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CHAPTER 1

Publication Bias in Meta-analysis

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PUBLICATION BIAS AS A THREAT TO VALIDITY

Publication bias is the term for what occurs whenever the research that appears in the published literature is systematically unrepresentative of the population of completed studies. Simply put, when the research that is readily available differs in its results from the results of *all* the research that has been done in an area, readers and reviewers of that research are in danger of drawing the wrong conclusion about what that body of research shows. In some cases this can have dramatic consequences, as when an ineffective or dangerous treatment is falsely viewed as safe and effective. This can be illustrated by two events that received much media attention as this book was going to press in late 2004. These are the debate surrounding Merck's recall of Vioxx, a popular arthritis drug (Merck maintained that it recalled Vioxx as soon as the data indicated the high prevalence of cardiovascular events among those who took Vioxx for more than 18 months, while media reports said that Merck hid adverse event evidence for years), and the use of selective serotonin reuptake inhibitor (SSRI) anti-depressants among adolescents (Elliott Spitzer, attorney general of New York State, filed a 2004 lawsuit against GlaxoSmithKline,

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01 charging that they had concealed data about the lack of efficacy and about the
02 increased likelihood of suicide associated with the use of Paxil for childhood and
03 adolescent suicide). In most cases, the causes of publication bias will not be as
04 clear, nor the consequences as serious as in these examples. Nevertheless these
05 examples highlight why the topic is critically important.

06 Publication bias is a potential threat in all areas of research, including qualitative
07 research, primary quantitative studies, narrative reviews, and quantitative reviews,
08 that is, meta-analysis. Although publication bias has likely been around for as
09 long as research has been conducted and reported, it has come to prominence in
10 recent years largely with the introduction and widespread adoption of the use of
11 systematic review and meta-analytic methods to summarize research. In part, this
12 is because, as methods of reviewing have become more scientific and quantitative,
13 the process of reviewing (and synthesizing) research has been increasingly seen as
14 paralleling the process of primary research. Parallels to the threats to the validity
15 of primary research have been uncovered at every step of the systematic review
16 process (Cooper, 1998; Shadish *et al.*, 2002). Furthermore, as methods of reviewing
17 have become more systematic and quantitative, it has been possible to empirically
18 demonstrate the existence of publication bias and to quantify its impact. Thus, a
19 problem that was viewed hazily through the looking glass of traditional reviews
20 came into sharp focus under the lens of meta-analysis.

21 In meta-analysis, publication bias is a particularly thorny issue because meta-
22 analysis has been put forward as providing a more accurate appraisal of a research
23 literature than is provided by traditional narrative reviews (Egger *et al.*, 2000), but
24 if the sample of studies retrieved for review is biased, then the validity of the results
25 of a meta-analytic review, no matter how systematic and thorough in other respects,
26 is threatened. This is not a hypothetical issue: evidence that publication bias has
27 had an impact on meta-analyses has been firmly established by several lines of
28 research (see Chapters 2 and 10 of this volume).

29 Since systematic reviews are promoted as providing a more objective appraisal
30 of the evidence than traditional narrative reviews, and since systematic review
31 and meta-analysis are now generally accepted in many disciplines as the preferred
32 methodology for summarizing a literature, threats to their validity must be taken
33 very seriously. Publication bias must be taken especially seriously, as it presents
34 perhaps the greatest threat to the validity of this method. On the other hand, the
35 vulnerability of systematic review and meta-analysis to publication bias is not an
36 argument against their use, because such biases exist in the literature irrespective
37 of whether systematic review or other methodology is used to summarize research
38 findings. In fact, we suggest that the attention given to objectivity, transparency and
39 reproducibility of findings in systematic reviews and meta-analyses has led to the
40 first serious attempt to confront the problems that have always existed because of
41 publication biases, and to ameliorate them. As demonstrated by this volume, there
42 are now several tools available with which meta-analysts can assess the potential
43 magnitude of bias caused by selective publication. When the potential for severe
44 bias exists in a given analysis, this can now be identified, and appropriate cautionary
45 statements about the meta-analytic results can be made. When potential bias can
46 effectively be ruled out, or shown not to threaten the results and conclusions

01 of a meta-analysis, the validity and robustness of these results and conclusions
02 are strengthened.

03 Publication bias was originally defined as the publication or non-publication of
04 studies depending on the direction and statistical significance of the results, and
05 the first systematic investigations of publication bias focused on this aspect of the
06 problem. However, as readers will appreciate as they work through the book, there
07 are numerous potential information suppression mechanisms that go well beyond
08 the simple definition given above, including: language bias (selective inclusion of
09 studies published in English); availability bias (selective inclusion of studies that
10 are easily accessible to the researcher); cost bias (selective inclusion of studies that
11 are available free or at low cost); familiarity bias (selective inclusion of studies
12 only from one's own discipline, and outcome bias (selective reporting by the author
13 of a primary study of some outcomes but not others, depending on the direction
14 and statistical significance of the results). All of these biases lead to the same
15 consequence, namely that the literature located by a systematic reviewer will be
16 unrepresentative of the population of completed studies; hence all present the same
17 threat to a review's validity. For this reason, it has been suggested that a single,
18 broadly encompassing term, dissemination bias (Song *et al.*, 2000), be used to refer
19 to the problem. We agree with this sentiment, but the widespread and established
20 use of the term publication bias has made us hesitant to tamper with, and potentially
21 confuse, the current terminology. Readers should bear in mind that when they
22 read 'publication bias' the broader but more cumbersome 'publication bias and
23 associated dissemination biases' is implied.

24 25 ORGANIZATION OF THE BOOK

26
27 The book is split into three parts, and there are three appendices. Part A contains a
28 set of chapters which together provide a non-technical introduction to publication
29 bias and describe how it can be minimized in future research. Part B presents
30 each of the currently available methods for assessing or adjusting for publication
31 bias in a meta-analytic context; these chapters also illustrate each method using
32 the data sets described in Appendix A. The chapters in Part C discuss several
33 advanced and emerging issues that have not yet received much attention elsewhere
34 in the literature. Finally, Appendix B is an annotated bibliography that provides
35 illuminating further reading on publication bias; it is presented in chronological
36 order to allow the reader to see how the field has developed over time. While we
37 have attempted to compile and edit the book so that the chapters are integrated
38 (with as much detailed cross-referencing of chapters as possible), we believe that
39 each chapter can stand on its own. A more detailed outline of the contents of each
40 section of the book is given below.

41 42 43 Outline of Part A

44
45 In Chapter 2, Kay Dickersin begins with a thoughtful review of the causes and
46 origins of publication bias, after which she presents a comprehensive overview

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01 of the history and findings of publication bias research. Her chapter concludes
02 with some suggestions for minimizing publication bias in the future, which are
03 elaborated upon in Chapter 3 by Jesse Berlin and Davina Gherzi. These authors
04 propose two strategies which, if widely adopted, would go a long way towards
05 alleviating publication bias in trials-based research areas. The first is prospective
06 registration of clinical trials, which would create an ‘unbiased sampling frame
07 for subsequent meta-analyses’. As Berlin and Gherzi point out, however, to avoid
08 publication bias, this would need to be coupled with open access to the results of
09 these trials. The second is prospective meta-analysis, whereby multiple groups of
10 investigators conducting ongoing trials agree, prior to knowing the results of their
11 studies, to combine their findings when the trials are complete. In a variant of this
12 strategy, the meta-analysis is *designed* prospectively to standardize the instruments
13 used to measure specific outcomes of interest across studies. In Chapter 4, Sally
14 Hopewell, Mike Clarke and Sue Mallett describe how to minimize publication bias
15 by attempting to locate and retrieve grey and unpublished literature. They also point
16 out the problems associated with the retrieval and inclusion of this literature, namely
17 that it is time-consuming and difficult, and that its methodological quality can be
18 hard to assess. They conclude by suggesting criteria for weighing the potential
19 benefits and costs of grey literature searches.

21 **Outline of Part B**

22
23 Despite the excellent suggestions made in Chapters 3 and 4, it is safe to say that
24 publication bias will remain a problem in many disciplines for the foreseeable
25 future. The second part of this book presents several statistical methods that have
26 been developed to identify, quantify and assess the impact of publication bias
27 on meta-analyses. Essentially three kinds of techniques have been developed to
28 help analysts deal with publication bias in meta-analysis. One set of techniques
29 is designed to detect publication bias. This set of techniques includes graphical
30 diagnostics such as the funnel plot and explicit statistical tests for the statistical
31 significance of publication bias. In Chapter 5, Jonathan Sterne, Betsy Becker and
32 Matthias Egger define funnel plots and demonstrate how they can be used as a
33 graphical tool to for the investigation of publication bias. Specific issues discussed
34 in this chapter are the effects of choice of axes for these plots, and the need to
35 consider explanations in addition to publication bias for funnel plot asymmetry. In
36 Chapter 6, Jonathan Sterne and Matthias Egger describe and illustrate two statistical
37 tests for funnel plot asymmetry, the Begg and Mazumdar (1994) non-parametric
38 test based on the rank correlation between intervention effect estimates and their
39 sampling variances, and the Egger *et al.* (1997) regression method, which tests for a
40 linear association between the intervention effect and its standard error. Sterne and
41 Egger also provide information about the power of these tests, and caution against
42 their use when a meta-analysis contains only a small number of studies.

43 The second set of techniques is designed to assess the sensitivity of conclusions
44 of an analysis to the possible presence of publication bias. Chapter 7, by Betsy
45 J. Becker, describes and illustrates the first statistical method developed for the
46 assessment of publication bias, file-drawer analysis, originally described by Robert

01 Rosenthal (1979). This method has been commonly referred to as the failsafe N ,
02 a term coined by Harris Cooper (1979). Becker also reviews other approaches to
03 file-drawer analysis, including one that was intended to overcome some of the
04 limitations of the original. Her conclusion is that all of these methods should be
05 abandoned in favour of the more sophisticated methods described in the other
06 chapters in this part of the book.

07 The third set of techniques is designed to adjust estimates for the possible
08 effects of publication bias under some explicit model of publication selection. In
09 Chapter 8, Sue Duval describes trim and fill, a method that she and the late Richard
10 Tweedie developed to estimate and adjust for the number of missing studies (due
11 to publication bias) in a meta-analysis. The trim and fill method is illustrated using
12 a detailed worked example, in addition to its application to the three common data
13 sets used throughout Part B. Chapter 9, by Larry Hedges and Jack Vevea, explicates
14 the general selection model approach to the assessment of publication bias, and
15 demonstrates how it is used to correct for bias. The authors show how their method,
16 as well as that of John Copas, can be used to detect and correct for bias in the three
17 common data sets used throughout the book. As the reader will see, trim and fill is
18 relatively simple to implement and involves relatively little computation, while the
19 Hedges–Veeva and Copas methods involve considerable computation.

20 In Chapter 10, Alex Sutton summarizes the results of empirical investigations
21 that have been carried out to assess the extent of publication bias present in various
22 scientific literatures, using the methods described earlier in Part B. He concludes on
23 the basis of these results that publication bias assessment should become a routine
24 part of every meta-analysis. In Chapter 11 Michael Borenstein discusses a number
25 of computer programs that can be used to address publication bias, and shows how
26 these would be used to apply the statistical procedures discussed throughout this
27 volume. This chapter should be of great practical value for any researcher who
28 wishes to investigate whether publication bias is likely to be a problem in his or
29 her meta-analysis.

30 While Part B of the book is necessarily more technical than the other parts,
31 we believe that it is generally accessible to the non-statistically minded reader.
32 Particularly technical sections of these chapters, which can be skipped by those who
33 are not interested in statistical fine points without loss of continuity, are identified
34 with an asterisk.

36 **Outline of Part C**

37
38 The final part of the book describes advanced and emerging issues related to
39 publication bias. Chapter 12, by Alex Sutton and Terri Pigott, provides a taxonomy
40 of types of missing data. Sutton and Pigott describe and evaluate the application of
41 standard missing-data imputation techniques to meta-analysis, and outline the need
42 for the development of new methods in this area. Chapter 13, by Tom Trikalinos
43 and John Ioannidis, considers how treatment effects in medicine evolve over time
44 and the impact that selective publication may have on such evolution. In Chapter 14,
45 Lesley Stewart, Jayne Tierney and Sarah Burdett discuss the advantages of obtaining
46 individual participant data, rather than relying on published summary results, in

01 combating publication bias. They suggest that high-quality individual participant
02 data meta-analyses may offer a ‘gold standard’ for research synthesis, at least in the
03 domain of randomized controlled trials. One of the difficulties in trying to diagnose
04 whether publication bias is present in a meta-analysis data set is that the influence
05 of other factors may mimic the appearance of publication bias. In Chapter 15, John
06 Ioannidis considers how to attack the difficult task of disentangling such factors
07 from true publication bias. In Chapter 16, Scott Halpern and Jesse Berlin reflect on
08 data suppression that may occur for other reasons than those traditionally considered
09 to cause publication bias. These factors include the financial, political, ideological
10 and professional competing interests of investigators, research sponsors, journal
11 editors and other parties. Notable events in the pharmaceutical industry, which we
12 mentioned at the beginning of this chapter, and that received much attention as this
13 book was being completed, suggest that these issues merit serious attention from
14 research synthesists.

16 OUR MODEST PROPOSAL

18 We hope that reading this book will convince our audience that is imperative for
19 every meta-analysis to include an analysis of publication bias and that this should be
20 reported as a standard part of the results. We suggest that such reports focus on the
21 practical impact of publication bias. To discuss the practical impact of publication
22 bias it helps to consider three levels of impact, based on the concordance between
23 (1) the results that *are* reported and (2) our best guess (informed by the results of
24 our publication bias analyses) of what the results might look like if all relevant
25 studies had been included. The impact of bias could be called ‘minimal’ when the
26 two versions of the analysis would yield essentially similar estimates of the effect
27 size. The impact could be considered ‘modest’ when the effect size would change
28 substantially but the key finding (that the treatment is or is not effective) would
29 remain in force. The impact could be labelled ‘severe’ when the basic conclusion of
30 the analysis (for example, that the treatment is clinically useful, or that it is not) is
31 called into question. The surveys on this topic, as reviewed by Sutton, in Chapter 10,
32 suggest that publication bias exists in most published meta-analyses, but that the
33 conclusions are nevertheless valid in most cases. In the meta-analyses surveyed so
34 far, the impact of bias is minimal in approximately 50%, modest in about 45%,
35 and severe in only 5% of the analyses surveyed. It also appears to be the case that
36 the amount of bias varies substantially between fields of research. For example, we
37 suspect that publication bias may be more likely in the social sciences, which are
38 characterized by many small and isolated studies, than in medicine, where studies
39 are more likely to be larger, better funded, and better publicized. The prevalence
40 of bias will also likely vary with the experience and resources of the researchers
41 conducting the meta-analysis. The bias cited in the surveys reviewed by Sutton is
42 based primarily on meta-analyses from the Cochrane database, whose researchers
43 are trained to do extensive searches, and which typically include some 30% more
44 studies than meta-analyses on the same topic that appear in journals. Therefore,
45 the bias cited in these surveys is probably less than the bias one would expect in
46 other fields.

01 In cases where publication bias analyses suggest that severe bias may exist, this
02 can serve as a warning to researchers and practitioners to regard the initial results
03 cautiously, and to avoid potentially serious mistakes such as recommending an
04 intervention or policy that could be useless or even harmful. Based on the existing
05 state of knowledge in the field, we are hopeful that, in the majority of cases, the
06 publication bias analysis will show that bias probably had little impact. This is
07 also critically important information, as it allows us to have confidence that the
08 meta-analysis is valid.

09 Finally, we note that it is important to address bias not only to ensure the
10 integrity of the individual meta-analysis, but also to ensure the integrity of the field.
11 When a meta-analysis is published that ignores the potential for bias and is later
12 found to be incorrect, the perception is fostered among editors and researchers that
13 meta-analyses cannot be trusted. By encouraging the prevention and assessment of,
14 and adjustments for, publication bias, we hope to further the use and usefulness
15 of meta-analysis.

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