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The Committee on Conflict of Interest in Medical Research, Education, and Practice, Institute of Medicine defined conflicts of interest (COIs) as "circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest."[1] Secondary interests may be personal, such as the pursuit of academic recognition, the desire to do favors for family members or colleagues and religious beliefs.[1,2] Secondary interests that are financial, however, have received a lot of attention because they have been recognized as the type of COI that can influence professionals the most, be quantified objectively and be regulated.[1,3]

In medicine, attention has been paid to the relationship between financial COIs and research results. Industry funding is associated with the reporting of significant pro-industry results,[4-6] and investigators in trials funded by for-profit

ABSTRACT

Background. The relationship between industry funding and study results has been explored widely in medicine but not in dentistry. The authors aimed to assess the relationship between conflicts of interest (COIs) and study results.

Methods. The authors assessed all randomized clinical trials (RCTs) published between July 2010 and June 2012 in the 10 dental journals with the highest impact factors in dentistry. The authors used three definitions of COI and explored their associations with positive study results.

Results. Depending on the definition of COI, the odds ratio for reporting positive results varied between 2.40 (95 percent confidence interval [CI], 1.16-5.13) and 9.19 (95 percent CI, 1.71-170.64). The authors found no association between positive study results and journal of publication or area of practice.

Conclusions. RCTs in which authors have some type of COI are more likely to have results that support the intervention being assessed.

Practical Implications. When reviewing the results of RCTs, clinicians need to be aware of the association between reporting positive study results and the type of COI disclosure and be even more careful when critically appraising and applying their results.

Key Words. Conflict of interest; randomized clinical trials; evidence-based dentistry.

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organizations are more likely to recommend the treatment being evaluated owing to a biased interpretation of the study results.[7] However, some studies' results have not shown these associations.[8,9]

On the other hand, to our knowledge in dentistry there is only one original study in which investigators examined this issue. This study was performed in the field of implantology, and its results showed that investigators in industry-funded trials reported lower rates of dental implant failures than did those in nonindustry-funded trials.[10] The study authors also found that potential COIs were reported in only 63 percent of the trials, which demonstrates the lack of attention that COIs have received in dental research.

Our aim was to determine whether there was an association between authors' COIs and the results of randomized clinical trials (RCTs) in dentistry by using different frameworks of the COI concept. We also explored whether this association was related to area of practice and journal of publication.

METHODS

We performed a systematic survey of the literature.

Search process and study selection. We used the 2011 release of Web of Knowledge's science edition of Journal Citation Report to identify the top 10 dental journals according to their 2011 impact factor. We conducted an electronic search in the PubMed database by using the filter "Randomized Controlled Trial [Publication Type]" to retrieve all RCTs published between July 1, 2010, and June 30, 2012, in the journals Periodontology 2000, Clinical Implant Dentistry and Related Research, Journal of Dental Research, Dental Materials, Journal of Clinical Periodontology, Journal of Dentistry, Journal of Endodontics, Oral Oncology, Oral Microbiology and Immunology, and Molecular Oral Microbiology. We included articles if their study designs met the following criteria[11]: the investigators studied interventions in human participants and allocated participants at random to receive one of several interventions being compared in terms of their effects on the presence or absence of events or outcomes. We included all RCTs with two or more arms, irrespective of the comparator used (either an active control or placebo), as long as the authors clearly identified an intervention and a control group. The authors performed title and abstract screening (C.U., J.V.), full-text screening (A.C.-L., C.U.) and data abstraction (R.B.-P., M.C.-O., N.Y., I.A., F.P.) independently and in duplicate by using standardized and piloted forms.

Assessment of study results. We classified the results of each RCT by using the framework proposed by Friedman and Richter,[4] in which we considered not only the statistical significance but also some clinical implications of the findings. Positive results were those in which investigators reported a statistically significant benefit ($P < .05$) or an absence of adverse effects ($P > .05$) of the intervention being assessed; the intervention being assessed was statistically equivalent to commonly used therapies; or the investigators reported that the comparator (competitive product) had no clinical benefits ($P > .05$) or had adverse effects. We considered results to be mixed if they showed both statistically significant clinical benefits and adverse effects. We considered the results to be negative if the investigators reported that the intervention being assessed had no clinical benefits ($P > .05$) or numerous adverse effects ($P < .05$).

Assessment of COI. We assessed the presence of COI by using the authors' disclosures in the manuscript according to the criteria used by Friedman and Richter[4] and the International Committee of Medical Journal Editors.[12] A broad COI includes "all financial relationships with companies whose products the researchers are evaluating in the manuscript."[4] A narrow COI includes financial relationships with the most severe examples of COI, such as consultancy, employment, stock ownership, patent licensing and honoraria.[12] In a commercial COI, the study must meet all the following criteria: one or more authors have financial associations with a private corporation or a personal financial interest; the product being studied is manufactured by the funding corporation; the product has current or near-future commercial potential; and the main study findings support the product, negate the value of a competitor's product, advocate a cost benefit or show a potential commercial value.[4]

Other variables of interest. We also collected data regarding journal of publication, area of practice, number of participants in the trial and the study's source of funding, which we classified as for profit (any company with the objective of developing products or interventions from which it can obtain financial gains), not for profit (such as government or related agency grants, foundation grants, funds from academic institutions and self-funding from authors) or not reported.

ABBREVIATION KEY. COI: Conflict of interest. **RCT:** Randomized clinical trial.

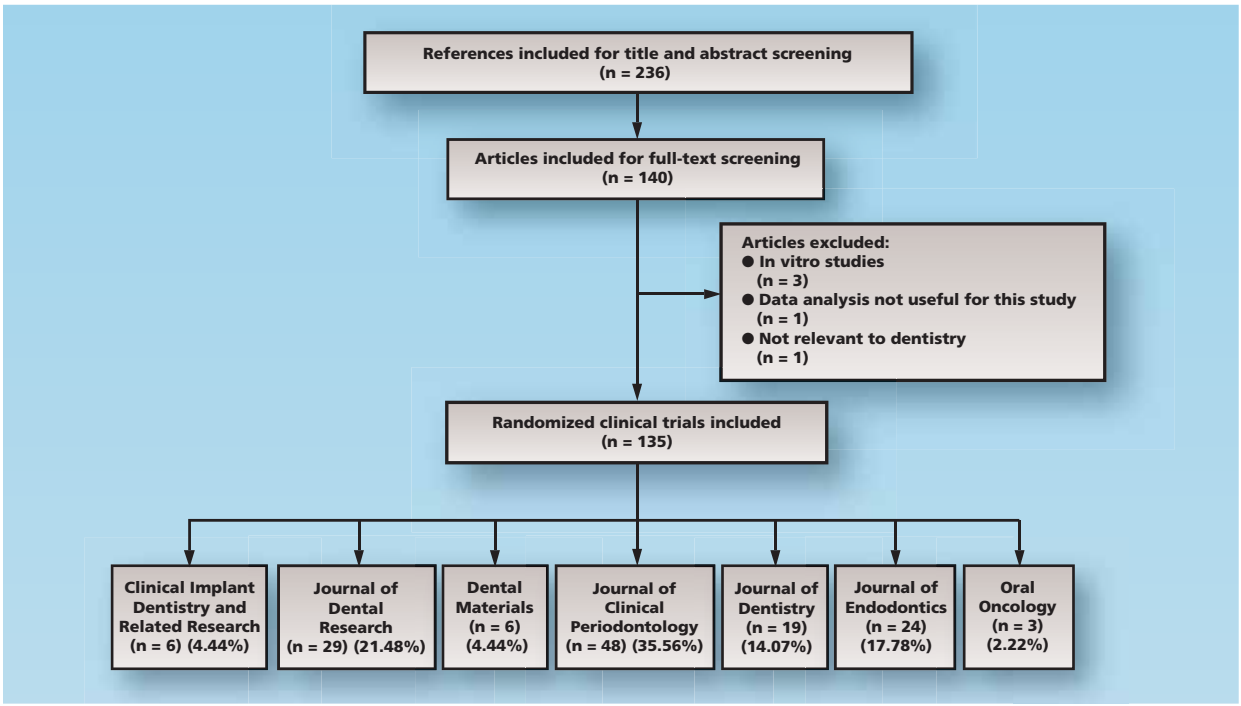

Figure. Flowchart showing the article selection process.

Statistical analysis. We used proportions as descriptive statistics. We also performed logistic regressions to assess the association between study results and COI, journal of publication, area of practice and source of funding. We combined mixed and negative results into one category. We also calculated corresponding odds ratios (ORs), 95 percent confidence intervals (CIs) and *P* values derived from χ^2 tests. We performed all analyses by using statistical software (R, Version 2.15.1, R Foundation for Statistical Computing 2011, Vienna).

RESULTS

Of the 236 references retrieved, 135 were RCTs, so we included them in our study. These RCTs were published in seven of the 10 journals. They were Clinical Implant Dentistry and Related Research, Journal of Dental Research, Dental Materials, Journal of Clinical Periodontology, Journal of Dentistry, Journal of Endodontics and Oral Oncology. The figure shows the article selection process.

In three of these journals (Dental Materials, Journal of Dentistry and Journal of Endodontics), COI reporting was not mandatory. These journals had 36.29 percent of the 135 RCTs, and in Journal of Endodontics, which had 17.78 percent of the 135 RCTs, authors declared COIs consistently. Journal of Clinical Periodontology and Journal of Dental Research accounted for 57.04 percent of the RCTs published (Figure), and RCTs with interventions relevant to general dentists and periodontists accounted for 65.18 percent of the total (Table 1). The median number of patients recruited in the trials was 44 (interquartile range, 28-84 patients). Among all RCTs, 37.03 percent had a source of funding we classified as for profit, 40.74 percent were funded by a not-for-profit organization, and 22.22 percent did not report any source of funding.

Investigators in 51 RCTs (37.78 percent) reported some type of COI. Table 2 shows the distribution of RCTs according to the COI definitions.[4,12] Among the areas of practice with the highest number of RCTs, periodontics had the highest proportion of any in which COI was reported (Table 3,[4,12] page 1169).

Overall, investigators in studies with broad COIs were more likely to report positive findings than were those in studies in which there were no COIs (Table 4,[4,12] page 1169). When the broad definition of COI was used, studies had 2.40 times the odds of reporting positive results than of reporting mixed or negative results. This association seemed to have bigger magnitudes when the narrow and commercial definitions for COI were used (Table 4[4,12]), although the confidence intervals of such magnitudes overlapped. All associations within COI categories were statistically significant ($P < .05$).

There was no association between broad COI

TABLE 1

RCT,* according to area of practice.

AREA OF PRACTICE	RCT, NO. (%)
Endodontics	12 (8.89)
Oral and Maxillofacial Pathology	2 (1.48)
Oral and Maxillofacial Surgery	5 (3.70)
Orthodontics and Dentofacial Orthopedics	6 (4.44)
Pediatric Dentistry	3 (2.22)
Periodontics	42 (31.11)
Prosthodontics	10 (7.41)
General Dentistry	46 (34.07)
Other	9 (6.67)

* RCT: Randomized clinical trial.

TABLE 2

Articles with reports of COIs,* according to COI definition.†

COI DEFINITION	TOTAL NO. OF ARTICLES	PERCENTAGE OF TOTAL (n = 135)	PERCENTAGE OF RANDOMIZED CLINICAL TRIALS WITH A COI (n = 51)
Broad	51	37.78	100.00
Narrow	15	11.11	29.41
Commercial	12	8.89	23.53

* COI: Conflict of interest.
† Sources: Friedman and Richter[4] and International Committee of Medical Journal Editors.[12]

and journal of publication ($\chi^2_8 = 7.73$; $P = .26$) or area of practice ($\chi^2_8 = 7.11$; $P = .52$); there was no evidence to claim that some journals or areas of practice were more likely to publish RCTs with broad COIs than with no COIs. Similarly, we observed no association when using the narrow definition of COI (journal of publication, $\chi^2_6 = 5.55$; $P = .48$ and area of practice $\chi^2_8 = 12.26$; $P = .14$). In other words, RCTs with narrow COIs were not more likely to be found in one journal or area of practice than were others. When we used the commercial definition of COI, we found no association between COI and journal of publication $\chi^2_8 = 3.20$; $P = .78$); however, we found a statistical association between COI and area of practice ($\chi^2_8 = 17.70$; $P = .023$) because there was a higher proportion of RCTs with commercial COIs in studies in the area of practice category "other" (44 percent as opposed to less than 11 percent found in all other areas of practice) (data not shown).

We also found no statistical association between the report of positive findings and the source of funding of the trial ($\chi^2_2 = 3.90$; $P = .14$ when considering the three categories of funding; $\chi^2_1 = 1.47$; $P = .23$ when considering only RCTs in which a clear source of funding was reported) (data not shown).

DISCUSSION

Our findings suggest that RCTs in which authors provided some type of COI were more likely to report results supporting the intervention being assessed. When COIs are defined as any type of relationship with the company whose product is being evaluated, the odds of reporting positive results relative to mixed or negative results was 2.40. When the COI definition was stricter—that is, either a severe example of COI such as consultancy or employment or a COI in which there is a potential for commercial profit—these odds were even higher.

We used three definitions of COI because, to date, there is not a widely accepted definition of COI. We chose to use the definitions used by Friedman and Richter[4] in the study they conducted to assess the association between COIs and study results in two of the most prestigious journals in medicine (The New England Journal of Medicine and The Journal of the American Medical Association), because these definitions covered a range of COIs (from any type of relationship with companies to strong ties to them). These definitions also addressed COIs related to a potential for commercial profit, which may be of particular interest in dentistry. In addition, Friedman and Richter's[4] study seems to be one of the few focused on COI as the concept of interest as opposed to the source of funding.

We consider that the approach of classifying study results as positive, mixed or negative on the basis of statistical significance and clinical implications is more appropriate than using only statistical significance as an indicator of a positive finding. For example, the results of an RCT could show that the intervention being assessed has both more statistically significant beneficial effects and adverse effects. If we were judging these results only on the basis of statistical significance, we could claim that these are positive results; however, from a clinical perspective these results would not support the use of the intervention because of its adverse effects, so the results could be considered mixed at best. The criteria we used for the classification (positive, negative, mixed) also allowed us to address cases in which an intervention

may have had effects similar to those of the comparator (statistical equivalence or no evidence of adverse effects). If such an intervention had other perceived benefits, such as lower costs, less burden or ease of administration, equivalence of benefits or safety would be enough to support the use of the intervention.

A surprising result was that the OR of reporting positive versus mixed or negative results was higher when we used the narrow definition of COI than when we used the commercial definition, contrary to what logic may suggest. We attribute this finding to the small number of trials in which both of these types of COI were found (15 trials with narrow COIs and 12 trials with commercial COIs), which made the estimates of the ORs imprecise. Table 4[4,12] shows that the lower boundary of the confidence interval of the OR of the association between narrow COI and positive results is lower than the point estimate of the OR of the association between commercial COI and positive results, which indicates that the magnitude of the former could be lower than that of the latter.

Another unexpected finding was the lack of evidence of an association between positive results and source of funding. Although we expected the source of funding to be correlated with the presence of COIs, we did not find this association, which may be because there was a high number of RCTs in which the authors did not report the source of funding. In addition, our definitions of COIs captured COIs from a broader perspective than did definitions of COIs arising only from funding the authors of a particular study reported in the article. This difference could explain the different results we found for the association between positive results and COI and positive results and source of funding.

To our knowledge, only one study with an aim similar to ours has been published in the dental literature.[10] The study's authors assessed the relationship between funding source and the reported failure rate of dental implants. They found that investigators in industry-initiated trials reported a lower annual implant failure rate than did those in nonindustry-associated trials. The overall annual failure rate was 1.09 percent (95 percent CI, 0.84-1.42), whereas for the nonindustry-funded trials the failure rate was 2.73 percent (95 percent CI, 1.14-6.55). Despite the differences in the study models and predictor and outcome definitions between their study and ours, the findings in both studies indicated that there was a positive association and went in the same direction.

TABLE 3

Articles with reports of COIs,* according to definition† and areas of practice with the highest numbers of randomized clinical trials.

COI DEFINITION	AREA OF PRACTICE, NO. (%) OF ARTICLES		
	General Dentistry (n = 46)	Periodontics (n = 42)	Endodontics (n = 12)
Broad	17 (36.96)	19 (45.24)	3 (25.00)
Narrow	6 (13.04)	5 (11.90)	0 (0)
Commercial	5 (10.87)	2 (4.76)	1 (8.33)

* COI: Conflict of interest.
† Sources: Friedman and Richter[4] and International Committee of Medical Journal Editors.[12]

TABLE 4

Association between different types of COIs*† and reporting of positive findings.

COI DEFINITION	ODDS RATIO	95% CONFIDENCE INTERVAL	*P* VALUE
Broad	2.40	1.16-5.13	.020
Narrow	12.25	2.35-225.49	.017
Commercial	9.19	1.71-170.64	.036

* COI: Conflict of interest.
† Sources: Friedman and Richter[4] and International Committee of Medical Journal Editors.[12]

Our study is a first attempt to assess the relationship between COI and study results in the whole field of dentistry, so it leaves many questions unanswered. Although the data we collected strongly support the existence of this relationship, the role of some confounding factors should be explored in future research. The role that the risk of bias may play in this relationship should be examined. In medicine, investigators in trials with higher risks of bias are more likely to overestimate treatment effects,[13] so these studies are more likely to yield positive results. However, results from a study in periodontology did not confirm this association.[14] If such an association exists, it would be interesting if investigators could determine whether risk of bias of RCTs in dentistry is associated with study results and COIs and if it affects the relationship between the two.

Another aspect relevant to our study was related to design bias. For example, investigators in trials in which a new intervention is compared with placebo are more likely to find positive results than are those in trials in which the comparator is an active agent. Therefore, investigators could choose a comparator that

increases their odds of finding positive results, such as placebo or a negative control (that is, an active intervention known to have a small effect or, in the case of a drug, a lower dose than the one commonly used). Whether this happens in RCTs in dentistry also should be studied.

Another phenomenon that might play a role in the association between positive findings and COIs is publication bias. The preference of journals and authors for publishing positive findings rather than negative ones is well known and documented, which could have biased our sample toward RCTs in which positive findings were reported.[15-17] Because investigators with commercial COIs might be more likely to publish only positive findings than are researchers with no industry ties, it is important to differentiate between COIs and positive findings and COIs and reports of positive findings. This latter association is the one we were able to assess.

The limitations of our study are related to the sample we chose. Although we reviewed 135 RCTs, these were drawn from only seven dental journals and within a specific time frame, which may lessen the generalizability of our findings. However, the systematic survey approach that includes studies from specific journals within a specific time frame balances generalizability and feasibility, and it has been used widely in articles regarding COIs and source of funding[5-8] as well as in articles involving assessment of methodology.[13,18,19]

The principles of evidence-based clinical practice state that the best evidence should be used for informing clinical decisions. When clinical decisions are related to an intervention, well-designed RCTs provide the highest level of evidence. Conducting such RCTs requires the use of resources that many times would not be available without corporate sponsorship. Therefore, rather than advocating for banning all relationships between researchers and industries, our results highlight the need for regulating such relationships. Before the trial starts, signing agreements with sponsors to guarantee the independence of the research team regarding the interpretation of the results and in the writing of the article may be of help. All dental journals should require disclosure of any potential COIs and all sources of funding and sponsorship. We also encourage clinicians to appraise a study even more critically and carefully when a COI is reported. Besides assessing the main study aspects pertaining to risk of bias, readers should try to interpret the results themselves and avoid reaching conclusions on the basis of interpretations that may be misleading owing to COI.

CONCLUSIONS

RCTs in which any author has any type of COI are more likely to have findings that support the intervention being assessed. When the COIs reported are severe (for example, narrow or commercial COIs as opposed to broad COIs), the association between COI and positive study results seems to be even stronger. When reviewing RCT results, clinicians need to be aware of the association between reporting positive study results and the type of COI disclosure and should exercise caution when appraising and applying these results. ■

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