SD 3.7) for industry-funded Mann-Whitney non-significant p=0.1	16 (1 study)	⊕⊖⊖⊖ **very low**	Downgraded for imprecision; single study of low quality

CI: Confidence interval

GRADE Working Group grades of evidence
High: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 3. Details of industry funding

Study	Number of groups	Amount of industry funding
Hemminki, 2010	21	Range: US$ 339 to 65,491
		Mean amount
Kopp, 2018	594	2015: US $195,305 (own calculation)
Perehudoff, 2010	14	2006: US$ 209,458
	13	2007: US$ 318,523
		2008: US$ 362,718
van Rijn van Alkmade, 2005	16	2002: US$ 33,218*
		2003: US$ 63,991*
		Mean proportion of funding
Perehudoff, 2010	14	2006: 47%
	13	2007: 51%
		2008: 57%
van Rijn van Alkmade, 2005	16	2002: 11.1%
		2003: 12.6%
		Median proportion of funding
Rose, 2017	156	Median: 45% IQR: 0% to 100%
	Proportion of groups with ≥ 20% industry funding	
Hemminki, 2010	4/20 (20%)	
Kopp, 2018	15/594 (3%)	
Marshall, 2006	7/24 (29%)	
	Proportion of groups with ≥ 10% industry funding	

McCoy, 2017	11/59 (19%)
	Proportion of groups with ≥ US$1 million industry funding
McCoy, 2017	23/59 (39%)

Currencies were converted to US$ using . (Date of conversion: November 14th 2018)
*Amounts under EUR 1000 (US$ 1,129) per organisation not included.

Table 4. Proportion of industry-funded patient groups which disclosed information about this funding

Study	Organisations disclosing funding	Amount disclosed	Proportion of income disclosed	Use disclosed
On websites				
Vitry, 2011	25/78 (32%)	-	-	-
Colombo, 2012	46/157 (29%)	3/157 (2%)	0/157 (0%)	25/157 (16%)
Jones, 2008	64/246 (26%)	14/246 (6%)	4/246 (2%)	18/246 (7%)
Rothman, 2011^	40/161(25%)	1/161 (1%)	-	-
In consultations				
Abola, 2016b	20/22 (91%)	-	-	-
Lin, 2017	0/9 (0%)*	-	-	-

^it only refers to funding from Eli Lilly
*Data received from the authors

Figure Legends

Figure 1. PRIMSA flow diagram of included articles

Figure 2. Quality appraisal of included studies

Figure 3. Forest plot of prevalence of industry funding of patient groups

Figure 4. Forest plot of proportion of industry funded patient groups which disclosed information about this funding on their websites

Figure 5. Forest plot of prevalence of policies governing corporate sponsorship

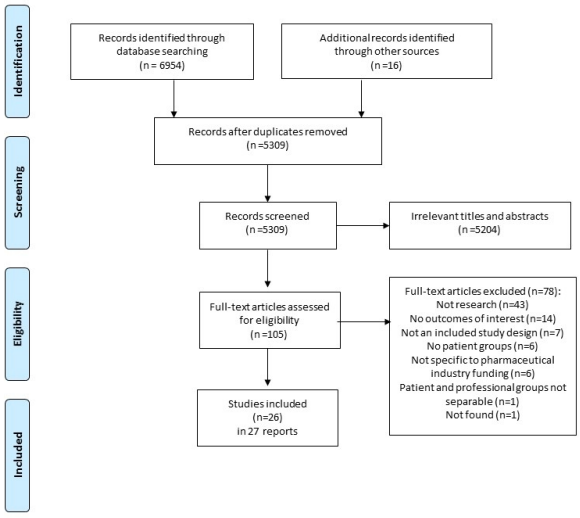
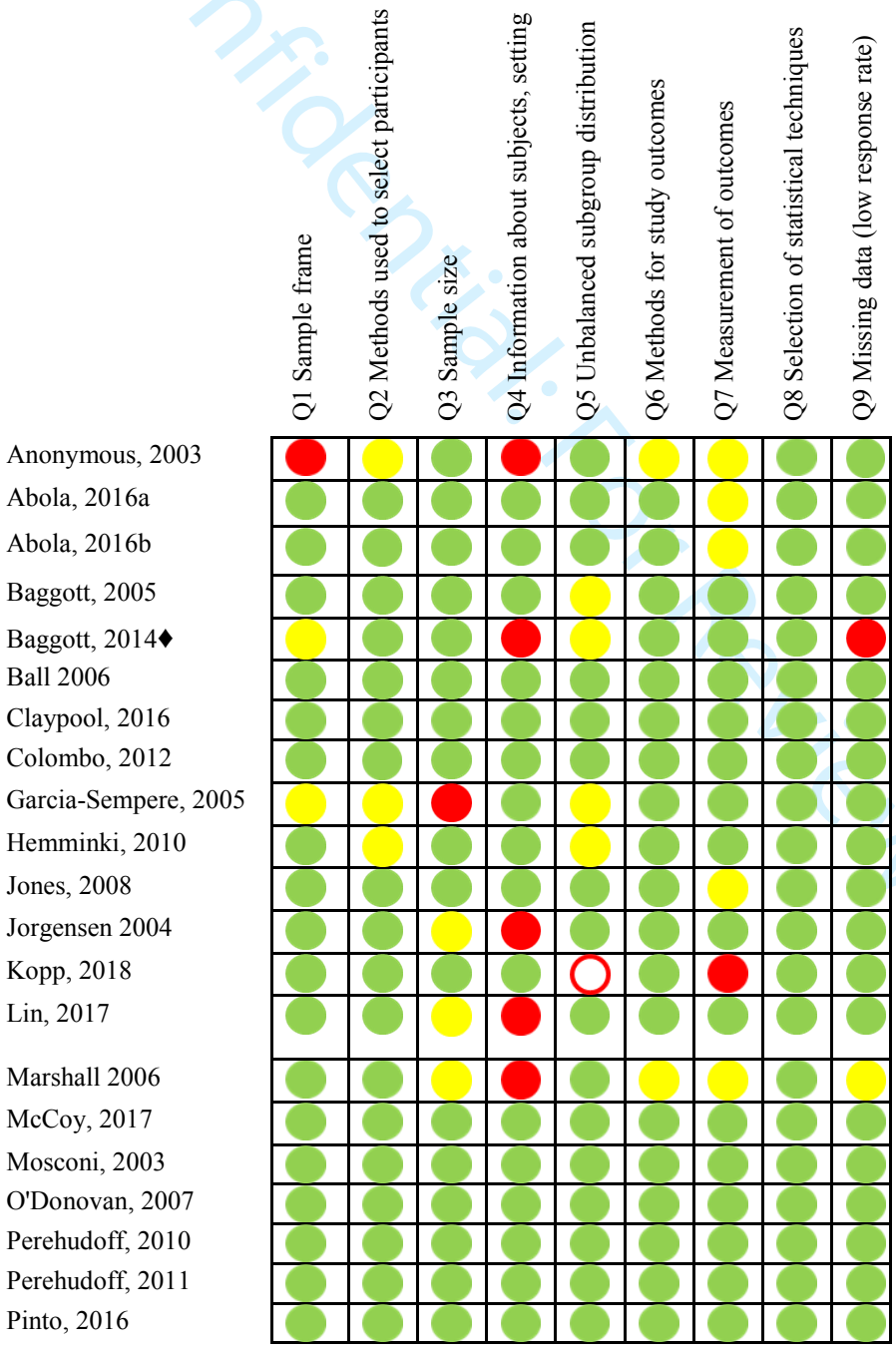
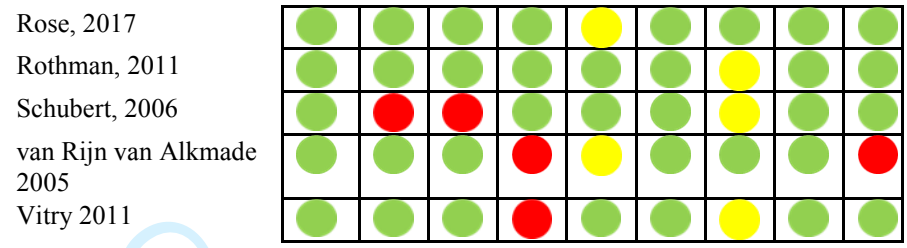


Figure 1. Study flow diagram

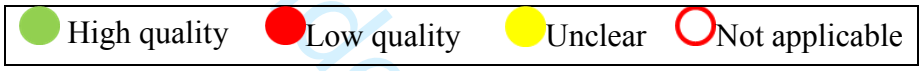
338x190mm (96 x 96 DPI)

Figure 2. Quality appraisal of included studies





♦ Baggott 2014 describes two studies, one of which is described in greater detail in Baggott 2005 (see row above); the listing for Baggott 2014 in this table covers only the second study.



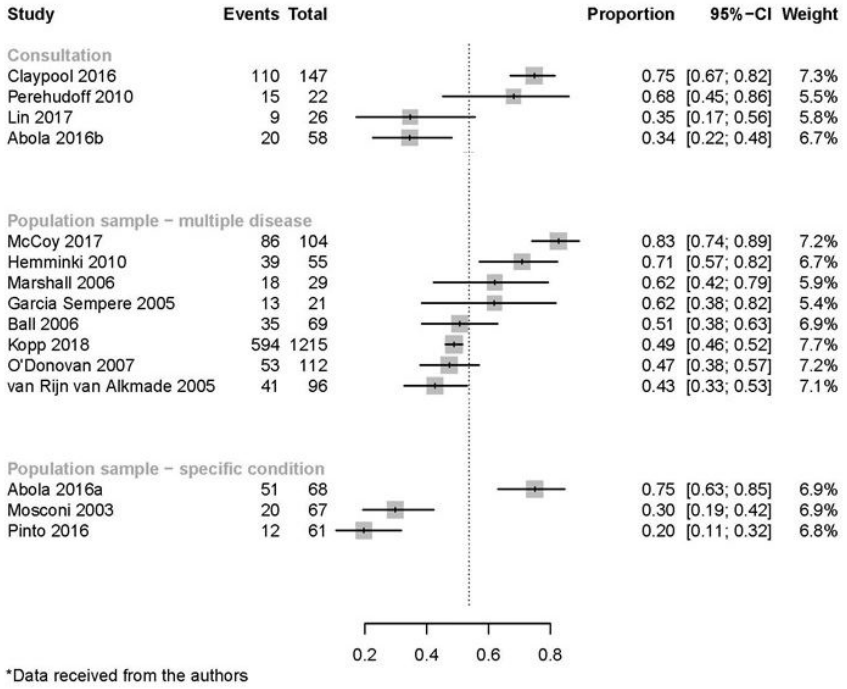


Figure 3. Forest plot of prevalence of industry funding of patient groups

217x170mm (96 x 96 DPI)

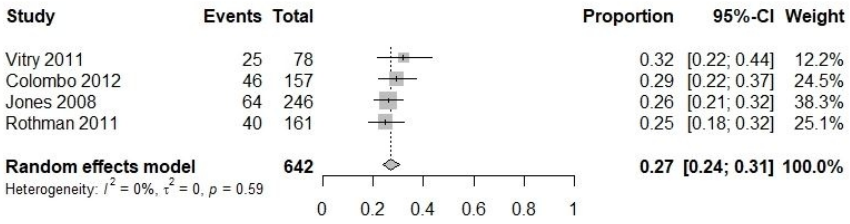


Figure 4. Forest plot of proportion of industry funded patient groups which disclosed information about this funding on their websites

237x140mm (96 x 96 DPI)

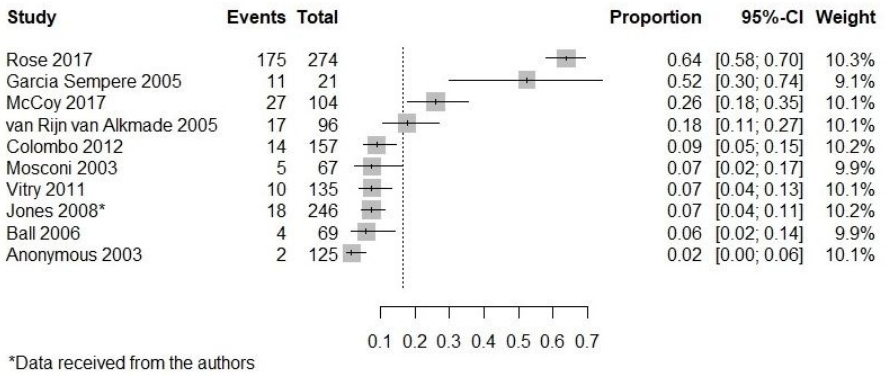


Figure 5. Forest plot of prevalence of policies governing corporate sponsorship

234x153mm (96 x 96 DPI)

Supplementary File 1. Search Strategy

Database: Ovid MEDLINE(R) and Epub Ahead of Print, and In-Process & Other Non-Indexed Citations <1946 to January 18, 2018>

Search Date: 20 January 2018

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1 consumer organizations/

2 patient advocacy/

3 consumer advocacy/

4 (citizen? adj2 (advocacy or advocat$ or association? or group? or organi?ation?)).mp.

5 (consumer? adj2 (advocacy or advocat$ or association? or group? or organi?ation?)).mp.

6 (health$ adj2 (advocacy or advocat$ or association? or group? or organi?ation?)).mp.

7 (patient? adj2 (advocacy or advocat$ or association? or group? or organi?ation?)).mp.

8 or/1-7

9 (biopharm$ adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

10 (bioscience? adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

11 (device$ adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

12 (drug? adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

13 (health adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

14 (healthcare adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

15 (health care adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

16 (life science? adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

17 (medical adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

18 (pharma$ adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

19 (industr$ adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

20 "conflict of interest"/

21 (conflict$ adj2 interest?).tw,kf.

22 or/9-21

23 8 and 22

24 animals/ not (humans/ and animals/)

25 23 not 24

26 remove duplicates from 25

****

Database: Embase <1974 to 2018 Week 04>

Search Date: 20 January 2018

---

1 consumer organization/

2 *patient advocacy/

3 *consumer advocacy/

4 (citizen? adj2 (advocacy or advocat$ or association? or group? or organi?ation?)).mp.

5 (consumer? adj2 (advocacy or advocat$ or association? or group? or organi?ation?)).mp.

6 (health$ adj2 (advocacy or advocat$ or association? or group? or organi?ation?)).mp.

7 (patient? adj2 (advocacy or advocat$ or association? or group? or organi?ation?)).mp.

8 or/1-7

9 (biopharm$ adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

10 (bioscience? adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

11 (device$ adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

12 (drug? adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

13 (health adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

14 (healthcare adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

15 (health care adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

16 (life science? adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

17 (medical adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

18 (pharma$ adj3 (compan$ or corporat$ or firm$ or industr$) adj5 (contribut$ or donat$ or financ$ or fund$ or grant? or influen$ or sponsor$ or support$)).mp.

19 (industr$ adj3 (contribut$ or donat$ or financ$ or fund$ or grant? or sponsor$ or support$)).mp.

20 "conflict of interest"/

21 (conflict$ adj2 interest?).mp.

22 or/9-21

23 8 and 22

24 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)

25 23 not 24

26 remove duplicates from 25

****

Databases: Web of Science <1900 to 2017> Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

Search Date: 20 January 2018

#19 #18 AND #5

#18 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6

#17 TS=(conflict* NEAR/2 interest*)

#16 TS=(industry NEAR/3 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#15 TS=(pharma* NEAR/3 (compan* or corporat* or firm* or industr*) NEAR/5 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#14 TS=(medical NEAR/3 (compan* or corporat* or firm* or industr*) NEAR/5 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#13 TS=(life science* NEAR/3 (compan* or corporat* or firm* or industr*) NEAR/5 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#12 TS=(health care NEAR/3 (compan* or corporat* or firm* or industr*) NEAR/5 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#11 TS=(healthcare NEAR/3 (compan* or corporat* or firm* or industr*) NEAR/5 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#10 TS=(health NEAR/3 (compan* or corporat* or firm* or industr*) NEAR/5 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#9 TS=(drug* NEAR/3 (compan* or corporat* or firm* or industr*) NEAR/5 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#8 TS=(device* NEAR/3 (compan* or corporat* or firm* or industr*) NEAR/5 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#7 TS=(bioscience* NEAR/3 (compan* or corporat* or firm* or industr*) NEAR/5 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#6 TS=(biopharm* NEAR/3 (compan* or corporat* or firm* or industr*) NEAR/5 (contribut* or donat* or financ* or fund* or grant* or influen* or sponsor* or support*))

#5 #4 OR #3 OR #2 OR #1

#4 TS=(patient* NEAR/2 (advoca* OR association OR group* OR organi*))

#3 TS=(health* NEAR/2 (advoca* OR association OR group* OR organi*))

#2 TS=(consumer* NEAR/2 (advoca* OR association OR group* OR organi*))

#1 TS=(citizen* NEAR/2 (advoca* OR association OR group* OR organi*))

****

Database: Google Scholar

Search Date: 20 January 2018

“consumer organisations” AND “medical device” AND “industry funding”

“consumer organisations” AND “pharmaceutical companies” AND “industry funding”

“consumer organisations” AND “pharmaceutical company” AND “industry funding”

“consumer organisations” AND “pharmaceutical companies” AND “conflict of interest”

“consumer organisations” AND “pharmaceutical company” AND “conflicts of interest”

“consumer organizations” AND “medical device” AND “industry funding”

“consumer organizations” AND “pharmaceutical companies” AND “industry funding”

“consumer organizations” AND “pharmaceutical company” AND “industry funding”

“consumer organizations” AND “pharmaceutical companies” AND “conflict of interest”

“consumer organizations” AND “pharmaceutical company” AND “conflicts of interest”

“patient advocacy” AND “medical device” AND “industry funding”

“patient advocacy” AND “pharmaceutical companies” AND “industry funding”

“patient advocacy” AND “pharmaceutical company” AND “industry funding”

"patient groups" AND " medical device " AND "industry funding"

"patient groups" AND "pharmaceutical companies" AND "industry funding"

"patient groups" AND "pharmaceutical company" AND "industry funding"

“patient organisations” AND “medical device” AND “industry funding”

“patient organisations” AND “pharmaceutical companies” AND “industry funding”

“patient organisations” AND “pharmaceutical company” AND “industry funding”

"patient organisations" AND "pharmaceutical companies" AND "conflict of interest"

“patient organizations” AND “medical device” AND “industry funding”

“patient organizations” AND “pharmaceutical companies” AND “industry funding”

“patient organizations” AND “pharmaceutical company” AND “industry funding”

“consumer organisations” AND “medical device” AND “industry support”

“consumer organisations” AND “pharmaceutical companies” AND “industry support”

“consumer organisations” AND “pharmaceutical company” AND “industry support”

“consumer organizations” AND “medical device” AND “industry support”

“consumer organizations” AND “pharmaceutical companies” AND “industry support”

“consumer organizations” AND “pharmaceutical company” AND “industry support”
“patient advocacy” AND “medical device” AND “industry support”
“patient advocacy” AND “pharmaceutical companies” AND “industry support”
“patient advocacy” AND “pharmaceutical company” AND “industry support”
"patient groups" AND "medical device" AND "industry support"
"patient groups" AND "pharmaceutical companies" AND "industry support"
"patient groups" AND "pharmaceutical company" AND "industry support"
“patient organisations” AND “medical device” AND “industry support”
“patient organisations” AND “pharmaceutical companies” AND “industry support”
“patient organisations” AND “pharmaceutical company” AND “industry support”
“patient organizations” AND “medical device” AND “industry support”
“patient organizations” AND “pharmaceutical companies” AND “industry support”
“patient organizations” AND “pharmaceutical company” AND “industry support”

****

Database: Scopus

Search Date: 20 January 2018

(TITLE-ABS-KEY (((citizen* OR consumer* OR health* OR patient*) W/2 (advoca* OR association* OR group* OR organisation* OR organization*)))) AND ((TITLE-ABS-KEY (("*pharm* compan*" OR "bioscience* compan*" OR "drug* compan*" OR "*pharm* firm*" OR "bioscience* firm*" OR "drug* firm*" OR "*pharm* industry*" OR "bioscience* industry*" OR "drug industry*")) AND TITLE-ABS-KEY ((contribut* OR donat* OR financ* OR fund* OR grant* OR influen* OR sponsor* OR support* OR "conflict* of interest*")))) AND (LIMIT-TO (DOCTYPE , "ar ") OR LIMIT-TO (DOCTYPE , "cp ") OR LIMIT-TO (DOCTYPE , "ch ") OR LIMIT-TO (DOCTYPE , "bk ") OR LIMIT-TO (DOCTYPE , "ip "))

****

Supplementary File 2. List of Excluded Studies

Author, Year	Title	Reason for Exclusion
Anonymous, 2017	Conflicts of interest in patient organizations: State of affairs in the US.	Not research
Balasegaram, 2017	An open source pharma roadmap	Not research
Charters, 1993	The patient representative role and sources of power	No outcomes of interest
Colombo, 2011	La ricerca risponde ai bisogni dei pazienti?	No outcomes of interest
Graham, 2016	Conflicts of Interest Among Patient and Consumer Representatives to U.S. Food and Drug Administration Drug Advisory Committees	No outcomes of interest
Hall, 2006	The role of advocacy groups in shaping federal cancer care policy for underserved people in the United States	Not one of the included study design
Helms, 2015 (Padiatrische Praxis)	Patient self-help. Conflicts of interest by pharmaceutical sponsorship	Not specific to pharmaceutical industry funding
Helms, 2015 (Gynakologische Praxis)	Patient self-help. Conflicts of interest by pharmaceutical sponsorship	Not specific to pharmaceutical industry funding
Helms, 2015 (Internistische Praxis)	Patient self-help. Conflicts of interest by pharmaceutical sponsorship	Not specific to pharmaceutical industry funding
Herxheimer, 2003	Relationships between the pharmaceutical industry and patients' organisations	Not one of the included study design
HSGAC Minority Staff Report, 2018	Fueling an epidemic. Report Two. Exposing the Financial Ties Between Opioid Manufacturers and Third Party Advocacy Groups.	Could not separate patient groups and professional societies
Jacobson, 2005	Lifting the veil of secrecy from industry funding of nonprofit health organizations	Not one of the included study design
Johnson, 2004	The risks of being a "patient advocate"	Not research
Klemperer, 2009	Self-help groups conflicts of interest through sponsoring by the pharmaceutical industry	Not research
Koivusalo, M. 2011	Commercial influence and global nongovernmental public action in health and pharmaceutical policies	Not one of the included study design

Korsia, S. 2000	Partnerships between the pharmaceutical industry and patient groups: The patients' view	Not research
Kuehn, B. M. 2009	Associations say no to industry funding	Not research
Landers, 2004	Health Care Lobbying in the United States	No outcomes of interest
Lambert, 2009	Patient Organisations & Medicines Policy Financial engagement with the pharmaceutical industry	Not research
Lapsley, 2003	Industry funding of patients' support groups	Not research
Latting, 1983	Selecting consumers for neighborhood health center boards	No outcomes of interest
Leto di Priolo, 2012	Assessing stakeholder opinion on relations between cancer patient groups and pharmaceutical companies in Europe	No outcomes of interest
Lewis, 1995	Paradox, process and perception: the role of organizations in clinical practice guidelines development	Not research
Lipworth, 2016	Pharmaceuticals, money and the health care organisational field	Not research
Lofgren, 2004	Pharmaceuticals and the consumer movement: the ambivalences of 'patient power'	Not research
Lofgren, 2001	Health Activism to Health 'Consumers'	Not research
Löfgren, 2011	From activism to state inclusion: health consumer groups in Australia. Democratizing Health: Consumer Groups in the Policy Process. 2011:177.	Not research
Lopes, 2015	Power relations and contrasting conceptions of evidence in patient involvement processes used to inform health funding decisions in Australia	Not one of the included study design
Marshall, 2006	Swallowing the best advice?	Not research
Medina, 2015	Associations de patients et laboratoires pharmaceutiques	Not research
Menkes, 2016	Industry sponsorship—what do patients think?	Not research
Mosconi, 1999	Italian Forum of Europa Donna: a survey of the breast cancer associations.	No outcomes of interest

Mosconi, 2002	Forum Europa Donna. Consumer health information: the role of breast cancer associations.	No outcomes of interest
Orlowski, 1996	Conflicts of interest, conflicting interests, and interesting conflicts, Part 3	No patient groups
Parry, 2008	Power shifts: How patient activism shapes the practice of medicine	Not one of the included study design
Patient View, 2017	The corporate reputation of Pharma in 2016 - the patient perspective	No outcomes of interest
Pinto, 2018	Chasing cures: Rewards and risks for rare disease patient organisations involved in research	No outcomes of interest
Prince, 2016	Care, Connect, Cure: Constructing Success for Health Consumer Organisations	Not one of the included study design
Rabeharisoa, 2013	The dynamics of patient organizations in Europe	Not research
Raz, 2006	Big Pharma Versus Small Patient	Not research
Read, 2008	Schizophrenia, drug companies and the internet	No patient groups
Roehr, 2011	US advocacy groups seldom disclose financial ties to industry	Not research
Roovers, 2016	Collaboration with the mesh industry: who needs who?	Not research
Rose, 2013	"Patient advocacy organizations: institutional conflicts of interest, trust, and trustworthiness."	Not research
Rothman, 2013	Medical communication companies	No patient groups
Sheldon, 2010	Patient groups must reveal corporate sponsorship, urges campaign group.	Not research
Simone, 2009	More interest in conflicts of interest.	Not research
Singh, 2008	Conflicts are everywhere.	Not research
Smith, 2015	Patient Engagement Practices in Clinical Research among Patient Groups, Industry, and Academia in the United States: A Survey	Not specific to pharmaceutical industry funding
Soares, 2012	Dangerous liaisons: The pharmaceutical industry, patients associations and the legal battles for access to medicines.	Not research

Spelsberg, 2009	Is disclosure of potential conflicts of interest in medicine and public health sufficient to increase transparency and decrease corruption?	Not research
Talesh, 2002	Breaking the learned helplessness of patients: why MCOs should be required to disclose financial incentives.	No patient groups
Tanne, 2008	Senator asks psychiatrists' association about drug company funding.	Not research
Taylor, 2017	Industry links with patient organisations.	Not research
Thompson, 1993	Understanding financial conflicts of interest.	Not research
Thomspon, 1996	Funding resuscitation research	Not research
Toivianen, 2004	Survey on Finnish Patient Organisations Shows Economic and Other Interactions with Drug Industry.	Not found
Toivianen, 2010	Patient organizations in Finland: increasing numbers and great variation	No outcomes of interest
Traulsen, 2005	Pharmaceutical policy and the lay public	Not research
Tuffs, 2006	Sponsorship of patients' groups by drug companies should be made transparent	Not research
Van De Bovenkamp,2011	Government influence on patient organizations	Not specific to pharmaceutical industry funding
Van Der Weyden, 2001	Confronting conflict of interest in research organisations: Time for national action	Not research
Vermeulen, 2007	The influence of the pharmaceutical industry in patient organisations	Not research
Vinicky, 1995	Conflicts of interest, conflicting interests, and interesting conflicts	Not research
Vitry, 2004	Is Australia free from direct-to-consumer advertising?	Not research
Vitry, 2011	Health consumer groups and the pharmaceutical industry: is transparency the answer?	Not research
Voelker, 2011	Study: Few advocacy groups disclose grants from drug companies	Not research
Von Tigerstrom, 2016	The patient's voice: Patient involvement in medical product regulation	Not research
Wadman, 2008	Pharma payment probe widens its net	No patient groups

Wagner, 1990	Drug marketing practices criticized	Not research
Wang, 2014	Press releases issued by supplements industry organisations and non-industry organisations in response to publication of clinical research findings: A case-control study	Not specific to pharmaceutical industry funding
Wang, 2011	Eliciting views of Australian pharmaceutical industry employees on collaboration and the concept of Quality Use of Medicines	No patient groups
Waterson, 2017	Health professional associations and industry funding-reply from Waterston et al	Not research
Watson Buchanan, 1986	Influence of lay associations and consumer groups on arthritis health care	Not research
Wear, 1991	The moral significance of institutional integrity	Not research
Woodward, 2016	An innovative and collaborative partnership between patients with rare disease and industry-supported registries: the Global aHUS Registry	No outcomes of interest
Yarborough, 2007	Bioethics consultation and patient advocacy organizations: expanding the dialogue about professional conflicts of interest	No outcomes of interest
Zhang, 2009	Allocation of control rights and cooperation efficiency in public-private partnerships: Theory and evidence from the Chinese pharmaceutical industry	No outcomes of interest

Supplementary File 3. Quality assessment for prevalence studies

PART 1. Tool adapted from the Checklist for Prevalence Studies developed by Joanna Briggs Institute

Possible answers: High quality/Low quality/Unclear/Not applicable

Domain	Guidance
1. Sample frame	Was the sample frame appropriate (e.g. drawn from a clearly defined population of patient groups)?
2. Methods used to select participants	Was the sample of patient groups recruited in an appropriate way? (random sampling, systematic representative approach, or population based)
3. Sample size	Was the sample size adequate? (population-based; over 50%, or sample size calculation indicates adequacy)
4. Information about subjects and setting	Were the study subjects and setting described in detail? Do the authors provide baseline characteristics of the included patient groups such as size of the organisations, number of members and/or disease area?
5. Unbalanced subgroup distribution	Was data analysis conducted with sufficient coverage of the identified sample?
6. Methods for study outcomes	Were valid methods used for the identification of the outcome? (misclassification bias)
7. Measurement of outcomes	Were the outcomes measured in a valid and reliable way? (similar for all groups, training of data extractors and/or duplicate independent coding)
8. Selection of statistical techniques	Was there appropriate statistical analysis? (methods section describes analytical techniques and variables; numerators and denominators clear; confidence intervals)

9. Missing data	Was the response rate adequate, and if not, was the low response rate managed appropriately? (if response rate <50%, were respondents compared to non-respondents and found to be similar)

PART 2. Reviewers' judgement on the domains judged as low quality or unclear

Study	Domain	Reviewers' judgement	Description
Anonymous, 2003	Sample frame	Low quality	No information provided
	Methods used to select participants	Unclear	No information provided
	Information about subjects, setting	Low quality	No information provided on the characteristics of the patient organisations
	Methods for study outcomes	Unclear	No information provided beyond having searched the websites
	Measurement of outcomes	Unclear	No information provided
Abola, 2016a	Measurement of outcomes	Unclear	No information on duplicate independent coding
Abola, 2016b	Measurement of outcomes	Unclear	No information on duplicate independent coding
Baggott, 2005	Unbalanced subgroup distribution	Unclear	No information on non respondents
Baggott, 2014	Sample frame	Unclear	Included patient groups were identified from the membership lists of several large alliance organisations, but the alliance organisations are not reported
	Information about subjects, setting	Low quality	No background provided about the included patient groups
	Unbalanced subgroup distribution	Unclear	No information was provided on non respondents
	Missing data	Low quality	Response rate: 39%
Garcia-Sempere, 2005	Sample frame	Unclear	Inadequate detail on sampling frame
	Methods used to select participants	Unclear	Not clear how the authors searched the internet (e.g. which keywords

			they used) in order to identify the sample
	Sample size	Low quality	Not clear what is the actual denominator and whether the 38 groups are all the potential participants.
	Unbalanced subgroup distribution	Unclear	Inadequate information on non respondents
Hemminki, 2010	Methods used to select participants	Unclear	Sample selection criteria unclear (sampling was by a TV company, not authors)
	Unbalanced subgroup distribution	Unclear	No information on non-respondents
Jones, 2008	Measurement of outcomes	Unclear	No information on duplicate independent coding
Jorgensen 2004	Sample size	Unclear	No information provided on sample size calculation; small total number of organisations (n=3 non-funded; n=13 funded)
	Information about subjects, setting	Low quality	No description provided
Kopp, 2018	Measurement of outcomes	Low quality	Only 20 pharmaceutical companies' records were checked; funding by other companies was not included
Lin, 2017	Sample size	Unclear	Relationship between those who participated in this consultation and consumer advocacy groups in general is unclear
	Information about subjects, setting	Low quality	No information provided on the groups
Marshall 2006	Sample size	Unclear	No information provided on sample size calculations
	Information about subjects, setting	Low quality	Names of all included patient groups reported but no other information
	Methods for study outcomes	Unclear	Limited information provided
	Measurement of outcomes	Unclear	Not reported
	Missing data	Unclear	The proportion responding to surveys was not stated
Rose, 2017	Unbalanced subgroup distribution	Unclear	No information on non-respondents
Rothman, 2011	Measurement of outcomes	Unclear	No information on duplicate independent coding

Schubert, 2006	Methods used to select participants	Low quality	Sample based on six disease areas chosen according to criteria of topicality. Unlikely to be a complete set of topical issues
	Sample size	Low quality	Small sample size
	Measurement of outcomes	Unclear	No information on duplicate independent coding
van Rijn van Alkmade,2005	Information about subjects, setting	Low quality	No information provided on the characteristics of the patient groups
	Unbalanced subgroup distribution	Unclear	No information on non respondents
	Missing data	Low quality	43.8% response rate
Vitry, 2011	Information about subjects, setting	Low quality	No information provided on the characteristics of the patient groups
	Measurement of outcomes	Unclear	No information on duplicate independent coding

Supplementary File 4

List of Figures:

Figure 1. Forest plot of prevalence of industry funding (with summary estimate)

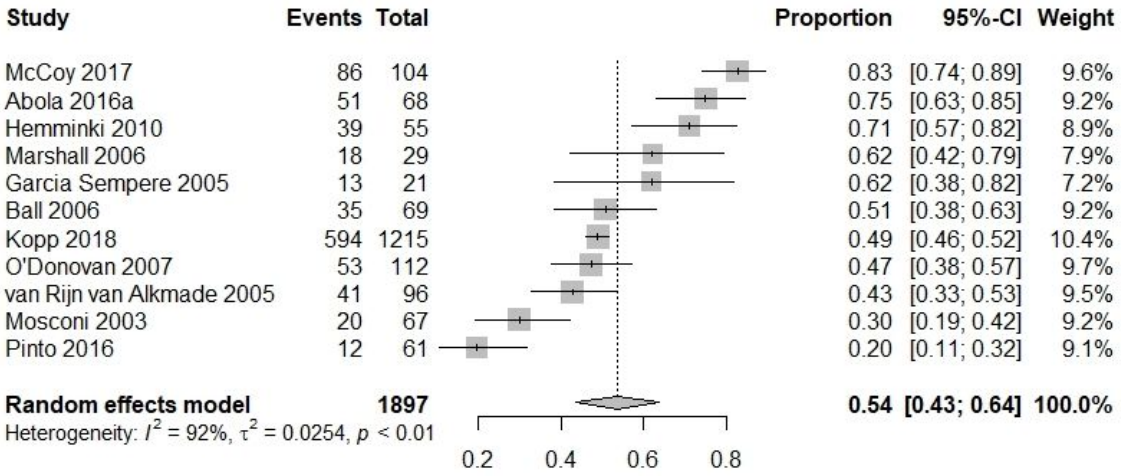


Figure 2. Forest plot of prevalence of industry funding by disease group ('patient groups from multiple disease areas' versus 'disease-specific patient groups')

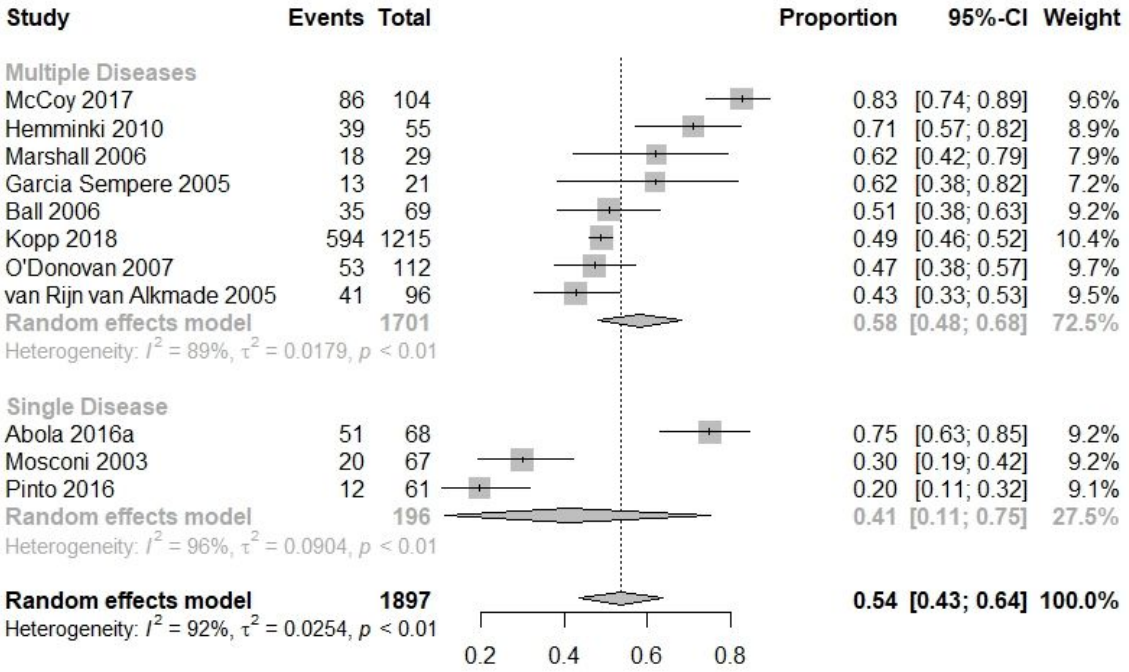


Figure 3. Forest plot of prevalence of industry funding by sample size (above or below median)

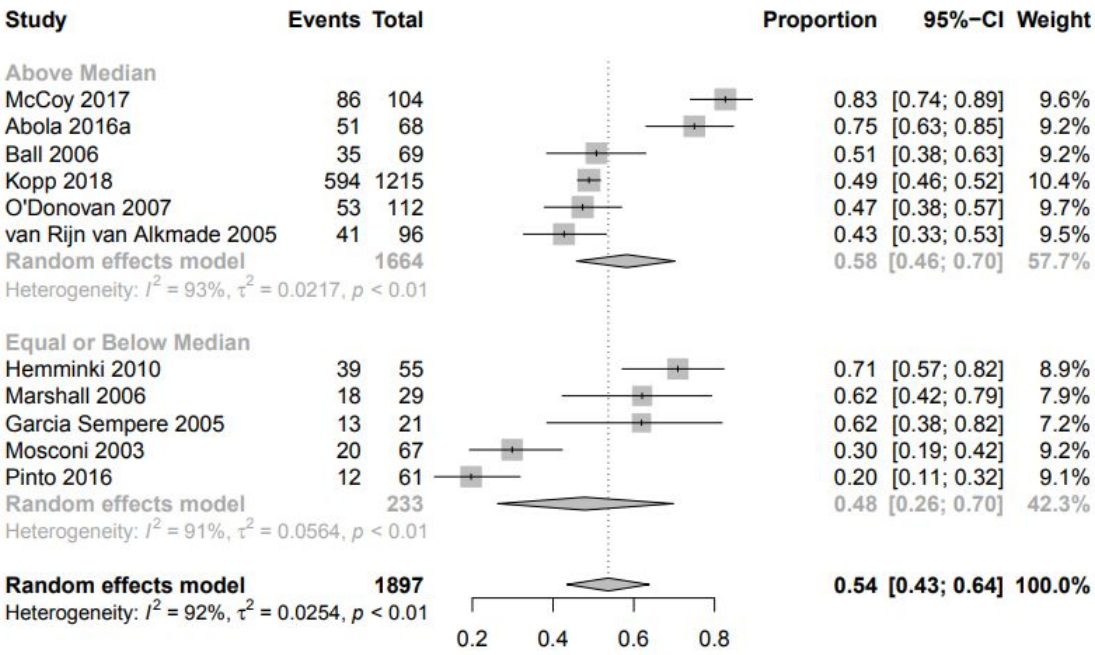


Figure 4. Forest plot of prevalence of industry funding by time of publication (before 2010 versus during or after 2010)

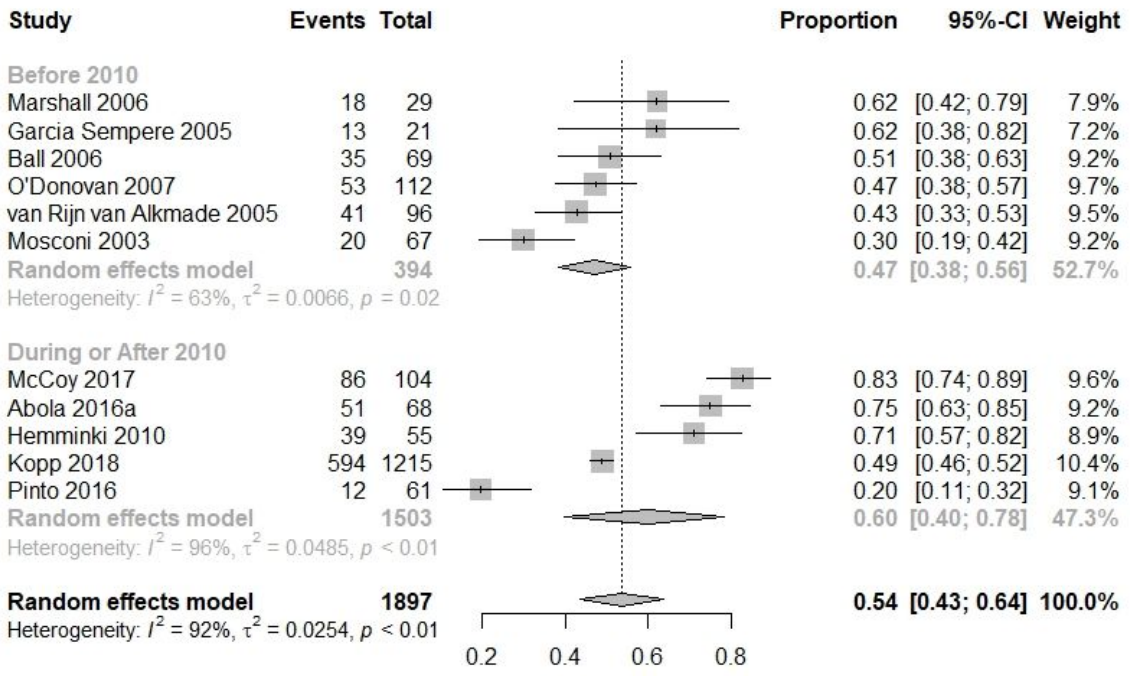


Figure 5. Forest plot of prevalence of industry funding by study quality

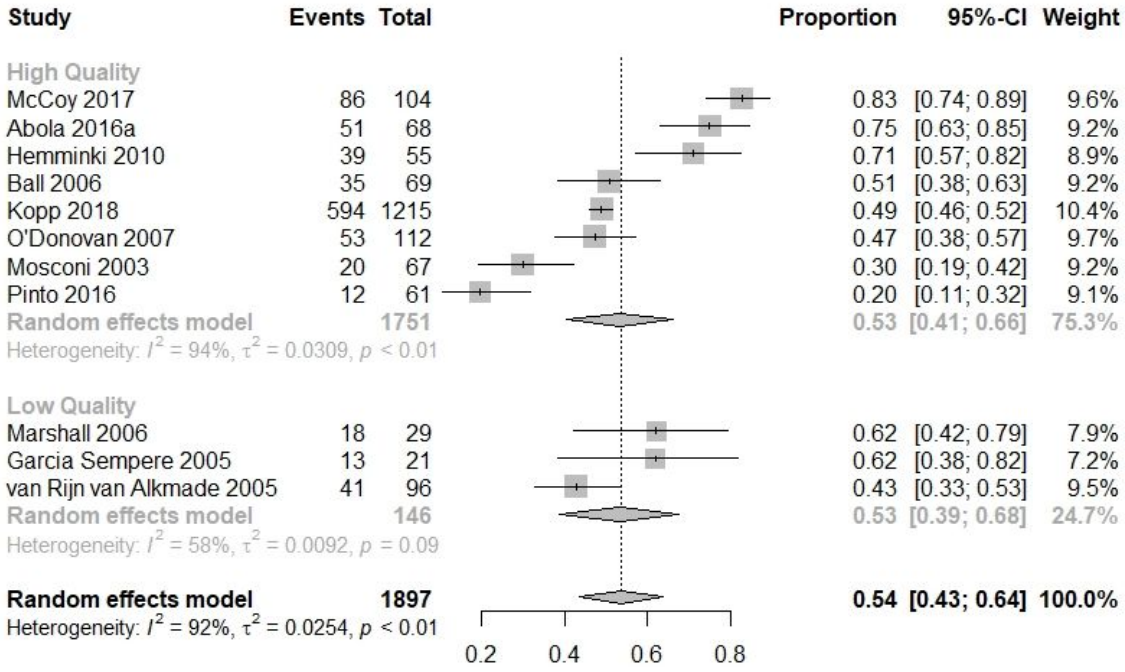


Figure 6. Funnel plot for prevalence of industry funding

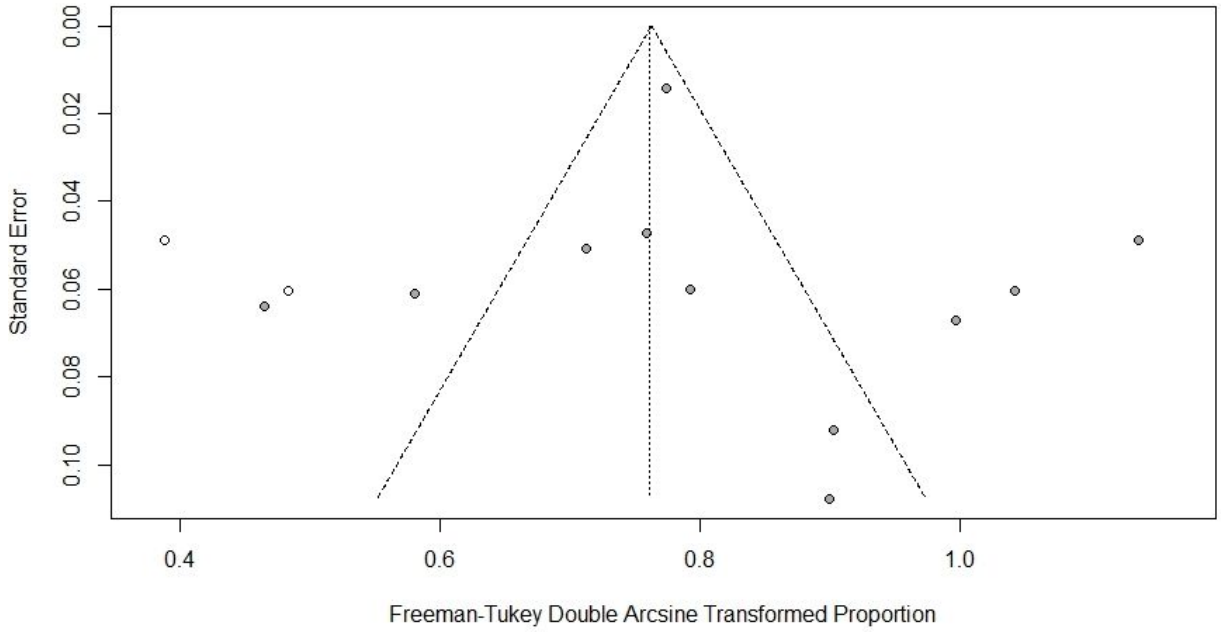


Figure 7. Funnel plot for prevalence of policies governing corporate sponsorship

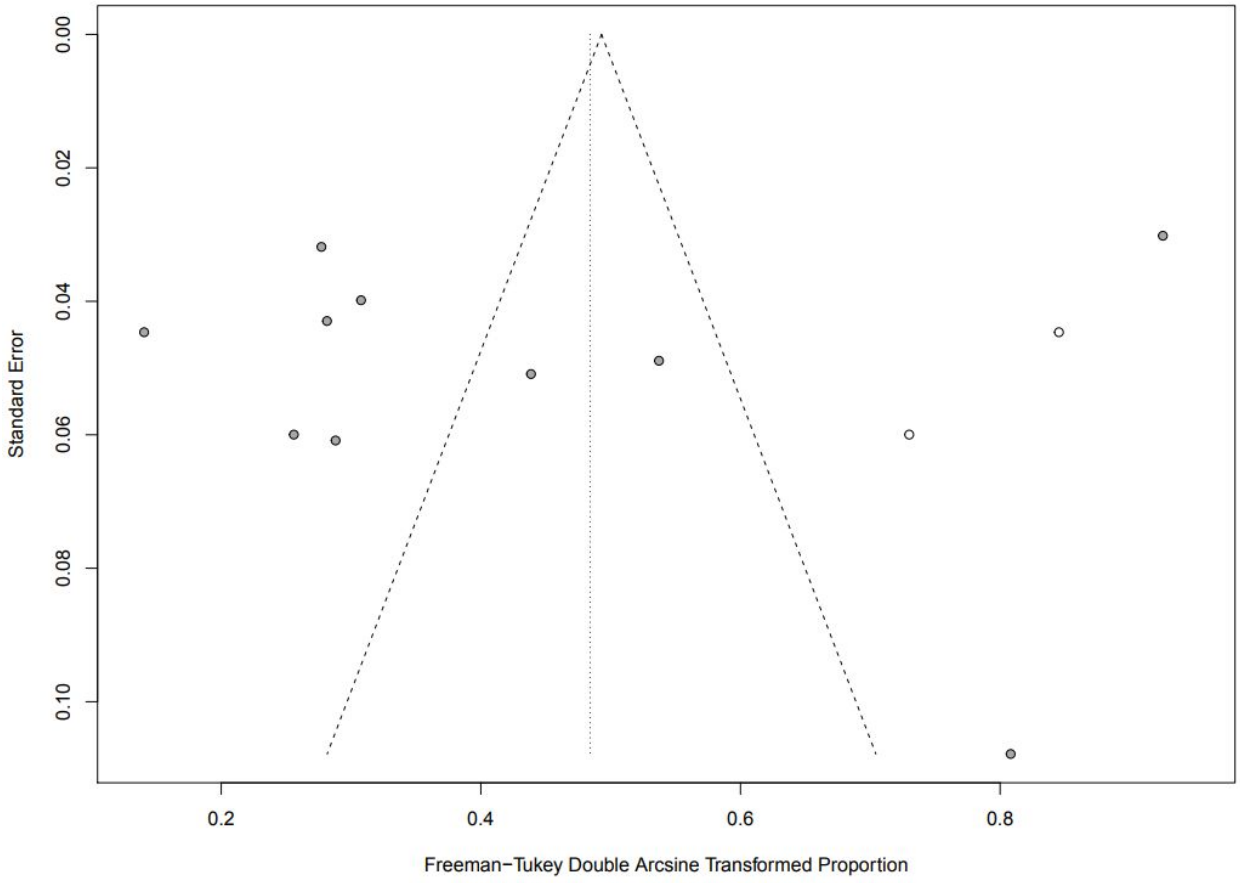


Figure 8. Forest plot of prevalence of policies governing corporate sponsorship

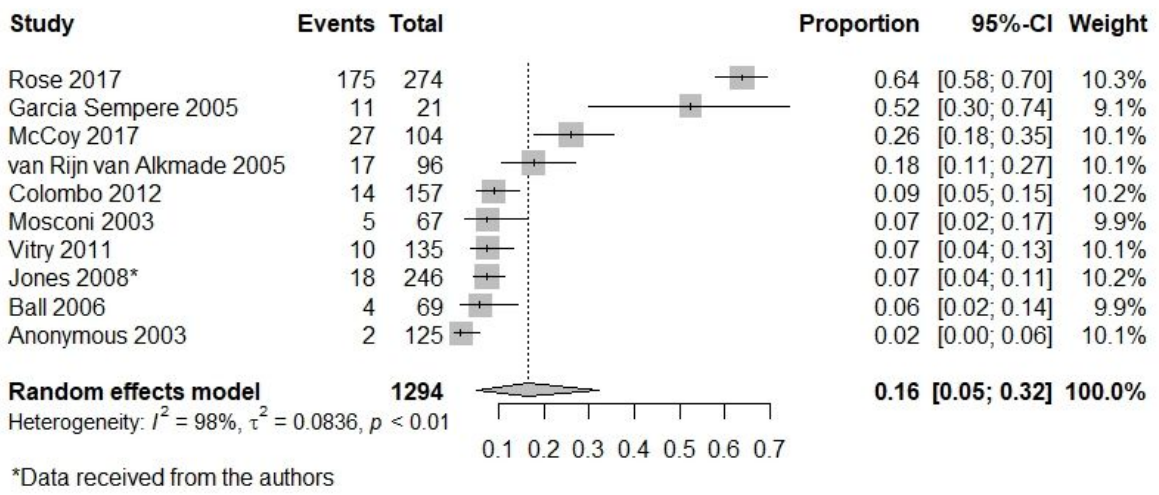
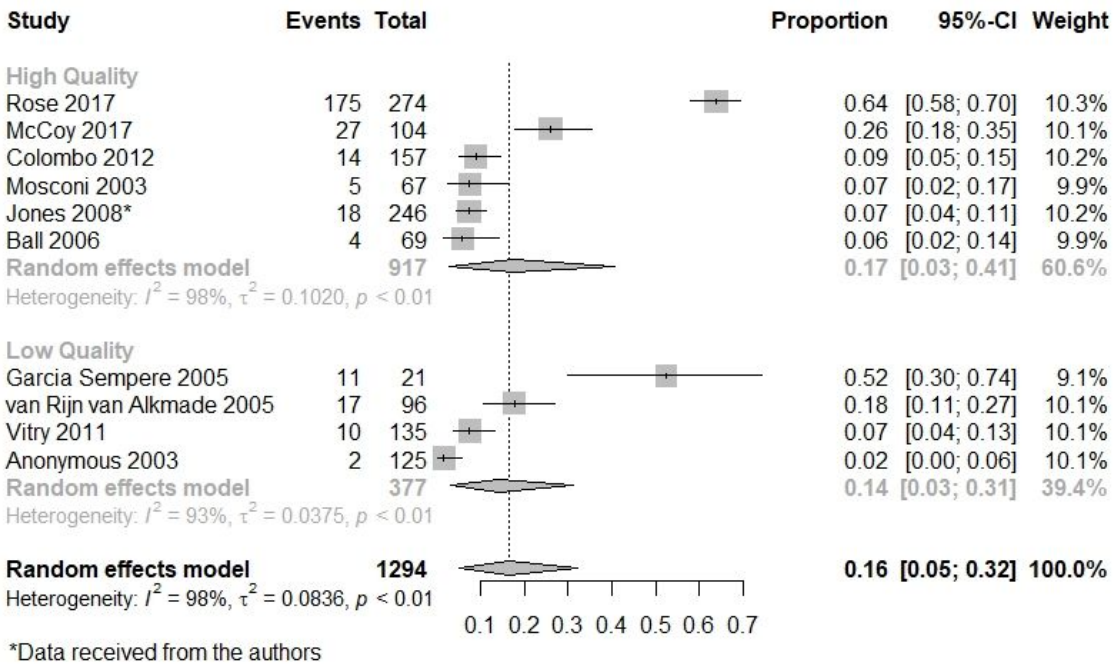


Figure 9. Forest plot of prevalence of policies governing corporate sponsorship by study quality



```
# ------------------------------------------------------------------------ #
#
# Code for industry_prevalence meta-analysis of single proportions
# Analysis code and figure generation
#
#
# Author:
#
# Cynthia M. Kroeger, University of Sydney (cynthia.kroeger@sydney.edu.au)
#
#
# ------------------------------------------------------------------------ #
# Read in data
# ------------------------------------------------------------------------ #
file_name <- "prevalence_reviewed_two.csv"
dat <- read.csv(file_name)
head(dat)
summary(dat)


# ------------------------------------------------------------------------ #
# Dependencies
# ------------------------------------------------------------------------ #
# install.packages("meta")
library(meta)


# ------------------------------------------------------------------------ #
# Random effects meta-analysis for prevalence data
# ------------------------------------------------------------------------ #
result <- metaprop(dat$industry_funded, # number of events
                   dat$total_sample, # number of observations
                   sm = "PFT", # Freeman-Tukey Double arcsine transformation
                   comb.fixed = FALSE)  # to only calculate random effects model
result # prints result
study_labels <- as.vector(dat$study)
forest(result,
       studlab = study_labels,
       xlab = "*Data received from the authors",
       xlab.pos = -0.56)


# ------------------------------------------------------------------------ #
# Subgroup analysis: consultation, multiple_disease, specific condition
# ------------------------------------------------------------------------ #
result_mult <- metaprop(dat$industry_funded, # number of events
```

```
                dat$total_sample, # number of observations
                sm = "PFT", # Freeman-Tukey transformation
                comb.fixed = FALSE, # random effects model only
                byvar = dat$division)
result_mult # prints result
forest(result_mult,
     studlab = study_labels,
     print.byvar = FALSE,
     test.effect.subgroup = TRUE,
     xlab = "*Data received from the authors",
     xlab.pos = -0.57) # create forest plot


# ------------------------------------------------------------------------ #
# Random effects meta-analysis for prevalence data - without consultations
# ------------------------------------------------------------------------ #
file_name <- "prevalence_reviewed_population.csv" # read in data
dat_p <- read.csv(file_name)
head(dat_p)
summary(dat_p)


result_p <- metaprop(dat_p$industry_funded, # number of events
            dat_p$total_sample, # number of observations
            sm = "PFT", # Freeman-Tukey Double arcsine transformation
            comb.fixed = FALSE)  # to only calculate random effects model
result_p # prints result
study_labels <- as.vector(dat_p$study)
forest(result_p,
     studlab = study_labels)


# ------------------------------------------------------------------------ #
# Subgroup analysis without consultations: population_sample
# ------------------------------------------------------------------------ #
result_pop <- metaprop(dat_p$industry_funded, # number of events
            dat_p$total_sample, # number of observations
            sm = "PFT", # Freeman-Tukey transformation
            comb.fixed = FALSE, # random effects model only
            byvar = dat_p$population_sample)
result_pop # prints result
forest(result_pop,
     studlab = study_labels,
     print.byvar = FALSE)
```

```
# ---------------------------------------------------------------------------- #
# Subgroup analysis without consultations: quality
# ---------------------------------------------------------------------------- #
result_rob <- metaprop(dat_p$industry_funded, # number of events
                       dat_p$total_sample, # number of observations
                       sm = "PFT", # Freeman-Tukey transformation
                       comb.fixed = FALSE, # random effects model only
                       byvar = dat_p$quality)
result_rob # prints result
forest(result_rob,
       studlab = study_labels,
       print.byvar = FALSE) # create forest plot


# ---------------------------------------------------------------------------- #
# Subgroup analysis without consultations: sample_size
# ---------------------------------------------------------------------------- #
result_sam <- metaprop(dat_p$industry_funded, # number of events
                       dat_p$total_sample, # number of observations
                       sm = "PFT", # Freeman-Tukey transformation
                       comb.fixed = FALSE, # random effects model only
                       byvar = dat_p$sample_size)
result_sam # prints result
forest(result_sam,
       studlab = study_labels,
       print.byvar = FALSE) # create forest plot


# ---------------------------------------------------------------------------- #
# Subgroup analysis without consultations: time
# ---------------------------------------------------------------------------- #
result_tim <- metaprop(dat_p$industry_funded, # number of events
                       dat_p$total_sample, # number of observations
                       sm = "PFT", # Freeman-Tukey transformation
                       comb.fixed = FALSE, # random effects model only
                       byvar = dat_p$time)
result_tim # prints result
forest(result_tim,
       studlab = study_labels,
       print.byvar = FALSE) # create forest plot


# ---------------------------------------------------------------------------- #
# Create funnel plots
# ---------------------------------------------------------------------------- #
# trim-and-fill
```

```
funnel(trimfill(result_p))


# metabias
metabias(result_p,
       method.bias = "peters")


# ------------------------------------------------------------------------ #
# Random effects meta-analysis for policies data
# ------------------------------------------------------------------------ #
# Read in data
file_name <- "policies_reviewed.csv"
dat_2 <- read.csv(file_name)
head(dat_2)
summary(dat_2)


# Freeman-Tukey Double arcsine transformation
result_pol <- metaprop(dat_2$policy_present, # number of events
                  dat_2$total_sample, # number of observations
                  sm = "PFT", # Freeman-Tukey transformation
                  comb.fixed = FALSE) # random effects model only
result_pol # prints result
study_labels_2 <- as.vector(dat_2$study) # create study labels for forest plot
forest(result_pol, # create forest plot
      studlab = study_labels_2,
      xlab = "*Data received from the authors",
      xlab.pos = -0.62) # add study labels


# # Tests for publication bias
# # trim-and-fill
# funnel(trimfill(result_pol)) # create funnel plot
#
#
# # metabias
# metabias(result_pol,
#         method.bias = "peters")


# ------------------------------------------------------------------------ #
# Policies subgroup analysis: quality
# ------------------------------------------------------------------------ #
# Freeman-Tukey Double arcsine transformation
result_pol_rob <- metaprop(dat_2$policy_present, # number of events
```

```
                dat_2$total_sample, # number of observations
                sm = "PFT", # Freeman-Tukey transformation
                comb.fixed = FALSE, # random effects model only
                byvar = dat_2$quality)
result_pol_rob # prints result
forest(result_pol_rob,
      studlab = study_labels_2,
      print.byvar = FALSE,
      xlab = "*Data received from the authors",
      xlab.pos = -0.62) # create forest plot


# ------------------------------------------------------------------------ #
# Random effects meta-analysis for disclosure data
# ------------------------------------------------------------------------ #
# Read in data
file_name <- "disclosure_reviewed.csv"
dat_3 <- read.csv(file_name)
head(dat_3)
summary(dat_3)


# Freeman-Tukey Double arcsine transformation
result_dis <- metaprop(dat_3$organisations_disclosing, # number of events
                dat_3$total_sample, # number of observations
                sm = "PFT", # Freeman-Tukey transformation
                comb.fixed = FALSE) # random effects model only
result_dis # prints result
study_labels_3 <- as.vector(dat_3$study) # create study labels for forest plot
forest(result_dis, # create forest plot
      studlab = study_labels_3,
      xlab = "*Data received from the authors",
      xlab.pos = -0.75,
      fs.hetstat = 10.12,
      xlim = c(0, 1))
```