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Financial ties and concordance between results and conclusions in meta-analyses: retrospective cohort study

Veronica Yank,¹ Drummond Rennie,² Lisa A Bero³

EDITORIAL by Epstein

¹Stanford University, Stanford Medical Group, Stanford, CA 94305-5765, USA

²University of California, San Francisco

³Clinical Pharmacy and Institute for Health Policy Studies, University of California, San Francisco

Correspondence to: V Yank
vyank@stanford.edu

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ABSTRACT

Objective To determine whether financial ties to one drug company are associated with favourable results or conclusions in meta-analyses on antihypertensive drugs.

Design Retrospective cohort study.

Setting Meta-analyses published up to December 2004 that were not duplicates and evaluated the effects of antihypertensive drugs compared with any comparator on clinical end points in adults. Financial ties were categorised as one drug company compared with all others.

Main outcome measures The main outcomes were the results and conclusions of meta-analyses, with both outcomes separately categorised as being favourable or not favourable towards the study drug. We also collected data on characteristics of meta-analyses that the literature suggested might be associated with favourable results or conclusions.

Results 124 meta-analyses were included in the study, 49 (40%) of which had financial ties to one drug company. On univariate logistic regression analyses, meta-analyses of better methodological quality were more likely to have favourable results (odds ratio 1.16, 95% confidence interval 1.07 to 1.27). Although financial ties to one drug company were not associated with favourable results, such ties constituted the only characteristic significantly associated with favourable conclusions (4.09, 1.30 to 12.83). When controlling for other characteristics of meta-analyses in multiple logistic regression analyses, meta-analyses that had financial ties to one drug company

remained more likely to report favourable conclusions (5.11, 1.54 to 16.92).

Conclusion Meta-analyses on antihypertensive drugs and with financial ties to one drug company are not associated with favourable results but are associated with favourable conclusions.

INTRODUCTION

A high and increasing proportion of biomedical researchers have financial ties to the pharmaceutical industry.¹⁻⁴ Such researchers are more likely to publish articles that support the industry's products.^{3,5-11}

Meta-analyses represent the highest level of research evidence,¹² and drug companies have started to reference them in their advertisements.¹³

Some antihypertensive drugs have been shown to dramatically improve mortality and morbidity. The market for these and other antihypertensive drugs is highly competitive and lucrative. Our literature search found many published meta-analyses on antihypertensive drugs. If these are unbiased they have the potential to guide policy and save lives. We examined whether financial ties to one drug company were associated with favourable results or conclusions in meta-analyses on antihypertensive drugs.

METHODS

We included meta-analyses published up to December 2004 that evaluated the effects of antihypertensive drugs on clinical outcomes in adults. The comparator could be placebo, no treatment, usual care, or active

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therapy. We defined meta-analyses as systematic reviews that combined data from at least two studies.

From each group of duplicate or overlapping meta-analyses (see bmj.com for definitions) we identified a representative meta-analysis to be included in the study, which was the meta-analysis published first. If two were published simultaneously, we randomly selected one.

Search strategy

We searched PubMed and the *Cochrane Database of Systematic Reviews* for relevant meta-analyses and hand searched the reference lists of identified meta-analyses. One of us (VY) reviewed the titles and abstracts of potential meta-analyses and, if these were uninformative or no abstract was available, retrieved and reviewed the full text.

Definitions

Financial ties were categorised as one drug company compared with all others. Information on financial ties was obtained from disclosures in the meta-analysis; disclosures of industry or other sponsorship in the journal supplement in which a meta-analysis was published; and disclosures of financial ties in previous research articles on antihypertensive drugs by the first author of the included meta-analysis, arbitrarily going back three years before the publication date of the referent meta-analysis. Meta-analyses with financial ties to one drug company as disclosed in any one of these sources were defined as having financial ties to one drug company. We designed this definition to be conservative.

We carried out sensitivity analyses using different definitions of financial ties—information disclosed only in the meta-analysis or information disclosed in the meta-analysis and in the supplement in which it was published. This shifted meta-analyses from the category of financial ties to one drug company to the category of all other financial ties.

We collected additional data on the financial ties of meta-analyses in the all other category. The subcategories were defined as having financial ties to multiple drug companies; non-profit (academic, government, foundation, or professional) groups; any drug company (single or multiple) and non-profit; and no statement.

The study drug and outcome measure were defined by the authors of the meta-analyses or if left unspecified we defined them as the first treatment and outcome described in the results. If multiple primary outcome

measures were identified, we deemed results or conclusions to be favourable if at least 50% of the outcome measures were favourable.

Primary outcome measures

The primary outcome measures for this study were results, as determined by us, and conclusions, as stated by the authors of the meta-analyses. Our per protocol analyses were prespecified to use dichotomous coding of the results and conclusions as being favourable towards the study drug or not favourable. We collected additional data on subcategories of the not favourable group.

Results and conclusions were coded from 1-5 (see bmj.com). In accordance with our protocol we considered results coded as 1 to be favourable towards the study drug and those coded as 2-5 to be not favourable.

Other potentially relevant variables

We wanted to determine whether certain financial ties were associated with skewed results or conclusions, even after controlling for other variables. We therefore collected data on other characteristics of meta-analyses that our literature review suggested might be associated with favourable results or conclusions.

We evaluated the methodological quality of each meta-analysis using a modified version of the Oxman and Guyatt quality instrument,¹⁴ which rates systematic reviews and meta-analyses on whether they include design features aimed at reducing bias, and assigns a summary score to each meta-analysis (see bmj.com). For each design feature the meta-analysis could receive a maximum of two points for fulfilling the criterion, one for partially fulfilling it, or zero for not fulfilling it. The quality score was the sum of these points. We also evaluated whether the quality scores correlated significantly with any of the other characteristics of the meta-analyses.

We also collected data on whether the meta-analyses were published in journal supplements versus in regular issues of journals; involved literature searches or included studies in languages other than English, as well as in English, versus in English only; included a description of data abstraction versus no description; included studies that were not randomised controlled trials versus included only randomised controlled trials; included unpublished plus published studies versus only published studies; included only studies that used placebo groups as the control versus studies that used other comparators; focused only on newer

Table 1 | Final model: multivariate analyses of associations between favourable results or conclusions and characteristics of meta-analysis

Meta-analysis characteristic	Favourable results		Favourable conclusions	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Financial ties with one drug company	0.99 (0.44 to 2.23)	0.99	5.11 (1.54 to 16.92)	0.008
Better quality*	1.16 (1.06 to 1.27)	0.001	1.07 (0.97 to 1.19)	0.19

*Quality score was continuous variable from 0-18, with higher scores indicating better quality and lower scores indicating worse quality.

classes of drugs versus older classes; used surrogate outcomes only versus morbidity and mortality outcomes; used composite outcomes only versus distinct outcomes; carried out evaluations of heterogeneity of studies versus no evaluations; and carried out sensitivity analyses of the results versus no sensitivity analyses.

Data extraction

One researcher (VY) unblinded to financial ties and author identity coded data for the meta-analyses. A second blinded coder (LAB) coded a random sample of 24 (19%) of the meta-analyses. Agreement between the reviewers was substantial ($\kappa=0.74$) for results and moderate ($\kappa=0.60$) for conclusions.¹⁵

Statistical analyses

We used univariate logistic regression analyses to evaluate whether financial ties or other characteristics of meta-analyses were associated with favourable results or conclusions. Variables that were found to be significant to the level of $P<0.05$ on univariate analyses were then entered into the final model, which used multiple logistic regression analyses.

RESULTS

The combined search strategies identified 691 potentially relevant meta-analyses on antihypertensive drugs in adults (see [bmj.com](#)). Overall, 124 meta-analyses met our inclusion criteria. See [bmj.com](#) for exclusions and the coding for results, conclusions, quality scores, and financial ties of included meta-analyses.

A substantial portion of the meta-analyses (49 of 124, 40%) had financial ties to one drug company. Of the 75 (60%) without such financial ties, the other financial ties were diverse, subcategorised as multiple drug companies (14, 19%), non-profit (27, 36%), drug and non-profit (9, 12%), and no statement (25, 33%).

In univariate analyses, meta-analyses with financial ties to one drug company were not more likely than others to have favourable results but were significantly more likely to have favourable conclusions (odds ratio 4.09, 95% confidence interval 1.30 to 12.83). Only meta-analyses with better quality, evaluations of heterogeneity, or sensitivity analyses were more likely

to have favourable results, but these variables were significantly associated. Because better quality was the strongest predictor of the three (1.16, 1.07 to 1.27), only it (along with financial ties to one drug company) was used in the final model.

In the final model, meta-analyses that had financial ties to one drug company again were not associated with favourable results but remained significantly associated with favourable conclusions, even when controlling for the quality of meta-analyses (table 1). Meta-analyses of better quality remained associated with favourable results.

To test the robustness of our final model we performed multiple sensitivity analyses (see [bmj.com](#)). For instance, meta-analyses that had financial ties to one drug company had poor concordance between results and conclusions, whereas other meta-analyses had excellent concordance (table 2).

DISCUSSION

Meta-analyses with favourable conclusions, but not results, were more likely to have financial ties to one drug company than other financial ties, even when controlling for characteristics of meta-analyses. These findings suggest discordance between the data that underlie the results and the interpretation of these data in the conclusions. In contrast, meta-analyses with financial ties to non-profit groups had excellent concordance between results and conclusions.

Because we used conservative assumptions in defining financial ties, the odds ratio for our main finding is likely to be an underestimate of the true relation between financial ties to one drug company and favourable conclusions.

We were not able to find any studies of financial ties and the results of meta-analyses that had statistically significant findings. In 1987 the authors of a study noted variability in their conclusions, despite similarity in results, but could not explain these differences from the inclusion criteria or statistical methods of the meta-analyses.¹⁶ Our findings of an association between financial ties to one drug company and favourable conclusions might explain their observations. They also reinforce the findings of similar studies, including one on Cochrane reviews.^{9 17}

We identified no association between meta-analyses of better quality and conclusions. In contrast, one study found that reviews of better quality on spinal manipulation were more likely to have favourable conclusions,¹⁸ whereas another study found that meta-analyses of better quality on analgesics were less likely to have favourable conclusions.¹⁹ One cause of these discrepancies may be that neither controlled for funding source.

Our study design has potential for confounding. We were able to adjust for this by collecting data on characteristics of the meta-analyses suggested by the literature to be potential confounders of results or conclusions. Few such confounders were found to be significant on univariate or multivariate analyses.

Table 2 | Proportion of meta-analyses with favourable results or conclusions, and proportion with poor concordance between results and conclusions, by financial ties*

Financial ties	No (%) with favourable results	No (%) with favourable conclusions	No (%) with poor concordance between results and conclusions*
One drug company (n=49)	27 (55)	45 (92)	18 (37)
All other (n=75):	49 (65)	55 (73)	6 (8)
Multiple drug companies (n=14)	8 (57)	11 (79)	3 (21)
No statement (n=25)	14 (56)	17 (68)	3 (12)
Both drug and non-profit (n=9)	6 (67)	6 (67)	0 (0)
Non-profit (n=27)	21 (78)	21 (78)	0 (0)

*Poor concordance for each row was determined by the calculation: [number of meta-analyses with favourable conclusions]-[number of meta-analyses with favourable results].

WHAT IS ALREADY KNOWN ON THIS TOPIC

The results and conclusions of randomised controlled trials with financial ties to one drug company are more likely to favour the sponsor's products

A study that compared Cochrane meta-analyses to industry supported meta-analyses in print journals suggests that the same holds true for meta-analyses

WHAT THIS STUDY ADDS

Meta-analyses with financial ties to one drug company are no more likely than others to have results that favour the company's drugs but are more likely to have favourable conclusions

Editors and peer reviewers failed to prevent publication of biased conclusions in meta-analyses

Another methodological limitation of our study is that only one of us reviewed the meta-analyses, both for inclusion in the study and for data extraction and quality assessment. This same reviewer was not blinded to important characteristics of the meta-analyses, including financial ties. It could be said that this method of evaluation introduces bias. However, evidence suggests that blinded data extraction does not make a clinically or statistically significant difference in study outcome and that blinded quality assessments may yield higher and lower scores.^{9 20-23} In our main study we found good intercoder reliability between the unblinded reviewer and a blinded reviewer who evaluated a randomly selected subset of meta-analyses.

We did not confirm disclosure of financial ties by other means, such as examining the authors' investment profiles. Sensitivity analyses of the primary outcomes using different definitions of financial ties were consistent, however, suggesting that our findings are robust.

Our definition of financial ties was conservative in that financial ties to one drug company derived from any of three sources. We chose to focus for one source on first authors and their articles going back three years because we hypothesised that these limitations would capture financial ties with the most immediacy, relevance, and potential to influence the meta-analyses of interest.

The generalisability of our study is limited by its restriction to one clinical topic. Our findings have relevance to the real world, however, as the marketing of antihypertensive drugs constitutes a multibillion dollar a year industry and antihypertensives are some of the most prescribed drug classes in the world.²⁴

Conclusions

That we found poor concordance between results and conclusions in some meta-analyses suggests that they are open to systematic bias, in this case by financial ties to one drug company. Our study also exposes a failure of peer review. Editors and peer reviewers should closely scrutinise the conclusions of meta-analyses to ensure that they are supported by the data.

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