Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2017;356:i6770
http://dx.doi.org/10.1136/bmj.i6770

Accepted: 06 December 2016

ABSTRACT

OBJECTIVE

To examine the association between the presence of individual principal investigators' financial ties to the manufacturer of the study drug and the trial's outcomes after accounting for source of research funding.

DESIGN

Cross sectional study of randomized controlled trials (RCTs).

SETTING

Studies published in "core clinical" journals, as identified by Medline, between 1 January 2013 and 31 December 2013.

PARTICIPANTS

Random sample of RCTs focused on drug efficacy.

MAIN OUTCOME MEASURE

Association between financial ties of principal investigators and study outcome.

RESULTS

A total of 190 papers describing 195 studies met inclusion criteria. Financial ties between principal investigators and the pharmaceutical industry were present in 132 (67.7%) studies. Of 397 principal investigators, 231 (58%) had financial ties and 166 (42%) did not. Of all principal investigators, 156 (39%) reported advisor/consultancy payments, 81 (20%) reported speakers' fees, 81 (20%) reported unspecified financial ties, 52 (13%) reported honorariums, 52 (13%) reported employee relationships, 52 (13%) reported travel fees, 41 (10%) reported stock ownership, and 20 (5%) reported having a patent related to the study drug. The prevalence of financial ties of principal investigators was 76% (103/136) among positive studies and 49% (29/59) among negative studies. In unadjusted analyses, the presence of a financial tie was associated with a positive study outcome (odds ratio 3.23, 95% confidence interval 1.7 to 6.1). In the primary multivariate analysis, a financial tie was significantly associated with positive RCT outcome after adjustment for the study funding source (odds ratio 3.57 (1.7 to 7.7). The secondary analysis controlled for additional RCT characteristics such as study phase, sample size, country of first authors, specialty, trial registration, study design, type of analysis, comparator, and outcome measure. These characteristics did not appreciably affect the relation between financial ties and study outcomes (odds ratio 3.37, 1.4 to 7.9).

CONCLUSIONS

Financial ties of principal investigators were independently associated with positive clinical trial results. These findings may be suggestive of bias in the evidence base.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Financial ties to industry are common among principal investigators of randomized clinical trials

Many studies have examined the relation between study funding source and trial outcomes

Very few studies have examined the relation between principal investigators' financial ties and study outcomes after accounting for the effect of industry funding

WHAT THIS STUDY ADDS

This study is a cross section of all randomized controlled trials published in 2013, taking advantage of new disclosure sources

It shows an independent association between the presence of personal financial ties of principal investigators to industry and positive trial outcomes

Introduction

Randomized controlled trials (RCTs) are considered the most reliable form of evidence in evaluating the safety and efficacy of drugs.[1] Because results of RCTs shape the evidence base, objectivity in the conduct of clinical trials has important implications for clinical practice and the health and safety of patients.[2] However, critics worry that involvement of the pharmaceutical industry may bias the design and interpretation of RCTs.[2-5] In a 2002 survey of 3247 National Institutes of Health scientists, 15.5% admitted to changing the design, methods, or results of a study in response to pressure from a funding source.[6] A systematic review of the role of funding on study outcome showed that industry funded studies were more likely than non-industry funded studies to have positive efficacy results (risk ratio 1.24, 95% confidence interval 1.14 to 1.35).[7] In addition, industry can subtly influence the conduct of RCTs through financial means other than study funding, including paid consultancy fees and honorariums to physicians.[8 9] Such relationships may alter physicians' perceptions of the company's products in a favorable light.[5 10]

Relationships with industry are common among investigators, raising concerns about the effect that financial ties between researchers and industry may have on the evidence base.[11 12] In recent years, these concerns have led to calls for transparent reporting of these relationships.[13] As a result, many journals now require authors to report their financial ties by using the International Committee of Medical Journal Editors' (ICMJE) disclosure form of competing interests.[14] The ICMJE recommends that all trials should be pre-registered in databases such as clinicaltrials.gov to minimize publication bias and increase transparency around trial conduct.[15] However, not all journals enforce the recommendations.[16] Even when trials are

registered, the lack of publication of negative trials can diminish the effect of these policies.[4]

The movement towards transparency provides an opportunity to examine the extent to which investigators' financial ties are associated with positive study outcomes. Several studies have examined this relation.[17-25] However, in most of these studies individual investigators' financial ties were not disentangled from the funding source for the study. These two variables, although related, are different. Funding is awarded to institutions and represents professional gain, not personal financial gain. In addition, most previous studies have been limited to one specialty,[17-21] drug type,[22 23] or journal.[24 25] Some studies have found a positive association between investigators' ties and outcomes,[19-21 23-25] and others have found no association,[17 18 22] although some negative studies may have been insufficiently powered. We examined the relation between financial ties with industry of principal investigators and study outcome across a random sample of RCTs published in 2013, which represents a cross section of the evidence base. We specifically focused on RCTs that examined the efficacy of drugs, because these studies have a high impact on both clinical practice and healthcare costs. We hypothesized that principal investigators' financial ties with industry would be independently associated with positive study outcomes.

Methods

Search strategy

We searched Medline for RCTs published between 1 January 2013 and 31 December 2013 in "core clinical" journals, as identified by Medline, and limited to English language, human subjects, and titles with available abstracts. Our search yielded 2851 papers.

Inclusion and exclusion criteria

Eligible studies were RCTs evaluating the efficacy of drug interventions. We included studies in which the drug of interest was specified (for example, to determine whether eritoran, a TLR4 antagonist, would significantly reduce sepsis induced mortality)[26] and excluded head-to-head studies in which the drug of interest was not specified in the paper or in clinicaltrials.gov, because we would be unable to determine whether the study was positive or negative. We excluded non-drug studies, such as studies of devices, supplements, and biomarkers. We also excluded non-primary studies, which included meta-analyses, subgroup analyses, and follow-up studies. We excluded studies without an identifiable funding source. We also excluded studies that did not have searchable financial ties because the manufacturer of the drug of interest was unclear.

Patient involvement

We did not include patients in this study. Our focus was published RCTs. Patients were not involved in any part of the research process.

Preliminary screen and sample size calculation

The 2851 titles and abstracts identified in the search were screened by one of four non-clinician abstractors (AA, RA, SS, AW) for possible relevance. Of the 1101 potentially relevant studies identified, we used a random number generator to select 250 for review. We did a κ test on a sample of 20 studies to determine the strength of the inter-rater agreement on study inclusion. κ was 0.87 (RA/AW) and 0.69 (AA/SS), indicating a high level of agreement for each pair.

In the preliminary review, 87 of 250 papers met the inclusion criteria. We determined the prevalence of financial ties among principal investigators in this initial sample (financial ties were present in 78% of studies with a positive outcome and 59% of those with a negative outcome). On the basis of the prevalence of financial ties in positive and negative studies, we determined that we needed a total of at least 184 papers that met inclusion criteria to test our hypothesis. Using a random number generator, we randomly selected an additional 396 papers for full text review, of which an additional 148 studies were identified for inclusion. A total of 235 papers were identified for possible inclusion by non-clinician abstractors.

Final sample

All 235 papers identified in the preliminary assessment were independently reviewed by two clinician reviewers (SK and DK) for inclusion. Disagreement on inclusion was resolved by discussion. A total of 45 papers were excluded in this stage.

Main outcome variable

We focused on the results section of each paper to identify outcomes. The primary efficacy outcome was the outcome of interest and had to be specified in the trial publication or on clinicaltrials.gov. We defined the study outcome as positive if the hypothesis was supported for the primary efficacy outcome of the study and negative if it was not. For superiority studies, the study outcome was defined as positive if the drug of interest was statistically superior to the control (eg, $P<0.05$). For non-inferiority studies, the study outcome was defined as positive if the drug of interest was not significantly worse than the control (statistically non-significant difference). In studies with multiple primary efficacy outcomes, we considered the study to be positive if at least one efficacy outcome was positive for superiority studies and not significantly different from the control in non-inferiority studies. For the five papers that included multiple studies, we abstracted data on the outcome for each study separately. Study outcomes were assessed independently and in duplicate. Any disagreement was resolved by discussion.

Main independent variable

We searched for financial ties among principal investigators, who we defined as the first author and senior author (last author) of each paper because these authors are generally most involved in major decisions about studies. If a study specified additional authors as first authors or senior authors, we included them all and considered them all to be principal investigators. We defined a financial tie as the direct compensation of

doi: 10.1136/bmj.i6770 | BMJ 2017;356:i6770 | the bmj

a principal investigator by the manufacturer of the drug of interest in the form of advisor/consultancy payments, employee relationships, honorariums, speaker's fees, stock ownerships, and travel/meal fees. We categorized papers in which the financial tie was not specified (eg, "financial interest with X company") as "type not specified." We also considered a financial tie to be present if the principal investigator was a named inventor of a patent related to the publication.

Financial ties were limited to the drug company that manufactured the drug and did not include any parent company of the manufacturer. For the few papers in which the manufacturer was not disclosed in the publication, we searched clinical trial registries and Google to identify the manufacturer. The unit of analysis was the study; any financial tie present for any study principal investigator resulted in the study being assessed as having a financial tie.

We searched five different sources for financial ties: the trial publication, Medline for other publications by the principal investigators, Google, ProPublica's Dollars for Doctors, and the US Patent Office. We defined a financial tie as self reported if it was disclosed in the trial publication. We searched for additional financial ties in the other four sources outlined above. We report both self reported financial ties and the total financial ties (sum of the self reported financial ties and the financial ties identified via the additional search).

Our method for searching for additional financial ties was based on a previously described method that used Medline and Google.[27] In Medline, we reviewed the first 10 publications of each principal investigator in which the principal investigator was either first or senior author. We limited the search for financial ties to the two years before the online publication date of the RCT. When we identified a financial tie, we confirmed the identity of the investigator of interest by matching his or her reported institutional affiliation with the one documented in the article. In Google, we combined the principal investigator's name with the name of the drug manufacturer and reviewed the first five pages of Google search results.[27]

We expanded our search and also included ProPublica's Dollars for Doctors and the US Patent Office. In both these sources, we searched the principal investigator's first and last name and reviewed all results in the two years before the online publication of the paper. For each study, one of four abstractors (AA, RA, SS, AW) identified the financial ties of the study authors and abstracted all the characteristics of the study, and a second abstractor independently verified the presence of a financial tie and abstracted all characteristics. Any disagreement was reviewed by two clinician reviewers (SK and DK) and resolved by consensus.

Covariates

Our main covariate of interest was industry funding (dichotomized to any industry funding versus no industry funding) because several studies have found that industry funding is associated with positive study outcomes.[7 28-32] We abstracted funding information from the information listed in the published trial and trial registries. We also collected data on multiple characteristics of studies that we thought may be related to the presence of financial ties, including RCT phase (phase III versus other), sample size (separated into four quarters), first author's country of origin (US versus other; if there were multiple first authors, we used the first listed author's country), specialty (cardiology versus oncology versus other), trial registration (registered versus unregistered), type of analysis (superiority versus non-inferiority), study design (active comparator versus placebo or nothing), outcome measure (clinical versus surrogate endpoint), and blinding (double blind versus other).

Statistical methods

We report the summary statistics to describe prevalence of self reported financial ties and total financial ties by trial characteristics and the frequency and type of compensation received by principal investigators. We examined differences by using a two sided, 0.05 level χ^2 test of significance. Using established methods, we examined possible multicollinearity between industry funding and principal investigators' self reported financial ties and total financial ties.[33-37] Firstly, we built a logistic regression model of study outcomes data to get weights for predictors, using Fisher's scoring at each iteration (for 50 iterations). We also calculated the correlations among the parameter estimates and found no unusually large parameter estimates or standard errors (largest coefficient=1.05, SE=0.43) as sometimes seen in multicollinearity. Next, we calculated the condition indices and variance inflation factors by using the weight values from the final iteration of the logistic regression model above. We found no large condition indices (all <14) or variance inflation factors (all <2). The variance inflation factors for self reported financial ties (1.63), total financial ties (1.65), and industry funded studies (1.48 when self reported financial ties were included in the model; 1.54 when total financial ties were included in the model) were small, suggesting that collinearity was not a problem.

Using logistic regression, we examined the association between financial ties and study outcomes after adjustment for study funding. In a secondary analysis, we examined the association between financial ties and study outcomes after adjustment for additional RCT characteristics. We also tested for interactions and specifically examined whether the relation between financial ties and outcomes was modified by the source of funding. We also did a stratified analysis examining the relation between financial ties and study outcome with studies categorized by industry funding.

In a sensitivity analysis, we examined the effect of excluding papers in which the authors had no opportunity to declare financial ties on the relation between financial ties and study outcomes. Finally, as five papers reported data from two studies, we did a sensitivity analysis in which we retained only data from the first study reported to prevent double counting of financial ties. We used SAS statistical software, version 9, for statistical analysis.

Results

Characteristics of included RCTs

Among the total sample of 646 papers reviewed, 190 papers comprising 195 studies met inclusion criteria and were included in the final sample (fig 1). Among the 456 excluded papers, most did not meet inclusion criteria because of non-efficacy study design (n=191; 42%), non-primary data (n=92; 20%), or non-drug intervention (n=61; 13%). Included studies were primarily phase III (52%) and were funded by industry (69%). First authors were predominately based in the US (74/195; 38%). Best represented specialties included cardiology (16%), oncology (11%), infectious diseases (11%), urology (7%), and gastroenterology (6%). The vast majority of RCTs were registered in clinicaltrials.gov or another registry (94%), designed as superiority trials (89%), double blinded (75%), and placebo controlled (75%) (table 1).

Prevalence of industry financial ties

Of the 195 studies, seven had multiple first or senior authors and one had a single author, making a total of 397 principal investigators. Among all principal investigators, 197 (50%) self reported financial ties at the time of publication, 186 (47%) self reported no financial ties, and 14 (4%) did not have an opportunity to do so (that is, the journal had no disclosure section) (table 2). Our online search found an additional 34 principal investigators with financial ties, all of whom had had an opportunity to disclose financial ties in the paper. Of these 34 principal investigators with additional ties found by search, 17 (50%) were US based authors. Overall, 231 (58%) principal investigators had financial ties. The prevalence of total financial ties (both self reported and identified by the additional search) was similar between first authors and senior authors (55.7% *v* 60.7%; P=0.31). Among all principal investigators, 156 (39%) had advisor/consultancy payments, 81 (20%) had speakers' fees, 81 (20%) had unspecified financial ties, 52 (13%) had honorariums, 52 (13%) had employee relationships, 52 (13%) had travel fees, 41 (10%) had stock ownership, and 20 (5%) had a patent related to the publication (table 2).

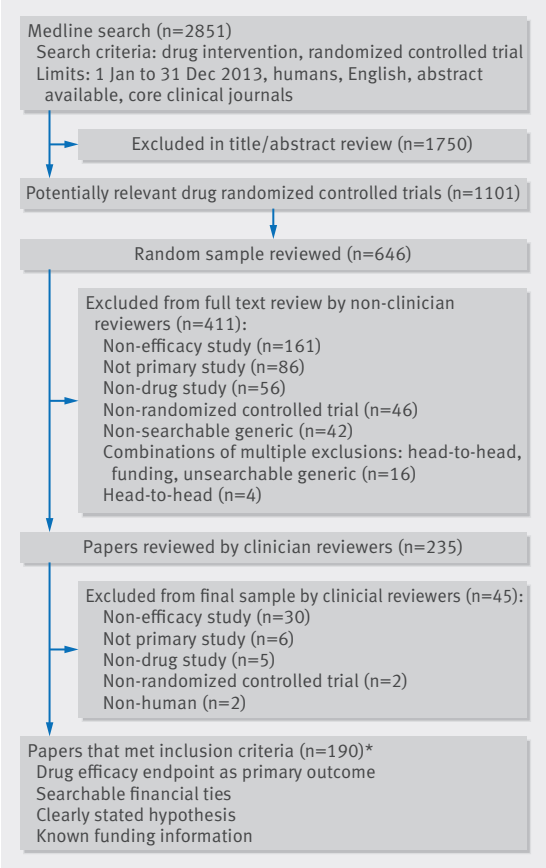

Fig 1 | Flowchart of articles in review. *190 papers, which included 195 distinct studies

Study characteristics and prevalence of financial ties

Self reported financial ties were present in 117 (60%) of the 195 included studies, and total financial ties (self reported and additional financial ties identified in the search) were present in 132 (68%) of the 195 included studies (table 3). The overall prevalence of financial ties was 76% (103/136) among positive studies and 49% (29/59) among negative studies. Authors from the US were more likely to have financial ties than were authors from other countries (70% *v* 49%; P<0.001).

Prevalence of financial ties did not differ by specialty (P=0.28). Registered trials were more likely to have financial ties than were non-registered trials (70% *v* 25%; P=0.001). Financial ties were more prevalent in industry funded trials than in non-industry funded trials (84% *v* 31%; P<0.001). The prevalence of financial ties was lower in superiority trials than in non-inferiority trials (64% *v* 95%; P=0.004). We found no significant differences in the prevalence of financial ties between placebo controlled and active controlled trials or between trials with surrogate and clinical outcomes (table 1).

Financial ties and study outcome

In the unadjusted analysis, both self reported financial ties and total financial ties were associated with positive study outcomes (table 3). After adjustment for study funding, self reported financial ties (odds ratio 2.94, 95% confidence interval 1.4 to 6.1; P=0.004) and total financial ties (3.57, 1.7 to 7.7; P=0.001) were still associated with positive study outcomes (table 3).

The interaction between total financial ties and industry funding on study outcomes was not significant (P=0.15). In the stratified analysis, self reported financial ties were associated with positive study outcome for industry funded studies (3.36, 1.2 to 9.8; P=0.027) and for non-industry funded studies (2.53, 0.42 to 15; P=0.31) (table 4).

In the secondary analysis, we controlled for additional factors: RCT phase, RCT type, sample size, country of first author, specialty, trial registration, study design, type of analysis, comparator, primary outcome measure, and study blinding. These characteristics did not appreciably affect the relation between financial ties and study outcomes (total financial ties: odds ratio 3.37, 1.4 to 7.9; P=0.006) (table 5).

We also examined the effect of excluding papers in which the investigators had no opportunity to declare

Table 1 | Prevalence of total financial ties by characteristics of trials (n=195). Values are numbers (percentages) unless stated otherwise

	No	Financial ties* present	Financial ties* absent	P value
RCT phase				
Phase II	50	38 (76)	12 (24)	<0.001
Phase III	102	81 (79)	21 (21)	
Phase IV	17	8 (47)	9 (53)	
Other	26	5 (19)	21 (81)	
RCT type				
Double blinded	147	102 (69)	45 (31)	0.47
Single blinded	7	5 (71)	2 (29)	
Open label	39	23 (59)	16 (41)	
Unknown	2	2 (100)	0 (0)	
Sample size				
Quarter 1 (13-118)	49	22 (45)	27 (55)	<0.001
Quarter 2 (119-315)	49	33(67)	16 (33)	
Quarter 3 (316-615)	49	33 (67)	16 (33)	
Quarter 4 (616-21 105)	48	44 (92)	4 (8)	
Specialty†				
Cardiology	31	22 (71)	9 (29)	0.28
Oncology	22	18 (82)	4 (18)	
Infectious disease	22	14 (64)	8 (36)	
Urology	13	11 (85)	2 (15)	
Gastroenterology	12	9 (75)	3 (25)	
Other	95	58 (61)	37 (39)	
Funding source				
Any industry funding	134	113 (84)	21 (16)	<0.001
No industry funding	61	19 (31)	42 (69)	
Trial registration				
Yes	183	129 (70)	54 (30)	0.001
No	12	3 (25)	9 (75)	
Type of analysis				
Superiority	174	112 (64)	62 (36)	0.004
Non-inferiority	21	20 (95)	1 (5)	
Comparator				
Placebo	146	94 (64)	52 (36)	0.09
Active	49	38 (78)	11 (22)	
Outcome measure				
Surrogate	65	42 (65)	23 (35)	0.52
Clinical	130	90 (69)	40 (31)	
First and senior author affiliation by continent (n=397)‡				
North America	191	137 (72)	54 (28)	<0.001
Europe	137	80 (58)	57 (42)	
Asia	52	8 (15)	44 (85)	
Other	17	6 (35)	11 (65)	
First and senior author affiliation by country, top 5				
United States	169	119 (70)	50 (30)	<0.001
United Kingdom	31	22 (71)	9 (29)	
Canada	21	17 (81)	4 (19)	
Germany	21	14 (67)	7 (33)	
France	19	11 (58)	8 (42)	
Other	136	48 (35)	88 (65)	

RCT=randomized controlled trial.
*Total financial ties (both self reported and found by additional search).
†Top five most common specialties in sample.
‡Of 190 papers reporting 195 studies, seven studies had multiple first or senior authors and one had single author for total of 397 authors.

conflicts on the relation between financial ties and study outcome. The exclusion of these papers had no effect on our findings (total financial ties: odds ratio 3.44, 1.4 to 8.4). Finally, we examined the effect of including only the first study in the five papers that reported multiple study results. This analysis had no effect on our findings (total financial ties: odds ratio 3.07, 1.6 to 5.9). The appendix includes a list of all included studies, their outcomes, presence of financial ties, and presence of industry funding.

Discussion

We found that more than half of principal investigators of RCTs of drugs had financial ties to the pharmaceutical

Table 2 | Prevalence of financial ties in principal investigators of 195 studies*

	Total No (%) (n=397)†	Financial ties self reported	Additional financial ties identified by search
Frequency of financial ties			
Any financial ties	231 (58)	197	34
No financial ties	166 (42)	NA	NA
Type of financial ties‡			
Consultant/advisor payments	156 (39)	104	21
Speakers' fees	81 (20)	43	10
Type not specified	81 (20)	40	10
Honorariums	52 (13)	16	5
Employee relationship	52 (13)	43	2
Travel fees	52 (13)	26	8
Stock ownership	41 (10)	25	3
Patent	20 (5)	13	1

NA=not applicable.
*Each study had one to four principal investigators.
†Includes 14 authors who had no opportunity to declare financial ties (no disclosure section in journal). These 14 principal investigators had no financial ties identified in search.
‡Principal investigators may have had more than one type of financial tie.

Table 3 | Association between financial ties and primary study outcome after adjustment for industry funding

	No (%)			Odds ratio (95% CI)	
	Positive study	Negative study	Total No	Unadjusted	Adjusted
Self reported financial ties					
Yes	92 (79)	25 (21)	117	2.84 (1.5 to 5.3)*	2.94 (1.4 to 6.1)
No	48 (62)	30 (38)	78	–	–
Industry funding					
Yes	98 (73)	36 (27)	134	1.65 (0.87 to 3.1)†	0.93 (0.43 to 2.0)
No	38 (62)	23 (38)	61	–	–
Total financial ties					
Yes	103 (78)	29 (22)	132	3.23 (1.7 to 6.1)*	3.57 (1.65 to 7.7)
No	33 (52)	30 (48)	63	–	–
Industry funding					
Yes	98 (73)	36 (27)	134	1.65 (0.87 to 3.1)†	0.83 (0.37 to 1.8)
No	38 (62)	23 (38)	61	–	–

*Unadjusted association between financial ties and study outcome.
†Unadjusted association between industry funding and study outcome.

industry and that financial ties were independently associated with positive clinical trial results even after we accounted for industry funding. These findings may raise concerns about potential bias in the evidence base.

Possible explanations for findings

The high prevalence of financial ties observed for trial investigators is not surprising and is consistent with what has been reported in the literature.[11 19-25] One would expect industry to seek out researchers who develop expertise in their field[38]; however, this does not explain why the presence of financial ties for principal investigators is associated with positive study outcomes.[9] One explanation may be "publication bias." Negative industry funded studies with financial ties may be less likely to be published. The National Institutes of Health (NIH)'s clinicaltrials.gov registry was intended to ensure the publication of all trial results, including both NIH and industry funded studies, within one year of completion. However, rates of publication of results remain low even for registered trials.[4 39] Although lack of publication of select industry funded studies may be an important explanation for our findings, small single site RCTs conducted in academic settings may also be less likely to get published because of a lack of interest from medical journals. Publication bias is an important factor to consider while reflecting on our findings, but the distribution of financial ties among unpublished papers is unknown and the effect of publication bias on the observed association is unclear and speculative.[4]

Other possible explanations for our findings exist. Ties between investigators and industry may influence study results by multiple mechanisms, including study design and analytic approach.[2 3 10 40 41] If our findings are related to such factors, the potential solutions are particularly challenging. Transparency alone is not enough to regulate the effect that financial ties have on the evidence base, and disclosure may compromise it further by affecting a principal investigator's judgment through moral licensing, which is described as "the unconscious feeling that biased evidence is justifiable because the advisee has been warned."[42] Social experiments have shown that bias in evidence is increased when conflict of interest is disclosed.[42] One bold option for the medical research community may be to adopt a stance taken in fields such as engineering, architecture, accounting, and law: to restrict people with potential conflicts from involving themselves in projects in which their impartiality could be potentially impaired.[43] However, this solution may not be plausible given the extensive relationship between drug companies and academic investigators.[44 45] Other, incremental steps are also worthy of consideration. In the past, bias related to analytic approach was tackled by a requirement for independent statistical analysis of major RCTs.[46 47] Independent analysis has largely

Table 4 | Association between financial ties and primary outcome stratified by funding source

	Industry funded (n=134)				Not industry funded (n=61)			
	No (%)		Odds ratio (95% CI)		No (%)		Odds ratio (95% CI)	
	Positive	Negative	Unadjusted	Adjusted	Positive	Negative	Unadjusted	Adjusted
Self reported financial ties								
Present	81 (79)	22 (21)	3.03 (1.3 to 7.1)	3.36 (1.2 to 9.8)	11 (79)	3 (21)	2.72 (0.67 to 11)	2.53 (0.42 to 15)
Absent	17 (55)	14 (45)	–	–	27 (57)	20 (43)	–	–
Total financial ties								
Present	89 (79)	24 (21)	4.94 (1.9 to 13)	5.01 (1.52 to 17)	14 (74)	5 (26)	2.10 (0.64 to 6.9)	3.49 (0.62 to 20)
Absent	9 (43)	12 (57)	–	–	24 (57)	18 (43)		–

Table 5 | Association between financial ties and study outcomes after adjustment for characteristics of RCT (n=195)

	No	Self reported financial ties		Total financial ties	
		Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Financial ties*					
Any	132*	2.84 (1.5 to 5.3)	2.85 (1.2 to 6.6)	3.23 (1.7 to 6.1)	3.37 (1.4 to 7.9)
None (reference)	63	–	–	–	–
Funding source					
Any industry funding	134	1.65 (0.87 to 3.1)	0.86 (0.37 to 2.0)	1.65 (0.87 to 3.1)	0.79 (0.34 to 1.9)
No industry funding (reference)	61	–	–	–	–
RCT phase					
Phase III	102	1.61 (0.87 to 3.0)	1.18 (0.56 to 2.5)	1.61 (0.87 to 3.0)	1.15 (0.54 to 2.4)
Other (reference)	93	–	–	–	–
RCT type					
Open label/single blind	46	1.23 (0.59 to 2.5)	1.08 (0.43 to 2.7)	1.23 (0.59 to 2.5)	1.13 (0.45 to 2.9)
Double blind (reference)	147	–	–	–	–
Sample size					
Quarter 4 (616-21 105)	48	2.10 (0.82 to 5.4)	1.03 (0.32 to 3.3)	2.10 (0.82 to 5.4)	1.05 (0.32 to 3.4)
Quarter 3 (316-615)	49	0.84 (0.36 to 1.9)	0.56 (0.21 to 1.5)	0.84 (0.36 to 1.9)	0.58 (0.22 to 1.5)
Quarter 2 (119-315)	49	1.00 (0.43 to 2.3)	0.72 (0.28 to 1.9)	1.00 (0.43 to 2.3)	0.65 (0.25 to 1.7)
Quarter 1 (13-118) (reference)	49	–	–	–	–
First author affiliation					
United States	74	0.94 (0.50 to 1.76)	0.81 (0.39 to 1.7)	0.94 (0.50 to 1.76)	0.81 (0.39 to 1.7)
Other (reference)	121	–	–	–	–
Specialty					
Cardiology	31	1.06 (0.45 to 2.5)	0.65 (0.24 to 1.8)	1.06 (0.45 to 2.5)	0.63 (0.23 to 1.7)
Oncology	22	0.93 (0.35 to 2.4)	0.78 (0.26 to 2.4)	0.93 (0.35 to 2.4)	0.73 (0.24 to 2.2)
Other (reference)	142	–	–	–	–
Trial registration					
Yes	183	2.45 (0.76 to 7.9)	1.75 (0.47 to 6.5)	2.45 (0.76 to 7.9)	1.70 (0.45 to 6.4)
No (reference)	12	–	–	–	–
Type of analysis					
Non-inferiority	21	9.99 (1.3 to 76)	5.34 (0.60 to 47)	9.99 (1.31 to 76)	5.55 (0.63 to 49)
Superiority (reference)	174	–	–	–	–
Comparator					
Active	49	1.97 (0.91 to 4.3)	1.46 (0.56 to 3.8)	1.97 (0.91 to 4.3)	1.35 (0.53 to 3.5)
Placebo (reference)	146	–	–	–	–
Outcome measure					
Clinical	130	0.52 (0.26 to 1.0)	0.42 (0.19 to 0.92)	0.52 (0.26 to 1.0)	0.43 (0.20 to 0.93)
Surrogate (reference)	65	–	–	–	–

OR=odds ratio; RCT=randomized controlled trial.
*Total financial ties (117 self reported).

been abandoned in favor of the strategy of transparency, but perhaps the time has come to reconsider this tool to reduce bias in the analysis of RCTs. This approach might be especially effective for studies that are likely to have a major effect on clinical practice or financial implications for health systems.[48] Another strategy to reduce bias at the analytic stage may be to require the publishing of datasets. ICMJE recently proposed that the publication of datasets should be implemented as a requirement for publication.[49] This requirement is increasingly common in other fields of inquiry such as economics.[50 51] Although independent analyses at the time of publication may not be feasible for journals from a resource perspective, the requirement to release the dataset to be reviewed later if necessary may discourage some forms of analytical bias. Finally, authors should be required to include and discuss any deviations from the original protocol. This may help to prevent changes in the specified outcome at the analytic stage.

Strengths and limitations of study

This study has several strengths. Previous studies examining the link between financial ties and study outcome have been limited to one specialty,[17-21] drug type,[22 23] or journal.[24 25] Our study provides a comprehensive examination of the link between principal investigators' financial ties and study outcomes after accounting for industry funding and represents a cross section of published RCTs. In addition, previous studies have not attempted to disentangle the effect of individual principal investigator's financial ties and industry funding on RCT outcomes. These two variables, although related, are different. Funding is awarded to institutions and represents professional gain and not personal financial gain. In the unadjusted analyses, we found that financial ties were strongly associated with positive study outcome. In multivariate analyses, financial ties had a strong and consistent relation with study outcome even after adjustment for source of funding. Although we did not find evidence

of multicollinearity in our statistical analysis, we further examined the relation between financial ties and RCT results in an analysis stratified by industry funding. Among studies with financial ties, the percentage of studies with financial ties was similar for both industry and non-industry funded studies (table 4). The point estimates for the odds ratios in the stratified analysis were both positive, which suggests that financial ties of non-industry funded researchers are also important to examine. However, this analysis was limited by a small sample size. Future studies with larger sample sizes that are powered to examine the relation between financial ties and study outcome in non-industry funded studies are an important direction for this research and could help to improve our understanding of the relation between principal investigators' financial ties and study outcome.

Our study also has several important limitations that deserve comment. Our analysis is cross sectional and cannot be used to draw conclusions about causation. In addition, we did not assess the quality of clinical trials included in our sample; this was beyond the scope of our study. However, we did assess sample size, study design, analysis type, and outcome measure, which are related to study quality, and none influenced the relation between financial ties and outcomes. Therefore, we believe it to be unlikely that formal quality assessment would have changed our findings. Our findings may also over-represent the financial ties of US (compared with non-US) investigators, as we used two US based resources to identify financial ties: US Patent Office and ProPublica's Dollars for Doctors. Although this may have led to an overestimation of financial ties of US based authors, we identified financial ties for only two additional principal investigators through these sources, diminishing the possibility that the emphasis on US sources in our search strategy affected our findings. In addition, our assessment of exposure was limited by necessity. We counted the financial ties to manufacturers because these were clear and measurable. Distributors and competitors change owing to mergers and acquisitions, and sources of information are variable. We relied on our conservative, but robust, approach of taking the clearly identifiable manufacturer. We extracted information on the financial ties of principal investigators, who we defined as first and last authors. The principal investigators of a publication are usually more closely identified with their publication and are more directly responsible for its content; we did an exhaustive search to identify their financial ties. However, our definition may have caused us to miss some financial ties of other study investigators, which in turn may have caused us to underestimate the association between financial ties and study outcomes. Finally, we did not consider research support as a financial tie because research support is awarded to institutions and not individual investigators. In this study, we focused on ties that were representative of personal financial gain. This may have underestimated financial ties but is unlikely to have affected our main finding.

Conclusions

Financial ties of principal investigators are prevalent and are independently associated with positive clinical trial results. Given the importance of industry and academic collaboration in advancing the development of new treatments, more thought needs to be given to the roles that investigators, policy makers, and journal editors can play in ensuring the credibility of the evidence base.

Contributors: SK had the idea for the study. SK, DK, RA, AW, AA, and SS created the study design. RA, AW, AA, and SS collected the data. SK and DK verified the data. EM, WJB, SK, RA, AW, AA, SS, and DK analyzed and interpreted the data. RA, AW, AA, SS, SK, DK, EM, and WJB wrote and revised the manuscript. All authors critically revised the manuscript and approved the final version for submission. RA, AW, AA, and SS contributed equally to the work and are considered co-first authors. SK is the guarantor.

Funding: This project was not directly supported by any research funds. SK is funded by grants from the National Institutes of Health (RO1 HL116522-01A1, RO1 HL114563-01A1) and Veterans Affairs Health Services Research and Development Service (1IP1HX001994). DK's work on this paper was supported by a Cancer Center Support Grant from the National Cancer Institute to Memorial Sloan Kettering Cancer Center (award number P30 CA008748).

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work, other than that described above; no financial relationships with any organizations 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.

Ethical approval: Not needed.

Data sharing: Dataset available from corresponding author on request.

Transparency: The lead author (the manuscript's guarantor) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix