Financial Conflicts of Interest and Study Results in Environmental and Occupational Health Research

Lee Friedman, PhD and Michael Friedman, BS

Objectives: To date, there is no comprehensive analysis of the relationship between financial conflict of interest (COI) and a potential publication bias in environmental and occupational health studies. **Methods:** We analyzed original research articles published in 2012 in 17 peer-reviewed journals. Multivariable ordinal logistic regression models were developed to evaluate the relationship between financial COI and the study outcome. **Results:** Of the 373 studies included in the analysis, 17.2% had a financial COI associated with organizations involved with the processing, use, or disposal of industrial and commercial products, and studies with this type of COI were more likely to report negative results (Adjusted Odds Ratio = 4.31), as were studies with any COI associated with the military (employment or funding; Adjusted Odds Ratio = 9.15). **Conclusions:** Our findings show a clear relationship between direction of reported findings and specific types of financial COI.

Learning Objectives

- Discuss the trend toward more transparent conflict of interest (COI) disclosures, and identify some COI issues specific to research in occupational and environmental health.
- Summarize the methods used in the new study to analyze the association between financial COIs and the results of occupational and environmental health research.
- Discuss the main study findings, including the types of COIs that are and are not associated with an increased likelihood of reporting negative results.

In discussions of biomedical ethics, experts have broadly defined three types of research behavior: (1) responsible conduct of research (RCR), (2) questionable research practices including most financial conflicts of interest (COI), and (3) deliberate misconduct, involving fabrication, falsification, and plagiarism.[1] The last example represents the most egregious form of misconduct and the first example represents the ideal situation for conducting research. However, some argue that it is the second type of research misconduct—questionable research practices that include misconduct resulting from financial COI—that is the most detrimental to the integrity of science.[1,2]

There has been a move toward more transparent conflict of interest disclosures that evolved slowly over the past 50 years and shifted from concerns exclusively regarding relationships with government agencies to a broader understanding of the prevalence of potential COI between researchers and nongovernmental bodies, in particular for-profit companies.[3] Key milestones include (1) the formation of multiple regulatory and policy agencies within the U.S. government that infused scientists with a greater direct policy role into the government, (2) the Bayh-Dole Act in 1980 and Economic Recovery Tax Act of 1981 that opened the door to greater financial collaboration between for-profit companies and public universities, (3) a substantial increase in both public and private investment in scientific research, and (4) an increase in scientific evidence of a clear association between funding sources and the direction of reported findings. However, concern regarding potential COI between researchers and the private sector has been raised by prominent scientific organization, such as the American Association for the Advancement of Science, well before the administrative and legislative changes cited above. Although important groups have adopted more restrictive COI reporting rules [eg, International Committee of Medical Journal Editors (ICMJE) in 2001 and the National Institute of Health (NIH) in 2004], the most recent policies only remedy public and institutional trust in research through improved transparency. However, these policies do little to manage financial conflicts of interest or provide uniform policies to help discourage abuses.[4]

There is also no broad consensus for any single definition of a financial COI. Thompson defines a financial COI as a *condition*, not a behavior, in which the circumstances and not the outcome determine the presence of COI.[5] Private sector employees, consultants, and academic researchers who might benefit financially from their work have a COI regardless of whether this status actually biases the direction, content, and findings of their research or decision-making. However, financial relationships in and of themselves are not detrimental. For example, if a grant from a company that has developed a new low cost screening test for a toxic exposure leads to more epidemiological investigations and discoveries of populations at risk, such a relationship can be beneficial to the public health. On the contrary, the same financial relationship could influence a researcher's judgment, or create an environment wherein the researcher lacks complete independence and is required to alter or suppress his/her findings.[1,6–9]

In environmental and occupational health research, funding organizations are generally interested in identifying adverse health effects from different exposures, rather than evaluating a new product and its associated health benefits. The research translates directly into civil suits, policies, and regulations to control the production, release, or disposal of certain products, or financial penalties to recover health and environmental costs. Therefore, the financial implications of research findings in the field of environmental and occupational health are as substantial as, if not greater than, other fields of health research, in which the results predominately impact market share or sales of a product.

The funding for research in the field of environmental and occupational health primarily comes from two sources: government agencies and private corporations. Funding from private corporations has been associated with findings favorable to the funding organization in studies evaluating drug treatments,[9–14] medical device and biotechnology,[13,15,16] food safety and nutrition,[17] energy and climate issues,[18] and across the field of public health.[19] However, COI among government funded projects has also been proposed as potentially problematic.[20] It has been suggested that research findings may be biased among researchers motivated to

From the University of Illinois at Chicago School of Public Health (L Friedman); and The Social Policy Research Institute, Skokie, Illinois (M Friedman).

Authors Friedman and Friedman have no relationships/conditions/circumstances that present potential conflict of interest.

The JOEM editorial board and planners have no financial interest related to this research.

Address correspondence to: Lee Friedman, PhD, University of Illinois at Chicago School of Public Health, Division of Environmental and Occupational Sciences, 2121 W. Taylor St, Chicago, IL 60612 (lfried1@uic.edu).

DOI: 10.1097/JOM.0000000000000671

improve their opportunities to extend short-term grants or receive renewal of federal grants, as well as by government agencies with policy/regulatory directives that selectively fund researchers who have a proven track record of validating the agency's agenda.[20]

The influence of commercial interests on researchers is an important and sensitive issue facing environmental and occupational research. There is a need to comprehensively evaluate the degree of influence of funding organizations on researchers. To date, there have been an array of editorials, commentaries, news reports, anecdotal evidence, and descriptions of specific cases on the relationship between COI and reporting of positive or negative findings in environmental and occupational research.[16,19,21,22] However, there are no comprehensive analytical research articles evaluating the influence of COI on the presentation of findings by researchers in the field. Sporadic anecdotal evidence is informative but cannot specifically address the overall question of whether relationships are pervasive or influence results.

The focus of this research project was to evaluate the relationship between financial COI from all funding sources (corporate and government) and direction of reported findings (positive, mixed, and negative; as defined in the methods section below) related to anthropogenic environmental and occupational health hazards in peer-reviewed research articles. Our specific aims are as follows: (1) describe the study design, sample size, country of origin, exposure type, health outcome, funding source, and type of financial relationships of peer-reviewed original research articles, (2) compare reported research findings by different types and sources of financial COI, (3) evaluate the degree to which the reported findings by researchers funded by government agencies and private corporations differ from findings of researchers without any reported financial COI, and (4) determine whether the association between reported research findings and financial COI is modified by the employer of the authors.

METHODS

Data Source

We electronically searched 22 journals for articles related to environmental and occupational health issues. Electronic searching was conducted first by downloading the full table of contents and citations via Thompson Reuters Web of Science, and then each journal was checked via the University online journal subscription to make sure that the table of contents downloaded via Web of Science was complete. Journals were screened on the basis of the following criteria: (1) the journal was highly cited within the category of ''public, environmental and occupational health'' with an average of 5000 or more citations for articles published between 2010 and 2012 as of October 2014 or journals with impact factors above 3.0, which represents the top 10% of journals publishing under this category as measured by impact factors based on 2012 ISI Journal Citation Reports,[23] (2) a history of publishing human health outcomes research relating to the field of environmental and occupational health, and (3) journals with conflict of interest disclosure policies for authors that require public disclosure to readers.

We focused on citations as the key index for identifying journals because we wanted to focus on journals that have the strongest influence on other researchers within the field. We identified 32 journals with more than 5000 citations and an additional 14 journals that had fewer than 5000 citations but an impact factor of 3.0 or greater. However, 29 of the journals did not meet the criterion of a focus on publishing human health outcomes research relating to the field of environmental and occupational health (second criterion). These journals focus on infectious diseases, clinical epidemiology, tobacco control, psychiatry, and social and economic risk factors.

However, we included five additional journals that did not meet the first criterion, but did meet the second two criteria. We added an industrial hygiene specialty journal (impact factor = 2.2) to make sure there were an adequate number of industrial hygiene and occupational exposure assessment studies in the analysis. We also added two prominent general medicine journals because they occasionally publish articles on environmental and occupational health. Finally, we added two journals because of indications that the editorial staff on these journals have financial COIs with private for-profit organizations or environmental/worker advocacy groups.

In the final analysis, we included original research manuscripts from 17 of the 22 journals (Table 1). None of the manuscripts from five of the journals met the inclusion criteria described below (these included: *American Journal of Public Health*, *New England Journal of Medicine*, *American Journal of Preventive Medicine*, *Annals of Epidemiology*, and *Health Promotion Practice*). Of the journals included in this analysis, 11 of the journals are specialty journals within the field of environmental and occupational health research. The remaining six are general epidemiology and medicine journals.

Inclusion Criteria

We only included original research articles published in 2012. Articles from supplemental issues were also included. Editorials, reviews, commentaries, and case reports were excluded because they often do not undergo peer review or provide original data. However, meta-analyses were included.

We focused only on studies that evaluated associations between adverse health outcomes in humans and anthropogenic environmental and occupational exposures to physical and chemical hazards. Studies assessing biological exposures (eg, viruses and bacteria) and ''natural'' background exposures (eg, sun; radon) were not included. For this analysis, we defined anthropogenic environmental and occupational contaminants as those hazards resulting from exposures to the processing, use, or disposal of industrial and commercial products, which includes consumer and agricultural products. Manuscripts using the following study types were included in the analysis: experimental, observational, exposure assessments, and risk assessments. Studies that only focused on the evaluation of analytic methods were excluded as well as studies based exclusively on animal models. Of the 1970 research studies published in the 17 journals listed in Table 1, 381 studies met our initial screening for inclusion. All of the potential articles were assessed by both reviewers to determine whether the manuscripts met the inclusion criteria. All manuscripts that either reviewer identified as meeting the inclusion criteria were included in the analysis.

Financial Conflict of Interest Definition

We used the published author affiliations, conflict of interest statements, and author acknowledgments to identify studies with potential COI. All the journals identified for this analysis require authors to disclose financial relationships with companies or groups directly or indirectly related to the hazard they evaluate in the manuscript. However, there is no broad consensus for any single definition of financial COI. For this analysis, we used a two-part definition for potential COI similar to one used in a previous analysis[15] and set forth by the International Committee of Medical Journal Editors,[24] both of which focus on financial relationships cited as the most serious examples of a potential COI. Receiving funding in of itself is not a considered a COI if the organization has no engagement in the product being evaluated. Both parts of the criteria below must be met for a financial COI designation, regardless of whether or not the authors reported a conflict of interest.

TABLE 1. List of Journals Included in the Analysis From Which Original Research Manuscripts in Environmental and Occupational Health Were Selected, 2012

Specialty Journals	General-Related Journals
Annals of Occupational Hygiene	American Journal of Epidemiology
Chemico-Biological Interactions	Epidemiology
Environmental Health Perspectives	European Journal of Epidemiology
Environmental Research	International Journal of Epidemiology
International Journal of Hygiene and Environmental Health	JAMA-Journal of the American Medical Association
International Journal of Occupational and Environment Health	Journal of Epidemiology and Community Health
Journal of Occupational and Environmental Medicine	
Journal of Toxicology and Environmental Health-Part A	
Occupational and Environmental Medicine	
Regulatory Toxicology and Pharmacology	
Scandinavian Journal of Work Environment & Health	

PART 1: A Clear Financial Relationship of One or More of the Following Is Present

One or more authors have financial associations with a private or government institution in the form of grants, unspecified funding, consultancy, employment, stock ownership, and honoraria. Free equipment, awards, fellowships, serving on advisory boards, or as speakers do not constitute COI in this definition.

One or more authors have a personal financial interest in the study because of a patent license in which an author is eligible to receive royalties or from personal investments.

PART 2: The Funding Agency/Employer/Author Is Engaged in One or More of the Following Activities or Has One or More of the Following Characteristics

The environmental or occupational hazard evaluated by the author/s, directly or indirectly, results from the processing, use or disposal of industrial and commercial products, or similar class of products with shared physical properties by the funding agency or employer. These include studies that identify an alternative cause for adverse health outcomes not related to the funding organization's processes.

The author/s is a government employee, including military personnel, evaluating risks to their own employees or general public affected by government activities

Is a government agency with direct regulatory control over issues related to the exposure, in which the agency is charged with investigating, monitoring, and enforcing legal standards as well as developing new legal standards for enforcement (eg, Environmental Protection Agency and Occupational Safety and Health Administration).

A government agency with direct policy control over issues related to the exposure, in which the agency is charged with writing and putting forward new regulations and laws related to the exposure or modifying existing regulations.

A plaintiff or defendant involved in a lawsuit or criminal case that involves allegations relating to the agents evaluated in the analysis. This does not include studies managed by the court in adherence with a settlement.

Classifying Reported Findings

To assess the association between COI and reported study findings, we classified the presentation of the results as follows: positive, mixed, and negative. For each manuscript included in the analysis, the two raters evaluated the content presented in the entire manuscript (not only the abstract or conclusions). Key elements evaluated by each reviewer included the study design, completeness of the data collected, coding of dependent and independent variables, appropriateness of statistical tests, adequate presentation of findings, authors' interpretation of findings, a description of the study limitations, and potential risk of bias. Positive results include studies that show a statistically significant ($P < 0.05$) increase in health risks associated with an environmental or occupational exposure. For exposure assessments, positive results include studies that report elevated exposure levels associated with adverse health outcomes in the literature or those exceeding permissible levels. Only one exposure assessment study evaluated agents without documentation of permissible or recommended exposure limits. Mixed results include studies noting both an increase and decrease/absence of risk for the principal health outcomes studied in the manuscript. Negative results include studies that report the absence of an association between the exposure and health outcome ($P > 0.05$), and/or evidence for a decreased risk for a specified health outcome ($P < 0.05$), and/or studies that find an alternative explanation for an increased risk in health outcomes, and/or exposure/risk assessments with exposure levels below those associated with adverse health outcomes in the literature or those below permissible levels (eg, levels at or below MCL, NAAQS, PEL, or excess cancer risk at or below 1/100,000). In the absence of EPA/OSHA standards for permissible levels, we used NIOSH recommended exposure limits (RELs), WHO guidelines, and European Environment Agency equivalent Reference Doses (RfDs).

Evaluation of Inter-Rater Reliability

Evaluation of the published original research was conducted in stages in order to minimize reviewer bias. In the first stage, both authors classified the reported findings (positive, mixed, negative) by thoroughly analyzing each manuscript. During this phase of the review, each reviewer was blinded to the COI statements, author affiliations and funding statements, as well as to each other's study classifications (positive, mixed, negative). After the initial review, the two reviewers disagreed on 54 out of 381 articles [14.2%; quadratic weighted kappa = 0.86; 95% confidence interval (95% CI) 0.81 to 0.90]. Agreement was highest on studies with positive and negative findings (94.5% and 93.8%, respectively) and lowest on studies with mixed findings (66.4%). After the initial review of the classification of the study findings, the two reviewers discussed each manuscript in which there was disagreement. Manuscripts in which the two investigators could not agree with each other's study classifications were omitted from the analysis ($n = 6$).

In the second stage of the review, the two reviewers determined whether a study had a potential COI. A potential COI was assessed using a summary of the exposure, the study design, and statements provided by the authors of each manuscript regarding any COI, funding sources, employment/affiliations, and acknowledgments. All of these data were abstracted into a dataset before making the COI assessment in order to blind each reviewer to the study findings (positive, mixed, negative) and detailed results. In

TABLE 2. Type of Financial Conflict of Interest (COI) by Reported Study Outcomes* Among Original Research Manuscripts in Environmental and Occupational Health, 2012

Type of COI†	Total	Positive Findings *N* (%)	Mixed Findings *N* (%)	Negative Findings *N* (%)
COI relating to the processing, use, or disposal of industrial and commercial products	64	18 (28.1%)	18 (28.1%)	28 (43.8%)
Processing	27	5 (18.5%)	6 (22.2%)	16 (59.3%)
Commercial use/Activities	43	10 (23.3%)	10 (23.3%)	23 (53.5%)
Disposal/Waste	6	0 (0.0%)	0 (0.0%)	6 (100.0%)
Consulting	22	8 (36.4%)	3 (13.6%)	11 (50.0%)
Negate competitor/Alternative cause	2	0 (0.0%)	1 (50.0%)	1 (50.0%)
COI relating to direct governmental control over policy and regulations	130	70 (53.8%)	44 (33.8%)	16 (12.3%)
Directly related to policy decision	125	67 (53.6%)	43 (34.4%)	15 (12.0%)
Direct jurisdiction/regulatory control	117	65 (55.1%)	38 (32.2%)	15 (12.7%)
No reported COI	193	116 (60.1%)	51 (26.4%)	26 (13.5%)

*Positive results include studies that show a statistically significant ($P < 0.05$) increase in health risks associated with an environmental or occupational exposure. For exposure assessments, positive results include studies that report elevated exposure levels associated with adverse health outcomes in the literature or those exceeding EPA/OSHA permissible levels. Mixed results include studies noting both an increase and decrease/absence of risk for the principal health outcomes studied in the manuscript. Negative results include studies that report the absence of an association between the exposure and health outcome ($P > 0.05$), and/or evidence for a decreased risk for a specified health outcome ($P < 0.05$), and/or studies that find an alternative explanation for an increased risk in health outcomes, and/or exposure assessments with exposure levels below those associated with adverse health outcomes in the literature or those below EPA/OSHA permissible levels.

†Each COI category is not independent; a study could be in more than one COI group, with the exception of studies that have no reported financial COI. $N = 14$ studies were classified in both major COI categories: (1) COI relating to the processing, use, or disposal of industrial and commercial products and (2) COI relating to direct governmental control over policy and regulations.

addition, each reviewer was blinded to each other's assessments of COI. The two investigators disagreed on 36 out of 375 articles (9.6%; Kappa = 0.81; 95 % CI 0.75 to 0.87). There was greater agreement between the reviewers on studies without potential COI (97.9%) than studies with potential COI (83.1%). After the initial review, the two reviewers discussed the coding for potential COI for each manuscript in which there was disagreement in order to reach consensus, and two manuscripts were omitted from the analysis when the two reviewers could not reach agreement.

Statistical Analysis

All statistical analyses were conducted using SAS software (v.9.4; SAS Institute Inc., Cary, NC). Multivariable ordinal logistic regression models were developed to evaluate the relationship between financial COI and the study outcome. The dependent variable was ordered as follows: positive findings (0), mixed findings (1), and negative findings (2), wherein positive studies were the reference group. The test for the proportional odds assumption was not statistically significant indicating that the relationship between each outcome group (positive, mixed, and negative) was approximately the same. In addition, financial COI was combined to form two main categories: (1) financial COI relating to the processing, use, or disposal of industrial and commercial products and (2) studies with a financial COI relating to direct governmental control over policy and regulations. Table 2 summarizes the types of COI included in each broad category.

A separate model was also developed to assess the association between reported study findings and any military COI (employment or funding; where the reference group includes studies without a military COI). For employment, military personnel included civilians directly employed by the military.

Statistical evaluation of covariates, as well as a priori knowledge, was used to determine inclusion of covariates in the final models. The final model controlled for study design, age of subjects, health outcome, and country of origin. Sample size, number of funding sources, environmental versus occupational focus, and exposure assessments study designs were not associated with the outcome variable and did not confound the relationship between COI and the outcome variable, and therefore were omitted from the final model. A two-sided *P* value less than 0.05 was considered statistically significant. Odds ratios (ORs) of reporting negative findings in the adjusted models are presented (Adjusted Odds Ratios), including the 95% CIs. No evidence of multicollinearity among the final independent variables was indicated (based on evaluation of standard errors and evaluation of variance of inflation and tolerance tests). Predicted probabilities of reporting negative results based on the multivariable models are also presented; the covariates were mean-centered to calculate the predicted probability.

RESULTS

Summary of Studies

A total of 373 studies were included in the analysis, of which 336 (90.1%) were published in specialty journals focusing on environmental and occupational health issues (Table 1). The most common study designs used were epidemiological cohorts ($n = 126$, 33.8%), followed by cross-sectional studies ($n = 85$, 22.8%) and exposure assessments ($n = 47$, 12.6%). The median sample size across all the studies was 500 (interquartile range: 96 to 3124). The majority of manuscripts focused on environmental hazards ($n = 202$, 54.2%), while only a small fraction focused on both environmental and occupational hazards simultaneously ($n = 21$, 5.6%). The remaining manuscripts focused on occupational health issues alone.

The manuscripts covered a broad range of health hazards, but 62.2% of the articles covered the following hazards: environmental air pollution and respirable hazards ($n = 72$), metals ($n = 59$), pesticides and agricultural hazards ($n = 33$), occupational respirable hazards ($n = 25$), injury and physical hazards ($n = 22$), and asbestos ($n = 21$). The most common health outcomes in humans evaluated were neoplasms ($n = 61$), disorders of the respiratory system ($n = 42$), reproductive health, congenital anomalies, and perinatal conditions ($n = 35$), disorders of the circulatory system ($n = 26$), and mental, behavioral, and neurodevelopmental disorders ($n = 23$). Among the studies, 21.5% evaluated health outcomes in children, 66.8% in adults, and 11.8% in both children and adults.

Study Outcomes: Positive, Mixed, Negative

The majority of studies reported positive findings ($n = 198$, 53.1%), followed by mixed results ($n = 108$; 29.0%) and negative

findings ($n = 67$; 18.0%). We identified one journal that only published studies with negative findings. Studies that did not report any funding to complete the investigations reported negative results in 22% of the manuscripts (11 out of 50), and had the highest proportion of positive findings (31 out of 50; 62%). In contrast, studies funded by for-profit corporations had the greatest proportion of studies with negative findings (13 out of 23 studies; 56.5%). In addition, studies funded from a governmental military source or in which an author was employed by the military disproportionately reported negative findings as well (7 out of 12; 58.3%). In fact, if the first author worked for a for-profit company or the military, the proportion of the studies that reported negative findings rose further (63.6% and 83.3%, respectively). In addition, among studies in which the first author worked for a consultant firm, the proportion of studies with negative findings was 50.0% (6 out of 12). The observed high proportion of reported negative findings declined if only a coauthor (not the primary author) was employed by the military, private for-profit company, or consultant firm (33%; 7 out of 21 studies). None of the studies funded by a plaintiff in cases wherein the defendant was accused of causing bodily injury or property damage reported negative results (three related to asbestos, one to tungsten and cobalt, and one to diacetyl-containing flavorings).

The study designs with the greatest proportion of negative findings were risk assessments (11 out of 16; 68.8%) and ecological studies (7 out of 22; 31.8%). Among the different exposure types assessed in the manuscripts, the studies with the greatest proportion of negative results were those evaluating nonionizing radiation (four out of six), perfluorinated compounds (PFCs; 6 out of 11), and rubber, plastic, and silicone products (four out of five). Data stratified by health outcomes showed that studies evaluating cancer risk were more likely to report negative results (21 out of 61; 34.4%), while studies evaluating risk of injury were more likely to report positive results (11 out of 16; 68.8%).

Funding and Potential Conflict of Interest

Almost half of the studies had some type of potential financial COI ($n = 180$; 48.3%); however, only 64 studies (17.2%) had a COI associated with organizations involved with the processing, use, or disposal of industrial and commercial products (Table 2). The majority of studies with financial COI had relationships with government organizations that have direct regulatory control over issues related to the investigated exposure or have direct policy control to write and implement regulations and laws related to the exposure. A small number of studies had financial COI with both government and private organizations ($n = 14$); among these studies, six reported positive findings (42.9%), five reported mixed results (35.7%), and three reported negative results (21.4%).

Table 3 presents detailed data on financial COI. Studies funded by the military (nine out of nine), for-profit companies (21 out of 23), industry consortiums/trade groups (six out of six), and consultant firms (18 out of 24) had the highest proportion of financial COI involving the processing, use, or disposal of industrial and commercial products. Risk assessments had a disproportionate number of studies with financial COI involving the processing, use, or disposal of industrial and commercial products (9 out of 16). Studies investigating the following exposures also had a disproportionate number with financial COI involving the processing, use or disposal of industrial and commercial products: asbestos (7/21), occupational respirable hazards (5/25), polycyclic aromatic hydrocarbons (4/11), and rubber, plastic, and silicone products (3/5).

Employment status of any of the authors appears to modify the relationship between financial COI relating to the processing, use, or disposal of industrial and commercial products and reported study outcomes. Only 22.2% of the studies published by authors with this type of financial COI reported negative findings when *none* of the authors were employed by an organization with potential COI. In contrast, 52.2% of the studies published by others with this type of financial COI reported negative findings when *any* of the authors were employed by an organization with potential COI.

Among studies with only financial COI by funding agencies with policy or regulatory control, we observed a small difference if any of the authors were also employed by an organization with policy or regulatory control compared to manuscripts in which none of the authors were employed by an organization with policy or regulatory control (12.7% vs 8.9% of studies reported were negative results, respectively).

Association Between Financial COI and Study Results

Table 2 presents the distribution of study findings by major COI categories. Although there were many journals with a high proportion of manuscripts without any COI, there were three journals with 30% or more manuscripts with financial COI relating to the processing, use, or disposal of industrial and commercial products; however, in only one of these journals did we also observe a disproportionate number of negative findings.

The crude analysis showed an association between reported negative results and studies with financial COI relating to the processing, use, or disposal of industrial and commercial products (unadjusted OR = 4.37; $P < 0.01$), but not among studies with financial COI relating to direct governmental control over policy and regulations (unadjusted OR = 0.95; $P = 0.804$). In the final multivariable model, wherein studies without a financial COI are the reference group, studies with a financial COI relating to the processing, use, or disposal of industrial and commercial products were strongly associated with negative findings (adjusted OR = 4.31; 95% CI 2.50 to 7.42; $P < 0.01$), while studies with a financial COI relating to direct governmental control over policy and regulations were not statistically significantly associated with negative findings (adjusted OR = 0.79; 95% CI 0.50 to 1.26; $P = 0.33$). The predicted probability that a study with a COI relating to the processing, use, or disposal of industrial and commercial products would report negative findings was 39.4%.

In models stratified by whether any of the authors were employed by an organization with a COI relating to the exposure, we observed substantial differences in reported study findings. In the adjusted models, employment did not modify the relationship between financial COI and reported study results among those with financial COI relating to direct governmental control over policy and regulations. However, among studies with financial COI relating to the processing, use, or disposal of industrial and commercial products, if any of the authors were employed by an organization with direct COI (adjusted OR = 5.62; 95% CI 2.46 to 12.87), the probability that the findings were negative was 58.8%, in contrast, if none of the authors were employed by an organization with direct COI (adjusted OR = 2.86; 95% CI 1.15 to 7.09), then the probability they reported negative findings was 28.3% (Table 4).

In a separate model assessing studies with any military COI (employment or funding; where the reference group are studies without a military COI), we observed a strong association with negative findings (adjusted OR = 9.15; 95% CI 2.73 to 30.65; $P < 0.01$), and the predicted probability was 52.4% that studies with a military COI reported negative findings.

DISCUSSION

Our findings show a clear relationship between negative results in studies evaluating adverse health outcomes in humans and financial COI arising from relationships with organizations involved in the processing, use, or disposal of industrial and commercial products. Employment of the authors, in particular

TABLE 3. Journal and Manuscript Characteristics by Type of Financial Conflict of Interest (COI) and Reported Study Outcomes* Among Original Research Manuscripts in Environmental and Occupational Health, 2012

	Total	Positive Findings *N* (%)	Mixed Findings *N* (%)	Negative Findings *N* (%)	COI Relating to the Processing, Use, or Disposal of Industrial and Commercial Products *N* (%)	COI Relating to Direct Governmental Control Over Policy and Regulations *N* (%)	Both Major Categories of COI *N* (%)	No COI Present *N* (%)
Journal								
American Journal of Epidemiology	5	3 (60.0%)	0 (0.0%)	2 (40.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	4 (80.0%)
Annals of Occupational Hygiene	26	18 (69.2%)	5 (19.2%)	3 (11.5%)	4 (15.4%)	2 (7.7%)	0 (0.0%)	20 (76.9%)
Chemico-Biological Interactions	3	3 (100.0%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	0 (0.0%)	2 (66.7%)	0 (0.0%)
Environmental Health Perspectives	70	39 (55.7%)	26 (37.1%)	5 (7.1%)	1 (1.4%)	32 (45.7%)	7 (10.0%)	30 (42.9%)
Environmental Research	52	28 (53.8%)	17 (32.7%)	7 (13.5%)	2 (3.8%)	22 (42.3%)	0 (0.0%)	28 (53.8%)
Epidemiology	19	7 (36.8%)	5 (26.3%)	7 (36.8%)	1 (5.3%)	10 (52.6%)	0 (0.0%)	8 (42.1%)
European Journal of Epidemiology	2	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)
International Journal of Epidemiology	4	1 (25.0%)	3 (75.0%)	0 (0.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	3 (75.0%)
International Journal of Hygiene and Environmental Health	22	12 (54.5%)	8 (36.4%)	2 (9.1%)	3 (13.6%)	5 (22.7%)	1 (4.5%)	13 (59.1%)
International Journal of Occupational and Environment Health	7	7 (100.0%)	0 (0.0%)	0 (0.0%)	2 (28.6%)	0 (0.0%)	0 (0.0%)	5 (71.4%)
JAMA-Journal of the American Medical Association	2	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)
Journal of Epidemiology and Community Health	5	5 (100.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (20.0%)	0 (0.0%)	3 (60.0%)
Journal of Occupational and Environmental Medicine	38	19 (50.0%)	11 (28.9%)	8 (21.1%)	12 (31.6%)	5 (13.2%)	4 (10.5%)	17 (44.7%)
Journal of Toxicology and Environmental Health-Part A	29	17 (58.6%)	5 (17.2%)	7 (24.1%)	3 (10.3%)	7 (24.1%)	0 (0.0%)	19 (65.5%)
Occupational and Environmental Medicine	64	31 (48.4%)	25 (39.1%)	8 (12.5%)	6 (9.4%)	19 (29.7%)	0 (0.0%)	39 (60.9%)
Regulatory Toxicology and Pharmacology	15	0 (0.0%)	0 (0.0%)	15 (100.0%)	12 (80.0%)	3 (20.0%)	0 (0.0%)	0 (0.0%)
Scandinavian Journal of Work Environment & Health	10	6 (60.0%)	1 (10.0%)	3 (30.0%)	1 (10.0%)	5 (50.0%)	0 (0.0%)	4 (40.0%)
Funding Source								
Government	270	146 (54.1%)	89 (33.0%)	35 (13.0%)	11 (4.1%)	112 (41.5%)	13 (4.8%)	134 (49.6%)
Military	9	1 (11.1%)	3 (33.3%)	5 (55.6%)	8 (88.9%)	0 (0.0%)	1 (11.1%)	0 (0.0%)
NFP	55	29 (52.7%)	20 (36.4%)	6 (10.9%)	7 (12.7%)	21 (38.2%)	4 (7.3%)	23 (41.8%)
Private for-profit	23	4 (17.4%)	6 (26.1%)	13 (56.5%)	20 (87.0%)	0 (0.0%)	1 (4.3%)	2 (8.7%)
Academic	28	16 (57.1%)	10 (35.7%)	2 (7.1%)	0 (0.0%)	8 (28.6%)	0 (0.0%)	20 (71.4%)
Law firm	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Court order	5	2 (40.0%)	1 (20.0%)	2 (40.0%)	0 (0.0%)	0 (0.0%)	1 (20.0%)	4 (80.0%)
Industry consortium/Trade group	6	2 (33.3%)	1 (16.7%)	3 (50.0%)	5 (83.3%)	0 (0.0%)	1 (16.7%)	0 (0.0%)
Consultant firm	2	2 (100.0%)	0 (0.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)
None	50	31 (62.0%)	8 (16.0%)	11 (22.0%)	7 (14.0%)	4 (8.0%)	1 (2.0%)	38 (76.0%)
First-author employer* may have more than one affiliation								
Government	82	47 (57.3%)	20 (24.4%)	15 (18.3%)	7 (8.5%)	31 (37.8%)	4 (4.9%)	40 (48.8%)
Military	6	0 (0.0%)	1 (16.7%)	5 (83.3%)	6 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Private for-profit	11	3 (27.3%)	1 (9.1%)	7 (63.6%)	10 (90.9%)	1 (9.1%)	0 (0.0%)	0 (0.0%)
NFP	10	4 (40.0%)	3 (30.0%)	3 (30.0%)	1 (10.0%)	2 (20.0%)	1 (10.0%)	6 (60.0%)
Consultant firm	12	3 (25.0%)	3 (25.0%)	6 (50.0%)	10 (83.3%)	0 (0.0%)	2 (16.7%)	0 (0.0%)
Academic	256	143 (55.9%)	83 (32.4%)	30 (11.7%)	17 (6.6%)	85 (33.2%)	9 (3.5%)	145 (56.6%)

TABLE 3. (*Continued*)

	Total	Positive Findings *N* (%)	Mixed Findings *N* (%)	Negative Findings *N* (%)	COI Relating to the Processing, Use, or Disposal of Industrial and Commercial Products *N* (%)	COI Relating to Direct Governmental Control Over Policy and Regulations *N* (%)	Both Major Categories of COI *N* (%)	No COI Present *N* (%)
Hospital	5	2 (40.0%)	2 (40.0%)	1 (20.0%)	0 (0.0%)	3 (60.0%)	0 (0.0%)	2 (40.0%)
Other Authors' Employers								
Government	159	82 (51.6%)	52 (32.7%)	25 (15.7%)	10 (6.3%)	70 (44.0%)	9 (5.7%)	70 (44.0%)
Military	10	0 (0.0%)	3 (30.0%)	7 (70.0%)	8 (80.0%)	0 (0.0%)	2 (20.0%)	0 (0.0%)
Private for-profit	21	5 (23.8%)	4 (19.0%)	12 (57.1%)	14 (66.7%)	2 (9.5%)	2 (9.5%)	3 (14.3%)
NFP	34	16 (47.1%)	12 (35.3%)	6 (17.6%)	5 (14.7%)	16 (47.1%)	3 (8.8%)	10 (29.4%)
Consultant firm	16	8 (50.0%)	2 (12.5%)	6 (37.5%)	8 (50.0%)	0 (0.0%)	2 (12.5%)	6 (37.5%)
Academic	314	172 (54.8%)	99 (31.5%)	43 (13.7%)	23 (7.3%)	106 (33.8%)	13 (4.1%)	172 (54.8%)
Hospital	32	15 (46.9%)	12 (37.5%)	5 (15.6%)	1 (3.1%)	11 (34.4%)	1 (3.1%)	19 (59.4%)
Industry consortium/Trade group	2	1 (50.0%)	1 (50.0%)	0 (0.0%)	2 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study focus								
Environmental	202	105 (52.0%)	63 (31.2%)	34 (16.8%)	14 (6.9%)	81 (40.1%)	10 (5.0%)	97 (48.0%)
Occupational	150	84 (56.0%)	39 (26.0%)	27 (18.0%)	31 (20.7%)	30 (20.0%)	3 (2.0%)	86 (57.3%)
Both	21	9 (42.9%)	6 (28.6%)	6 (28.6%)	5 (23.8%)	5 (23.8%)	1 (4.8%)	10 (47.6%)
Any military involvement (employees, funding agency)	12	1 (8.3%)	4 (33.3%)	7 (58.3%)	10 (83.3%)	0 (0.0%)	2 (16.7%)	0 (0.0%)
Type of hazard/Exposure								
asbestos	21	13 (61.9%)	5 (23.8%)	3 (14.3%)	5 (23.8%)	3 (14.3%)	2 (9.5%)	11 (52.4%)
BPA and phthalates	13	7 (53.8%)	6 (46.2%)	0 (0.0%)	0 (0.0%)	6 (46.2%)	0 (0.0%)	7 (53.8%)
Broad environmental exposures	6	3 (50.0%)	2 (33.3%)	1 (16.7%)	1 (16.7%)	1 (16.7%)	2 (33.3%)	2 (33.3%)
Broad occupational exposures	4	0 (0.0%)	2 (50.0%)	2 (50.0%)	1 (25.0%)	2 (50.0%)	0 (0.0%)	1 (25.0%)
Chemical intermediate, binding agent a	7	5 (71.4%)	1 (14.3%)	1 (14.3%)	2 (28.6%)	0 (0.0%)	1 (14.3%)	4 (57.1%)
Chlorination by-products	6	1 (16.7%)	3 (50.0%)	2 (33.3%)	0 (0.0%)	3 (50.0%)	0 (0.0%)	3 (50.0%)
Dioxins, PCBs, and Dibenzofurans	13	5 (38.5%)	4 (30.8%)	4 (30.8%)	1 (7.7%)	5 (38.5%)	1 (7.7%)	6 (46.2%)
Environ air pollution and respiratable	72	41 (56.9%)	24 (33.3%)	7 (9.7%)	3 (4.2%)	40 (55.6%)	5 (6.9%)	24 (33.3%)
Injury and physical hazards excluding RA	22	15 (68.2%)	3 (13.6%)	4 (18.2%)	1 (4.5%)	4 (18.2%)	0 (0.0%)	17 (77.3%)
Ionizing radiation	2	1 (50.0%)	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)
Metals	59	35 (59.3%)	15 (25.4%)	9 (15.3%)	6 (10.2%)	19 (32.2%)	2 (3.4%)	32 (54.2%)
Military exposures	6	1 (16.7%)	2 (33.3%)	3 (50.0%)	4 (66.7%)	1 (16.7%)	1 (16.7%)	0 (0.0%)
Nonionizing radiation	6	1 (16.7%)	1 (16.7%)	4 (66.7%)	2 (33.3%)	0 (0.0%)	0 (0.0%)	4 (66.7%)
Occupational respiratable Hazards	25	16 (64.0%)	5 (20.0%)	4 (16.0%)	5 (20.0%)	5 (20.0%)	0 (0.0%)	15 (60.0%)
PAHs	11	6 (54.5%)	3 (27.3%)	2 (18.2%)	4 (36.4%)	3 (27.3%)	0 (0.0%)	4 (36.4%)
PBDEs	5	1 (20.0%)	4 (80.0%)	0 (0.0%)	0 (0.0%)	3 (60.0%)	0 (0.0%)	2 (40.0%)
Perfluorinated compounds (PFCs)	11	2 (18.2%)	3 (27.3%)	6 (54.5%)	1 (9.1%)	2 (18.2%)	0 (0.0%)	8 (72.7%)
Pesticides and agricultural hazards	33	16 (48.5%)	11 (33.3%)	6 (18.2%)	2 (6.1%)	9 (27.3%)	0 (0.0%)	22 (66.7%)
Rubber, plastic, and silicone products	5	0 (0.0%)	1 (20.0%)	4 (80.0%)	3 (60.0%)	0 (0.0%)	0 (0.0%)	2 (40.0%)
Solvents	13	6 (46.2%)	6 (46.2%)	1 (7.7%)	1 (7.7%)	6 (46.2%)	0 (0.0%)	6 (46.2%)
Work conditions	13	11 (84.6%)	2 (15.4%)	0 (0.0%)	1 (7.7%)	1 (7.7%)	0 (0.0%)	11 (84.6%)
Other	20	12 (60.0%)	4 (20.0%)	4 (20.0%)	6 (30.0%)	3 (15.0%)	0 (0.0%)	11 (55.0%)

[a]Positive results include studies that show a statistically significant ($P < 0.05$) increase in health risks associated with an environmental or occupational exposure. For exposure assessments, positive results include studies that report elevated exposure levels associated with adverse health outcomes in the literature or those exceeding EPA/OSHA permissible levels. Mixed results include studies noting both an increase and decrease/absence of risk for the principal health outcomes studied in the manuscript. Negative results include studies that report the absence of an association between the exposure and health outcome ($P > 0.05$), and/or evidence for a decreased risk for a specified health outcome ($P < 0.05$), and/or studies that find an alternative explanation for an increased risk in health outcomes, and/or exposure assessments with exposure levels below those associated with adverse health outcomes in the literature or those below EPA/OSHA permissible levels.

TABLE 4. Multivariable Ordinal Logistic Regression Model Evaluating Association Between Type of Financial Conflict of Interest and Reporting Negative Findings, Among Original Research Manuscripts in Environmental and Occupational Health, 2012

	Number of Studies	Standard Error	Adjusted Odds Ratio of Reporting Negative Findings (95% CI)	*P*
COI relating to direct governmental control over policy and regulations	130	0.2355	0.79 (0.50–1.26)	0.328
COI relating to the processing, use, or disposal of industrial and commercial products	64	0.2778	4.31 (2.50–7.42)	<0.001
Study design				
Risk assessment studies	16	0.5609	5.03 (1.67–15.09)	0.004
Cohort studies	126	0.2238	1.63 (1.05–2.53)	0.029
Age of subjects				
Children only (under 18 years of age)	80	0.2776	1.55 (0.90–2.67)	0.114
Health outcome studied				
Reproductive health/ congenital anomalies/ perinatal conditions	35	0.3696	2.00 (0.97–4.13)	0.060
Neoplasms	61	0.2896	1.55 (0.88–2.74)	0.130
Country of affiliation of any author				
United Kingdom	34	0.3488	2.07 (1.04–4.09)	0.038
China	26	0.498	0.34 (0.13–0.91)	0.031
Taiwan	9	0.6397	4.16 (1.19–14.57)	0.026

C-statistic for final model = 0.70; Test for the proportional odds assumption, $P = 0.11$.

the primary author, appears to be an even more important predictor of the direction of a manuscript's reported findings. We observed something akin to a dose–response relationship. As author affiliation with the funding organization increased, the proportion of negative findings also increased (% negative findings based on the multivariable models): 13.5% among studies without financial COI, 28.3% among studies with any financial COI but none of the authors were employed with the funding organizations, and 58.8% among studies with any financial COI and one or more of the authors were employed with the funding organizations.

This study also identified investigations funded by the military, and especially studies in which any of the authors were military personnel, to be strongly associated with reporting negative findings. The focus of most financial COI studies is on private corporations, but the disparity in results was most pronounced among these military-funded research projects. All of the studies with financial COI involving the military evaluated exposures to soldiers during active duty ($n = 10$) or to civilian populations exposed to environmental releases from military point sources ($n = 2$).

The distribution of results among studies funded by government agencies with either direct policy or regulatory authority did not differ from studies with no financial COI, and within this group of manuscripts, employment by these government agencies was not associated with a substantial change in the distribution of reported study results. The assertion that government-funded studies would disproportionately report positive findings because of a systematic bias by the employees within these organizations (eg, Environmental Protection Agency)[20] is not supported by the findings in this study. In fact, when studies funded by agencies with direct policy or regulatory control also had authors employed by these respective agencies, they were slightly more likely to report *negative* findings.

Although it is assumed that scientific research is undertaken independently and provides objective findings exclusively, this is difficult when the financial interests of the varied stakeholders are directly intermingled. There are six primary stakeholders in environmental and occupational health research with their own financial dimensions (although this list is not exhaustive)—(1) researchers, (2) research institutions including universities, (3) government entities, including regulatory agencies, research agencies, and the military, (4) private companies involved in the processing, use, or disposal of industrial and commercial products, (5) private research companies and consulting firms, and (6) private interest groups and not-for-profit granting agencies. All these stakeholders invest in research, directly and indirectly, but the interests of each group vary dramatically. A difficulty in the field is that oversight is fragmented. The peer review process is intended to provide some systematic oversight, but no two scientific journals are the same. The type of manuscripts published in any given journal is a function of the journal's editorial focus, the editor-in-chief, the editorial board, the publisher's staff, the reviewer pool, institutional affiliations, and the readers. Although bias has been reported at the editor level and among reviewers,[25–31] both groups lack the resources to adequately assess COI. Neither group has the resources to check the veracity of reported conflicts of interest nor do they have the authority to manage COIs if present, which raises the question of whether editors and reviewers are the appropriate individuals to police publication bias.

Compared with other fields of health research, we observed a relatively low proportion of studies with financial COI from commercial sources (17.2%). The proportion of studies funded by private industry in basic medicine and pharmacology journals has been reported to be as high as 67%.[32] However, the concern is not whether a financial COI is present but whether a publication bias occurs, as well as the direction and magnitude of the bias. A publication bias can be caused by multiple factors, including inappropriate study design,[21,33] biased interpretation or presentation of results,[22] legal obstruction preventing an author from publishing results,[34] and failure to report findings that are found to be damaging to the interests of the funding organization.[35] The findings presented in this analysis show a clear association between financial COI and reported findings, and the direction, magnitude, and observed ''dose-response'' effect of the relationship is consistent with the vast majority of similar studies in other scientific fields (eg, pharmacology, biomedicine, and so on), which demonstrates the need for further research in the field of environmental and occupational health to determine whether this observed association is a product of an underlying publication bias, in particular the omission of studies showing ''positive'' findings within the public forum.

LIMITATIONS

Determination of a clear publication bias is difficult. Only studies with self-reported COIs are recognized. Studies with hidden ties are not identified including those with ghost writers, and therefore the relationship is likely underestimated.[15,21,36] Furthermore, a potential publication bias among academics who are unable

or fail to publish negative findings[16] can bias the interpretation of this study. However, the propensity to publish only positive findings is not supported in this analysis. Nearly 50% of the original research studies in environmental and occupational health published in 2012 reported some negative results. This could reflect the belief among researchers, in academia at least, that editors do not like to publish negative results, or it could reflect a phenomenon specific to human research studies, although studies using animal models may differ substantially (which were excluded from this analysis).

Because of the lack of data on the association in question in the field of environmental and occupational health sciences, we conducted a very general search with no specific population, intervention, comparison, or outcome (PICO) in order to first determine whether an association existed and if it differed by funding source and employment. This approach precluded the use of a keyword search for identifying articles. The heterogeneity of the inclusion criteria made it difficult to identify overlapping or general search terms that could be used efficiently and guarantee adequate coverage of the related literature. When the subject matter is broad and there is little homogeneity in MeSH terms or related keywords, a keyword search introduces its own selection bias. The bias occurs when the keywords do not adequately characterize the material because of a lack of specificity and precision.[37] As an illustration of the inadequate coverage of appropriate articles, using a keyword search of MEDLINE based on very broad search terms that would result in overinclusion of potential manuscripts (''Environment'' or ''Occupation''; limited to 2012 in the journal Environmental Health Perspectives, clinical trials/meta analyses/evaluation studies), we only identified 97 articles of which 16 met our final inclusion criteria. In contrast, we identified 193 articles in Environmental Health Perspectives using the hand searching approached, of which 70 met the inclusion criteria and were included in the final analysis. On the basis of internal discussions as well as recommendations from various sources in the literature,[37] we chose to use the hand searching approach instead of keywords. Although there are drawbacks with this approach, it does address the more important limitation that a keyword search would have very poor specificity and precision, which we felt was the more critical issue because of the broad inclusion criteria.

Some degree of homogeneity is also critical for assessing study quality and bias. Although there are many instruments developed to assess methodological quality, they generally fall into two categories based on the study design: (1) instruments used for random controlled trials and (2) instruments for observational studies. We were unable to use a single instrument to assess study quality because our analysis included all types of study designs, and there is no evidence that the scoring methods are comparable across multiple instruments that assess study quality or bias. Furthermore, observational studies, in particular, frequently do not provide adequate descriptions of the methods. In our current study, this impacted our ability to comprehensively describe the selection criteria of cases, types of interviews, data collection procedures, nonresponse rates, type of follow-up or follow-back, and clinical documentation for health outcomes. However, through the inclusion of predominately top-tier journals in the field of environmental and occupational health for this analysis, we made the assumption that the rigor of the review process within these journals would ensure that the majority of studies included in the analysis met a certain level of acceptable study quality even if adequate descriptions of the methods were unavailable. The fact is that a broad keyword search would have potentially introduced another bias in the form of overinclusion of ''junk science'' published by some online journals through predatory publishing practices. The pay to play journals frequently have less rigorous peer review and COI reporting requirements, or simply none at all,[38] which would likely result in weakening the magnitude of the association primarily because of misclassification of COI. Furthermore, as was done in most other studies evaluating COI, we attempted to control for study quality through statistical modeling.

Manuscripts without reported financial COI were used as the reference group in this analysis. However, it cannot be determined whether these manuscripts are entirely without bias. Notwithstanding those that simply did not report financial relationships, the authors of these manuscripts may share similar views that could influence their interpretation of the results. This analysis only identifies reporting patterns among persons with financial COI, the direction, and magnitude of other types of COI are not analyzed in this study, but merit investigation in order to better describe the objectivity of scientific research.

It is possible that inclusion of different journals, years of publications, and the investigators involved in this project may have resulted in different conclusions. In addition, disagreement between the researchers of this study may have resulted in one reviewer's interpretation superseding the other, and biasing the results. In this study, disagreement between the reviewers on study results occurred in 14.2% of the manuscripts and disagreement on COI occurred in 9.6% of the studies. However, the disagreement was uncommon for negative findings (6.2% of manuscripts) and studies with financial COI of a corporate nature (11%). In two sensitivity models using the initial independent assessments of study results and financial COI by each investigator continued to show a strong association between negative findings and COI from organizations involved in the processing, use, or disposal of industrial and commercial products as well as the military (Rater1, adjusted OR = 4.54, 95% CI = 2.64 to 7.80; Rater2, adjusted OR = 4.00, 95% CI = 2.31 to 6.94), while associations with a financial COI relating to direct governmental control over policy and regulations continued to not be statistically significant.

CONCLUSIONS

Research does not occur in a vacuum and many research questions require substantial funding to adequately investigate them. Funding from the private sector should be a good thing, because, in theory, it provides access to resources and information not readily available from public sources and can catalyze highly creative interactions that promote and protect the public's health. However, financial relationships are clearly associated with the direction of reported scientific findings. There have been numerous articles written recently providing an array of recommendations to improve the quality of peer-reviewed research that help frame this discussion.[16,19,39] An initial step proposed to help to ensure transparency is the public release of all original deidentified datasets in order to allow for reassessment of analyses[40]; however, for some researchers, the public release of data may be prohibited.

Whatever the agreed upon solutions, they need to be adopted internationally. Environmental and occupational health research involves collaborations of different stakeholders from across the globe. Of the studies analyzed in this manuscript, 59.5% ($n = 222$ articles) of the primary authors resided in a country outside of the United States, and 33.0% ($n = 123$) of the studies had authors from two or more different countries. Much of the discussion of financial COI narrowly focuses on the countries of the authors; however, as is clearly demonstrated in this analysis, this is an international issue that requires international consensus in order to effectively manage financial COI.

REFERENCES

1. Steneck NH. Fostering integrity in research: definitions, current knowledge, and future directions. *Sci Eng Ethics*. 2006;12:53–74.
2. Angell M. *The Truth About the Drug Companies: How They Deceive Us and What to do About it.* Random House: Inc., New York; 2004.

3. Parascandola M. A turning point for conflicts of interest: the controversy over the National Academy of Sciences' first conflicts of interest disclosure policy. *J Clin Oncol*. 2007;25:3774–3779.
4. IOM (Institute of Medicine). *Conflict of Interest in Medical Research, Education, and Practice*. Washington, DC: The National Academies Press; 2009.
5. Thompson DF. Understanding financial conflicts of interest. *N Engl J Med*. 1993;329:573–576.
6. Kahn JO, Cherng DW, Mayer K, Murray H, Lagakos S. Evaluation of HIV-1 Immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 X106/L CD4 counts: a randomized controlled trial. *JAMA*. 2000;284:2193–2202.
7. Martinson BC. Institutions' expectations for researchers' self-funding, federal grant holding, and private industry involvement: manifold drivers of self-interest and researcher behavior. *Acad Med*. 2009;84: 1491–1499.
8. Stelfox HT, Chua G, O'Rourke K, Detsky A. Conflict of interest in the debate over calcium-channel antagonists. *N Engl J Med*. 1998;338:101–106.
9. Rochon PA, Gurwitz JH, Simms RW, et al. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med*. 1994;154:157–163.
10. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA*. 2003;289:454–465.
11. Davidson RA. Source of funding and outcome of clinical trials. *J Gen Intern Med*. 1986;1:155–158.
12. Flacco ME, Manzoli L, Boccia S, et al. Head-to-head randomized trials are mostly industry sponsored and almost always favor the industry sponsor. *J Clin Epidemiol*. 2015;68:811–820.
13. Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*. 2012;12:MR000033.
14. Roseman M, Milette K, Bero LA, et al. Reporting of conflicts of interest in meta-analyses of trials of pharmacological treatments. *JAMA*. 2011;305:1008–1017.
15. Friedman L, Richter ED. Relationship between conflicts of interest and research results. *J Gen Int Med*. 2004;19:51–56.
16. Okike K, Kocher MS, Mehlman CT, Bhandari M. Industry-sponsored research. *Injury*. 2008;39:666–680.
17. Rowe S, Alexander N, Clydesdale FM, et al. Funding food science and nutrition research: financial conflicts and scientific integrity. *Am J Clin Nutr*. 2009;89:1285–1291.
18. Shrader-Frechette K. Climate change, nuclear economics, and conflicts of interest. *Sci Eng Ethics*. 2011;17:75–107.
19. Baur X, Budnik LT, Ruff K, Egilman DS, Lemen RA, Soskolne CL. Ethics, morality, and conflicting interests: how questionable professional integrity in some scientists supports global corporate influence in public health. *Int J Occup Environ Health*. 2015;21:172–175.
20. Pickar JH. Conflicts of interest in government-funded studies. *Climacteric*. 2015;18:1–4.
21. Hardell L, Walker MJ, Walhjalt B, Friedman LS, Richter ED. Secret ties to industry and conflicting interests in cancer research. *Am J Ind Med*. 2007;50:227–233.
22. Melnick RL, Ward JM, Huff J. War on carcinogens: industry disputes human relevance of chemicals causing cancer in laboratory animals based on unproven hypotheses, using kidney tumors as an example. *Int J Occup Environ Health*. 2013;19:255–260.
23. ISI Web of Knowledge. Journal Citation Reports. Available at: http://admin-apps.webofknowledge.com.proxy.cc.uic.edu/JCR/JCR?PointOfEntry=Home&SID=3CgLeohQuVZAvW3b8qO. Accessed March 17, 2015.
24. International Committee of Medical Journal Editors. Uniform Requirements for Manuscripts Submitted to Biomedical Journals. 2004. Available at: http://www.icmje.org/. Accessed March 17, 2015.
25. Bhargava N, Qureshi J, Vakil N. Funding source and conflict of interest disclosures by authors and editors in gastroenterology specialty journals. *Am J Gastroenterol*. 2007;102:1146–1150.
26. Bosetti F, Toscano CD. Is it time to standardize ethics guiding the peer review process? *Lipids*. 2008;43:107–108.
27. Broome M, Dougherty MC, Freda MC, Kearney MH, Baggs JG. Ethical concerns of nursing reviewers: an international survey. *Nurs Ethics*. 2010;17:741–748.
28. Dyer O. Former journal editor had potential conflicts of interest in nine of 10 articles he authored. *BMJ*. 2014;349:g7589.
29. Gleicher N. Avoiding currently unavoidable conflicts of interest in medical publishing by transparent peer review. *Reprod Biomed Online*. 2013;26:411–415.
30. Grandjean P, Ozonoff D. Transparency and translation of science in a modern world. *Environ Health*. 2013;12:70.
31. Steinbrook R, Lo B. Medical journals and conflicts of interest. *J Law Med Ethics*. 2012;40:488–499.
32. Buchkowsky SS, Jewesson PJ. Industry sponsorship and authorship of clinical trials over 20 years. *Ann Pharmacother*. 2004;38:579–585.
33. Tong EK, Glantz SA. Tobacco industry efforts undermining evidence linking secondhand smoke with cardiovascular disease. *Circulation*. 2007;116: 1845–1854.
34. Schafer A. Biomedical conflicts of interest: a defence of the sequestration thesis-learning from the cases of Nancy Olivieri and David Healy. *J Med Ethics*. 2004;30:8–24.
35. Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B. Evidence b(i)ased medicine-selective reporting from studies sponsored by pharmaceutical industry: review of studies in new drug applications. *BMJ*. 2003;326: 1171–1173.
36. Wislar JS, Flanagin A, Fontanarosa PB, Deangelis CD. Honorary and ghost authorship in high impact biomedical journals: a cross sectional survey. *BMJ*. 2011;343:d6128.
37. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. *The Cochrane Collaboration*. Available at: www.cochrane-handbook.org. Accessed October 7, 2015.
38. Boumil MM1, Salem DN. In ... and out: open access publishing in scientific journals. *Qual Manag Health Care*. 2014;23:133–137.
39. Oleinik A. Conflict(s) of interest in peer review: its origins and possible solutions. *Sci Eng Ethics*. 2014;20:55–75.
40. Califf RM, McCall J, Harrington RA. Assessing research results in the medical literature: trust but verify. *JAMA Intern Med*. 2013;173: 1053–1055.

