Publication Bias and Its Implications for Evidence-Based Clinical Decision Making

John M. Crawford, B.D.S., Ph.D.; Charlotte L. Briggs, Ph.D.; Christopher G. Engeland, Ph.D.

Abstract: In this review, we define and discuss several aspects of publication bias: why it occurs; its importance to dental practitioners, dental educators, and dental students; its potential to affect treatment decisions; and how it can be detected. In addition, we briefly discuss attempts to reduce publication bias. Ideally, clinical decision making should be based on the totality of evidence and not on a sample biased by the selective publication of studies that show significant results. Dentistry increasingly depends on evidence-based decision making for treatment planning and therapy. As a result we, as a profession, need to fully appreciate the potential for publication bias to hinder advancements in oral health care by decreasing the availability of scientific evidence and threatening the validity of evidence-based practice.

Dr. Crawford is Professor of Clinical Periodontics, Department of Periodontics; Dr. Briggs is Director of the Office of Dental Education; and Dr. Engeland is Assistant Professor, Department of Periodontics—all at the College of Dentistry, University of Illinois at Chicago. Direct correspondence and requests for reprints to Dr. John M. Crawford, Department of Periodontics, College of Dentistry, University of Illinois at Chicago, 801 South Paulina Street, Chicago, IL 60612; 312-996-1266 phone; 312-996-0943 fax; jimmy@uic.edu.

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Scientific evidence is an increasingly important component of dental education and practice. As described by Winning et al.,[1] evidence-based oral health care includes the search for the best evidence, critical evaluation of the evidence, and integration of the evidence with the practitioner's experience and expertise. Therefore, dental educators, dental students, and dental practitioners need to be aware of the uncertainties surrounding scientific evidence, the ways that the results of clinical studies are collected and analyzed, and the importance of unbiased research on which to base clinical decision making. The most powerful and increasingly used analytic tool for summarizing the results and conclusions of clinical research is the systematic review, particularly those employing meta-analysis (see Petrie et al.[2] for review). For example, entering the MESH terms "periodontitis" or "dental caries" in the PubMed database and limiting the search to meta-analysis retrieved increasing numbers of publications in five-year increments from 1989 through 2008 (Table 1). However, meta-analyses can only be valid if the studies included in the review represent the complete body of research and are not biased in such a way that conclusions misrepresent the effectiveness and/or safety of clinical interventions. For meta-analyses to be valid and useful guides to clinical decision making, four conditions must be satisfied: 1) there are enough internally valid studies to analyze; 2) the strategy employed in searching for studies to include in the meta-analysis is rigorous enough to find all the relevant studies; 3) the studies included in the analysis are an unbiased representation of the research in the field; and 4) the studies focused on the research question are sufficiently homogeneous methodologically and clinically to permit their integration. If this is not the case—that is, if the published studies are biased with respect to the total (published and unpublished) studies—publication bias exists and the conclusions of the review may be invalid.

Table 1. Frequency of meta-analyses related to MESH terms "periodontitis" and "dental caries" in five-year increments in the PubMed database, 1989–2008

Publication Period	Periodontitis	Dental Caries
2004–08	43	32
1999–2003	24	30
1994–98	6	12
1989–93	4	10

Note: Database accessed on April 6, 2009.

In this article, we discuss the following questions: What is publication bias? Why does publication bias occur? Is publication bias a significant concern? How is publication bias detected? How can publication bias be reduced? The answers to these questions present a challenge not only to dental researchers, authors, and journal editors, but also to dental educators who must prepare graduates to evaluate dental literature through the evidence-based dentistry (EBD) process.

What Is Publication Bias?

Hypothesis testing—and, more specifically, rejecting or failing to reject the null hypothesis—is a central concept in testing the significance of differences between groups of subjects. In this article, publications that report data associated with rejection of the null hypothesis will be referred to as "positive" studies, and publications reporting data associated with failure to reject the null hypothesis will be referred to as "negative" studies. In 1959, Sterling[3] pointed out that 97 percent of the articles that used tests of significance rejected the null hypothesis. He concluded, "There is some evidence that, in fields where statistical tests of significance are commonly used, research which yields non-significant results is not published."

As defined by Møller and Jennions,[4] publication bias occurs whenever the strength or direction of the results of published and unpublished studies differs. In practice, published studies tend to report research that has significant results, while studies with nonsignificant findings are more likely to remain unpublished. Some reasons for publication bias are benign and others are duplicitous, but, whatever the cause, publication bias has the potential to reduce the quality and safety of health care outcomes. As Johnson and Dickersin[5] eloquently state, "The consent form approved by the institutional review board did not have an escape clause stating that if the investigator is not excited by the results he or she can 'toss them out.' We make a covenant with the human volunteers who agree to take pills of undefined toxicity, or spend months swallowing placebos, or submit to serial blood lettings or lumbar punctures that what we learn will benefit society." Unpublished studies waste resources when they are repeated. Possibly more importantly, experiments may be repeated until, by chance, positive results are obtained and published. The essential problem, therefore, is that publication bias can prevent data of potential importance from reaching practicing health care providers.

There is little published research on publication bias in the dental literature other than Scholey and Harrison,[6] Moradi et al.,[7] and Needleman et al.[8] Scholey and Harrison[6] briefly reviewed publication bias to raise the awareness of the dental research community to this potential problem. They conclude, "The level of publication bias and time lag to publication appear to be the same in dentistry as in medicine."

Systematic reviews in the dental literature are beginning to include tests for publication bias, and it is therefore timely to review, in some depth, the subject of publication bias and its importance for dental education and practice.

Why Does Publication Bias Occur?

Several authors have discussed the various factors that contribute to publication bias. In this section, we briefly review those factors that have had a demonstrable impact on failure to publish or delayed publication of clinical research studies. A common reason for failure to publish is that investigators have not submitted the paper for publication: "submission bias" or the "file drawer effect." A number of studies strongly suggest that studies "left in the file drawer" are likely to be those that do not show a positive result. Scherer et al.[9] have thoroughly investigated the literature on publication bias, and in their most recent review, they summarized the findings of seventy-nine reports involving 30,394 abstracts that investigated full publication after abstract presentation at scientific meetings. Their overall conclusion was that only about 50 percent of studies first presented as abstracts are published in full. Moreover, studies that show a significant effect of the experimental treatment or have significant results are more likely to be published in full.

Turner et al.[10] compared U.S. Food and Drug Administration (FDA) reviews of twelve antidepressant drugs and searched the literature for published studies derived from the trials submitted to the FDA. They concluded that there was a significant bias favoring publication of positive results compared to negative results and the FDA reviews that were negative were often published in a way that conveyed a positive outcome. Corry[11] examined a random

selection of abstracts at the 1983 and 1984 International Association for Dental Research/American Association for Dental Research (IADR/AADR) meetings and determined that less than 25 percent of the abstracts were subsequently published as articles. Similar results were obtained by Dahllöf et al.[12] when they analyzed the publication rate of abstracts presented at the 1999 and 2001 International Association of Paediatric Dentistry congresses. They were able to find evidence of publication of only 27 percent of 771 abstracts in Medline/PubMed indexed journals between 1999 and 2006, although the publication rate of oral presentations was 40 percent.

The work of Dickersin[13,14] suggests that rejection by journals of studies with negative results is a relatively small contribution to publication bias and the larger contribution is attributable to authors who did not write up and submit research for publication. When authors were contacted to determine the reasons for failure to submit research for publication, they cited "uninteresting or negative results," operational problems with writing the manuscript, and the claim that publication was not the aim.[13] Sprague et al.[15] retrieved all abstracts from the 1996 annual meeting of the American Academy of Orthopaedic Surgeons and determined how many had been published six years later. They found that 35.7 percent had not been submitted for publication. When these investigators were contacted about the reasons for nonpublication, the most common reasons they gave were lack of time to prepare the paper for publication, the study was ongoing, and another author was responsible for writing the manuscript. Lack of time was also cited as the main reason for failure of investigators to submit manuscripts for publication after presentation at the 1991 Society for Academic Emergency Medicine meeting.[16] Lack of time may be of particular importance for publication bias, as given time constraints, it seems likely that positive results will be prioritized over negative results for publication submission. Misakian and Bero[17] investigated the median time to publication of sixty-one studies on passive smoking conducted between 1981 and 1995 and found that it was three years for statistically significant studies and five years for statistically nonsignificant studies. The reasons given by investigators for unpublished results were ongoing data collection or analysis, lack of time, and competing priorities.

Song et al.[18] recently conducted a meta-analysis to determine the strength and consistency of the association between study results and formal publication. They categorized studies into four types according to when they began tracking research as it moved toward publication or dropped out of the process: 1) at study inception, 2) when submitted to a regulatory agency, 3) when submitted as conference abstracts, and 4) when manuscripts were submitted to journals. Their pooled odds ratios for the publication of studies with positive results ranged from 2.78 for studies followed from their inception to 1.06 for studies followed from the time of manuscript submission. They concluded that publication bias does exist and it occurs early in the path towards submission to journals. These findings, therefore, support the conclusions of Dickersin[13,14] and Sprague et al.[15]

Journal editors and reviewers have also contributed to publication bias. In 1998, Egger and Smith[19] quoted a comment in the "Instructions for Authors" section of the journal *Diabetologia*: "mere confirmation of known facts will be accepted only in exceptional cases; the same applies to reports of experiments and observations having no positive outcome." However, attitudes may be changing, because the same journal now says: "And remember—a negative answer to an interesting question is more important than a positive answer to a boring question." Encouragingly, nine of the top ten (non-review) medical journals now refer authors to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals." Under a section entitled "Obligation to Publish Negative Studies," it is stated: "Editors should consider seriously for publication any carefully done study of an important question, relevant to their readers, whether the results for the primary or any additional outcome are statistically significant. Failure to submit or publish findings because of lack of statistical significance is an important cause of publication bias."

More insidiously, a number of studies have demonstrated that industry-supported research is more likely to present positive results than research funded from non-industry sources. For example, Bekelman et al.[20] in a systematic review and meta-analysis of thirty-seven articles investigating the extent, impact, and management of conflicts of interest in biomedical research found that industry sponsorship was very strongly associated with pro-industry conclusions (odds ratio >3.60, 95 percent confidence interval: 2.63–4.91). These findings were supported by Ridker and Torres,[21] who carefully analyzed randomized cardiovascular trials published in *JAMA*, *The Lancet,* and the *New England Journal of Medicine* between 2000 and 2005. They found that the proportion of studies favoring newer treatments

over the standard of care was significantly higher in trials funded by for-profit organizations compared with trials funded by not-for-profit organizations. Lee et al.[22] identified all new drugs approved by the FDA between January 1998 and December 2000 and then identified the clinical trials submitted to the FDA by the sponsor. They then searched for original research reports in full journal articles as evidence of publication. They found that 57 percent of all trials for the approved drugs remained unpublished 5.5 years after approval. This study also found strong evidence that trials with significant results were approximately three times more likely to be published than studies with non-significant results ($p<0.001$).

Another form of publication bias occurs when published studies selectively report on outcomes that are detailed in the study protocols. This has been called "outcomes bias."[23] For example, Chan et al.[23] compared the outcomes detailed in the forty-eight trial protocols approved for funding by the Canadian Institutes of Health Research with those reported in journal articles describing the research. They found incomplete reporting in 31 percent of efficacy outcomes and 59 percent of harm outcomes. Their investigation also found that 73 percent of significant outcomes were fully reported but only 50 percent of the non-significant outcomes. Rising et al.[24] studied new drug applications from 2001 to 2002 and compared them with their corresponding published clinical trials. These researchers found that one-quarter of the primary outcomes and 47 percent of the outcomes that did not favor the new drug were absent in the published articles. One explanation for these findings is that studies funded by for-profit companies that fail to demonstrate a positive outcome for the company's product are not published.

Is Publication Bias a Significant Concern?

Drug companies have obvious financial interests in how their products are presented in research publications. Selection of which trials or parts of trials are published is one way to present the product in a more favorable light and thereby affect clinical decision making. But can this form of publication bias cause harm to patients? Turner et al.[10] compared published studies of twelve antidepressants with the FDA reviews of the same drugs and found that the effect size of each of the twelve drugs studied was significantly greater in the published articles compared with the FDA reviews. They state, "By altering the apparent risk-benefit ratio of drugs, selective publication can lead doctors to make inappropriate prescribing decisions that may not be in the best interest of their patients and, thus, the public health." Whittington et al.[25] came to similar conclusions when they compared the risks and benefits of selective serotonin reuptake inhibitors in the management of depression in children: for two of the drugs—Sertraline and Paroxetine—inclusion of unpublished data changed the risk/benefit ratio so that the risks outweighed the benefits of the drugs. Simes[26] compared the survival impact of treating patients with advanced ovarian cancer with an alkylating agent and combined chemotherapy. When the analysis was limited to published reports, a significant survival advantage was found for the combined chemotherapy. However, when the analysis pooled registered trials, no significant difference was found between the two regimens.

The well-publicized problems with the nonsteroidal anti-inflammatory drug Vioxx (Rofecoxib) have been documented in the medical literature[27] and the lay press.[28] Psaty and Kronmal[27] reviewed documents from Merck that became available in litigation proceedings and found that the company had failed to provide mortality analysis from pooled data from two trials in a timely way and thereby minimized the appearance of the risk of mortality from myocardial infarction for patients taking this drug. Graham et al.[29] estimated that 88,000 to 140,000 excess cases of serious coronary heart disease probably occurred in the United States over the market-life of Rofecoxib. Merck withdrew this drug from the market worldwide in September 2004. This episode illustrates the inherent conflict between a pharmaceutical company's role as a product manufacturer, distributor, and seller and its responsibility to the public to provide unbiased information about its products' safety and effectiveness.

How Is Publication Bias Detected? How Can It Be Reduced?

The use of tests to assess publication bias in meta-analyses in peer-reviewed journals has grown significantly over the past decade.[30] This, in part, is driven by statements and guidelines on the conduct

of meta-analyses such as the QUOROM (Quality Of Reporting Of Meta-analyses) statement[31] and the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) guidelines,[32] both of which call for the use of tests to determine bias. Several publications have described the various methods used to detect publication bias.[4,30,33,34] The best-known test is the funnel plot in which studies are plotted with the *y* axis denoting some measure of the sample size (for example, the standard error) and the *x* axis denoting a measure of the effect size (for example, the log odds ratio).[35] In the absence of publication bias, the plot resembles a symmetrical inverted funnel with a wide dispersion of studies with small sample size and a narrower dispersion for large sample size. However, asymmetry in the funnel due to the absence of small studies with small effect sizes (Figure 1) suggests the presence of publication bias. Advocates of bias-free reporting generally agree that authors of meta-analyses should be responsible for investigating the potential for publication bias.[4,30]

Since publication bias occurs when published data is not representative of all research data in the field, requiring that all research data (positive and negative) be made freely available to other researchers and the public would, in theory, eliminate publication bias. One way to achieve this ideal in medical research would be to make all clinical trials available for public scrutiny when they are planned or approved by the ethics or institutional review boards. In 1974, Mary Lasker, the American health activist, suggested that the National Cancer Institute publish a register of cancer treatment protocols and update it every six months.[36] Her objective was to enable physicians to identify trials for their patients to enroll in, but over the next thirty years her idea has been expanded, notably by Chalmers,[37] to include clinical trials in all areas of patient care. In 1997, the FDA Modern-

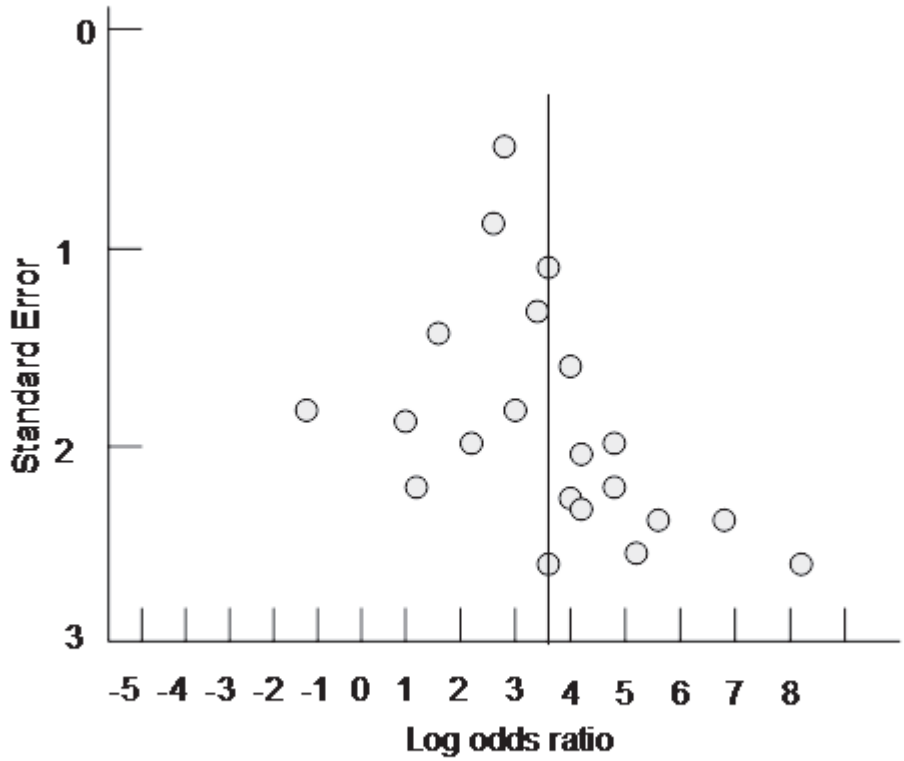

Figure 1. Example of a funnel plot that may indicate publication bias

Note: A funnel plot of twenty-one studies showing asymmetry about the effect size (vertical line), suggesting that smaller studies with small (or negative) effect studies are "missing" in the lower left of the inverted "funnel." "Missing studies" may be due to publication bias.

ization Act required the Department of Health and Human Services, through the National Institutes of Health, to establish a registry of clinical trials for both federally and privately funded trials "of experimental treatments for serious or life-threatening diseases or conditions." In 2005, the International Committee of Medical Journal Editors (ICMJE) began requiring investigators who wished to publish the results of trials in their member journals to enter information about the design of the trial in an approved publicly accessible database before patient enrollment. Public dissatisfaction with biased reporting of safety issues surrounding Vioxx led to the drug's withdrawal from the market and stimulated the U.S. Congress to introduce companion bills in the House and Senate. These bills aim to create a mandatory public electronic database of clinical trials administered by the federal government that will meet the minimum criteria for a trial registry set by the ICMJE and will include "all publicly and privately funded clinical trials involving drugs, biological products, or devices regardless of the outcome of the trial" (Fair Access to Clinical Trials Act of 2004[38]). The latest version of this bill was referred to committee in January 2007.

Concluding Remarks

Health care professionals can access evidence on which to base clinical decision making from a variety of sources. How they do so is not well documented. One common source is the Clinical Practice Guideline (CPG). CPGs, some of which are available in the National Guideline Clearinghouse (www.guideline.gov), are published by many discipline-based organizations. Although CPGs may be the result of deliberations by expert panels, the more authoritative ones are based on systematic reviews of randomized clinical trials,[39,40] such as those included in the Cochrane Collaboration. However, it should be noted that some investigators have expressed reservations about overreliance on meta-analysis in clinical decision making.[41-43] Bailar, in an editorial in the *New England Journal of Medicine,*[41] points out the many difficulties in conducting meta-analyses so they produce valid conclusions—particularly when the meta-analyses reduce the results to a single value with confidence intervals. One dilemma is whether to accept the conclusions of a single, large, well-conducted randomized controlled trial (RCT) or a meta-analysis on the same topic if they arrive at discrepant conclusions. LeLorier et al.[42] compared the results of twelve large RCTs (involving 1,000 patients or more) with the results of meta-analyses published earlier on the same topic. They found that the outcomes of the RCTs were not predicted accurately 35 percent of the time by the meta-analyses. Reasons for the discrepancies included publication bias, the inappropriate combination of heterogeneous studies in meta-analyses, and differing meta-analytic premises, inclusion criteria, or outcome measures.

As discussed above, nine of the top ten medical journals ranked by impact factor encourage the submission of important negative scientific findings (although this is done by referring authors to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," published by the ICMJE at www.icmje.org). However, as of January 2010, only two of the top ten similarly ranked dental journals offer any encouragement for the submission of negative research findings or require authors to conform to those uniform requirements. We therefore challenge dental research journals to help reduce publication bias by encouraging the submission of articles of high quality and interest to the oral health community that report negative findings. Ideally, this should be done in a direct statement in the instructions to authors and instructions to reviewers, indicating that the submission of important negative findings will be given full consideration by the journal or, at the least, by referring authors to the ICMJE uniform requirements.

We also encourage those responsible for EBD instruction in dental schools and continuing education programs to discuss publication bias as an important threat to scientific validity. The sophistication by which dental practitioners can judge the rigor and validity of systematic reviews and weigh them in treatment decisions may be significantly shaped by the EBD instruction they receive in dental school. Such instruction should also increase expectations from the "consumers" of dental literature, thereby increasing the demand that publication bias be routinely assessed in reviews and diligently avoided by researchers and journal editors.

By the statements we make and the examples we cite in this publication, we do not intend to imply that publication bias undermines the principles of evidence-based decision making or provides a rationale for empirical decision making. We firmly believe that evidence-based dentistry is a movement that has significantly improved (and will continue to improve) the quality of dental education and practice.

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