CHAPTER 30

Publication Bias

INTRODUCTION

While a meta-analysis will yield a mathematically accurate synthesis of the studies included in the analysis, if these studies are a biased sample of all relevant studies, then the mean effect computed by the meta-analysis will reflect this bias. Several lines of evidence show that studies that report relatively high effect sizes are more likely to be published than studies that report lower effect sizes. Since published studies are more likely to find their way into a meta-analysis, any bias in the literature is likely to be reflected in the meta-analysis as well. This issue is generally known as publication bias.

The problem of publication bias is not unique to systematic reviews. It affects the researcher who writes a narrative review and even the clinician who is searching a database for primary papers. Nevertheless, it has received more attention with regard to systematic reviews and meta-analyses, possibly because these are promoted as being more accurate than other approaches to synthesizing research.

In this chapter we first discuss the reasons for publication bias and the evidence that it exists. Then we discuss a series of methods that have been developed to assess

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the likely impact of bias in any given meta-analysis. At the end of the chapter we present an illustrative example.

THE PROBLEM OF MISSING STUDIES

When planning a systematic review we develop a set of inclusion criteria that govern the types of studies that we want to include. Ideally, we would be able to locate all studies that meet our criteria, but in the real world this is rarely possible. Even with the advent of (and perhaps partly due to an over-reliance on) electronic searching, it is likely that some studies which meet our criteria will escape our search and not be included in the analysis.

If the missing studies are a *random* subset of all relevant studies, the failure to include these studies will result in less information, wider confidence intervals, and less powerful tests, but will have no systematic impact on the effect size. However, if the missing studies are *systematically* different than the ones we were able to locate, then our sample will be biased. The specific concern is that studies that report relatively large effects for a given question are more likely to be published than studies that report smaller effects for the same question. This leads to a bias in the published literature, which then carries over to a meta-analysis that draws on this literature.

Studies with significant results are more likely to be published

Several lines of research (reviewed by Dickersin, 2005) have established that studies with statistically significant results are more likely to find their way into the published literature than studies that report results that are not statistically significant. And, for any given sample size the result is more likely to be statistically significant if the effect size is larger. It follows that if there is a population of studies that looked at the magnitude of a relationship, and the observed effects are distributed over a range of values (as they always are), the studies with effects toward the higher end of that range are more likely to be statistically significant and therefore to be published. This tendency has the potential to produce very large biases in the magnitude of the relationships, particularly if studies have relatively small sample sizes (see, Hedges, 1984; 1989).

A particularly enlightening line of research was to identify groups of studies as they were initiated, and then follow them prospectively over a period of years to see which were published and which were not. This approach was taken by Easterbrook, Berlin, Gopalan, & Matthews (1991), Dickersin, Min, & Meinert (1992), Dickersin & Min (1993a), among others. Nonsignificant studies were less likely to be published than significant studies (61–86% as likely), and when published were subject to longer delay prior to publication. Similar studies have demonstrated that researchers selectively report their findings in the reports they do publish, sometimes even changing what is labeled *a priori* as the main hypothesis (Chan *et al*., 2004).

Published studies are more likely to be included in a meta-analysis

If persons performing a systematic review were able to locate studies that had been published in the grey literature (any literature produced in electronic or print format that is not controlled by commercial publishers, such as technical reports and similar sources), then the fact that the studies with higher effects are more likely to be published in the more mainstream publications would not be a problem for meta-analysis. In fact, though, this is not usually the case.

While a systematic review *should* include a thorough search for all relevant studies, the actual amount of grey/unpublished literature included, and the types, varies considerably across meta-analyses. When Rothstein (2006) reviewed the 95 meta-analytic reviews published in *Psychological Bulletin* between 1995 and 2005 to see whether they included unpublished or *grey* research, she found that 23 of the 95 clearly did not include any unpublished data. Clarke and Clarke (2000) studied the references from healthcare protocols and reviews published in The Cochrane Library in 1999, and found that about 92% of references to studies included in reviews were to journal articles. Of the remaining 8%, about 4% were to conference proceedings, about 2% were to unpublished material (for example personal communication, *in press* documents and data on file), and slightly over 1% were to books or book chapters. In a similar vein, Mallet, Hopewell, & Clarke (2002) looked at the sources of grey literature included in the first 1000 Cochrane systematic reviews, and found that nearly half of them did not include any data from grey or unpublished sources. Since the meta-analyses published in the Cochrane Database have been shown to retrieve a higher proportion of studies than those published in many journals, these estimates probably understate the extent of the problem.

Some have suggested that it is legitimate to exclude studies that have not been published in peer-reviewed journals because these studies tend to be of lower quality. For example, in their systematic review, Weisz *et al*. (1995) wrote ‘We included only published psychotherapy outcome studies, relying on the journal review process as one step of quality control’ (p. 452). However, it is not obvious that journal review assures high quality, nor that it is the *only* mechanism that can do so. For one thing, not all researchers aim to publish their research in academic journals. For example, researchers working for government agencies, independent think-tanks or consulting firms generally focus on producing reports, not journal articles. Similarly, a thesis or dissertation may be of high quality, but is unlikely to be submitted for publication in an academic journal if the individual who produced it is not pursuing an academic career. And of course, peer review may be biased, unreliable, or of uneven quality. Overall, then, publication status cannot be used as a proxy for quality; and in our opinion should not be used as a basis for inclusion or exclusion of studies.

Other sources of bias

Other factors that can lead to an upward bias in effect size and are included under the umbrella of publication bias are the following. Language bias (English-language databases and journals are more likely to be searched, which leads to an oversampling of statistically significant studies) (Egger *et al*., 1997; Jüni *et al*., 2002); availability bias (selective inclusion of studies that are easily accessible to the researcher); cost bias (selective inclusion of studies that are available free or at low cost); familiarity bias (selective inclusion of studies only from one's own discipline); duplication bias (studies with statistically significant results are more likely to be published more than once (Tramer *et al*., 1997)) and citation bias (whereby studies with statistically significant results are more likely to be cited by others and therefore easier to identify (Gøtzsche, 1997; Ravnskov, 1992)).

METHODS FOR ADDRESSING BIAS

In sum, it is possible that the studies in a meta-analysis may overestimate the true effect size because they are based on a biased sample of the target population of studies. But how do we deal with this concern? The only true test for publication bias is to compare effects in the published studies formally with effects in the unpublished studies. This requires access to the unpublished studies, and if we had that we would no longer be concerned. Nevertheless, the best approach would be for the reviewer to perform a truly comprehensive search of the literature, in hopes of minimizing the bias. In fact, there is evidence that this approach is somewhat effective. Cochrane reviews tend to include more studies and to report a smaller effect size than similar reviews published in medical journals. Serious efforts to find unpublished, and *difficult to find* studies, typical of Cochrane reviews, may therefore reduce some of the effects of publication bias.

Despite the increased resources that are needed to locate and retrieve data from sources such as dissertations, theses, conference papers, government and technical reports and the like, it is generally indefensible to conduct a synthesis that categorically excludes these types of research reports. Potential benefits and costs of grey literature searches must be balanced against each other. Readers who would like more guidance in the process of literature searching and information retrieval may wish to consult Hopewell, Mallett and Clarke (2005), Reed and Baxter (2009), Rothstein and Hopewell (2009), or Wade, Turner, Rothstein and Lavenberg (2006).

Since we cannot be certain that we have avoided bias, researchers have developed methods intended to assess its potential impact on any given meta-analysis. These methods address the following questions:

- Is there evidence of any bias?
- Is it possible that the entire effect is an artifact of bias?
- How much of an impact might the bias have?

We shall illustrate these methods as they apply to a meta-analysis on passive smoking and lung cancer.

ILLUSTRATIVE EXAMPLE

Hackshaw *et al*. (1997) published a meta-analysis with data from 37 studies that reported on the relationship between so-called second-hand (passive) smoking and lung cancer. The paper reported that exposure to second-hand smoke increased the risk of lung cancer in the nonsmoking spouse by about 20%. Questions were raised about the possibility that studies with larger effects were more likely to have been published (and included in the analysis) than those with smaller (or nil) effects, and that the conclusion was therefore suspect.

THE MODEL

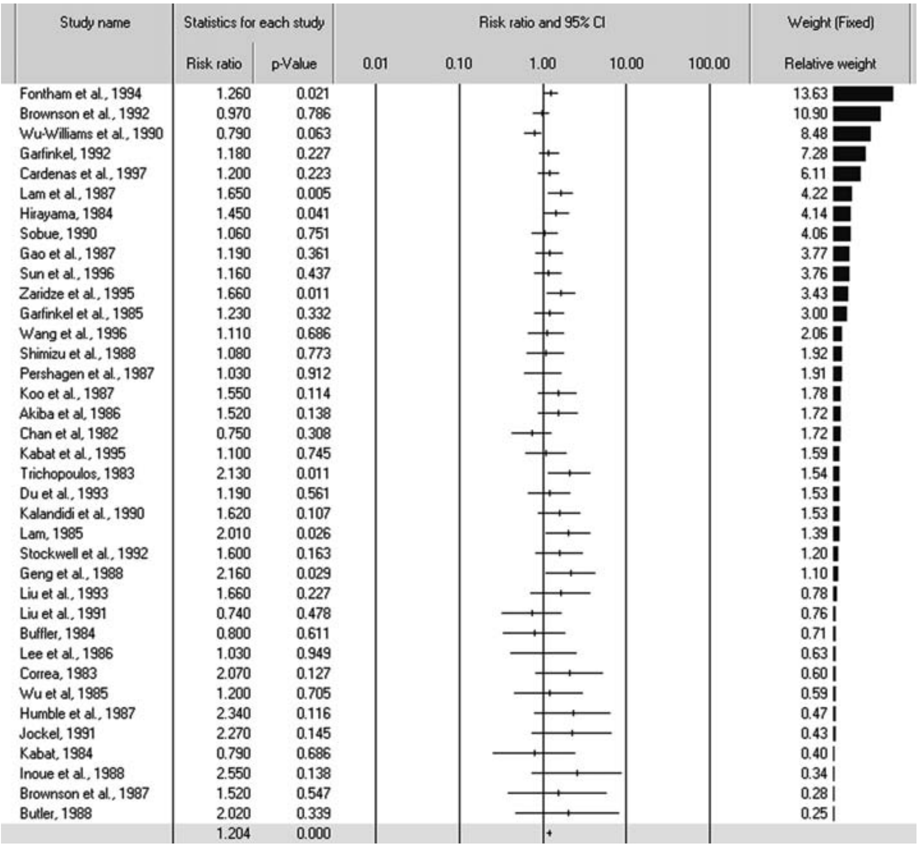
In order to gauge the impact of publication bias we need a model that tells us which studies are likely to be missing. The model that is generally used (and the one we follow here) makes the following assumptions: (a) Large studies are likely to be published regardless of statistical significance because these involve large commitments of time and resources. (b) Moderately sized studies are at risk for being lost, but with a moderate sample size even modest effects will be significant, and so only some studies are lost here. (c) Small studies are at greatest risk for being lost. Because of the small sample size, only the largest effects are likely to be significant, with the small and moderate effects likely to be unpublished.

The combined result of these three items is that we expect the bias to increase as the sample size goes down, and the methods described below are all based on this model. Other, more sophisticated methods have been developed for estimating the number of missing studies and/or adjusting the observed effect to account for bias. These have rarely been used in actual research because they are difficult to implement and also because they require the user to make some relatively sophisticated assumptions and choices.

Before proceeding with the example we call the reader's attention to an important caveat. The procedures that we describe here look for a relationship between sample size and effect size, and if such a relationship is found, it is attributed to the existence of missing studies. While this is *one possible reason* that the effect size is larger in the smaller studies, it is also possible that the effect size *really is larger* in the smaller studies. We mention this caveat here to provide a context for the discussion that follows, and return to it near the end of the chapter, in the section entitled *small-study effects*.

GETTING A SENSE OF THE DATA

A good place to start in assessing the potential for bias is to get a sense of the data, and the forest plot can be used for this purpose. Figure 30.1 is a forest plot of the studies in the passive smoking meta-analysis. In this example, an increase in risk is indicated by a risk ratio greater than 1.0. The overwhelming majority of studies show an increased risk for second-hand smoke, and the last row in the spreadsheet



Study name	Statistics for each study		Weight (Fixed)
	Risk ratio	p-Value	Relative weight
Fontham et al., 1994	1.260	0.021	13.63
Brownson et al., 1992	0.970	0.786	10.90
Wu-Williams et al., 1990	0.790	0.063	8.48
Garfinkel, 1992	1.180	0.227	7.28
Cardenas et al., 1997	1.200	0.223	6.11
Lam et al., 1987	1.650	0.005	4.22
Hirayama, 1984	1.450	0.041	4.14
Sobue, 1990	1.060	0.751	4.06
Gao et al., 1987	1.190	0.361	3.77
Sun et al., 1996	1.160	0.437	3.76
Zaridze et al., 1995	1.660	0.011	3.43
Garfinkel et al., 1985	1.230	0.332	3.00
Wang et al., 1996	1.110	0.686	2.06
Shimizu et al., 1988	1.080	0.773	1.92
Pershagen et al., 1987	1.030	0.912	1.91
Koo et al., 1987	1.550	0.114	1.78
Akiba et al, 1986	1.520	0.138	1.72
Chan et al, 1982	0.750	0.308	1.72
Kabat et al., 1995	1.100	0.745	1.59
Trichopoulos, 1983	2.130	0.011	1.54
Du et al., 1993	1.190	0.561	1.53
Kalandidi et al., 1990	1.620	0.107	1.53
Lam, 1985	2.010	0.026	1.39
Stockwell et al., 1992	1.600	0.163	1.20
Geng et al., 1988	2.160	0.029	1.10
Liu et al., 1993	1.660	0.227	0.78
Liu et al., 1991	0.740	0.478	0.76
Buffler, 1984	0.800	0.611	0.71
Lee et al., 1986	1.030	0.949	0.63
Correa, 1983	2.070	0.127	0.60
Wu et al, 1985	1.200	0.705	0.59
Humble et al., 1987	2.340	0.116	0.47
Jockel, 1991	2.270	0.145	0.43
Kabat, 1984	0.790	0.686	0.40
Inoue et al., 1988	2.550	0.138	0.34
Brownson et al., 1987	1.520	0.547	0.28
Butler, 1988	2.020	0.339	0.25
	1.204	0.000	

Figure 30.1 Passive smoking and lung cancer – forest plot.

shows the summary data for the fixed-effect model. The risk ratio is 1.204 and the 95% confidence interval is 1.120 to 1.295.

The studies have been plotted from most precise to least precise, so that larger studies appear toward the top and smaller studies appear toward the bottom. This has no impact on the summary effect, but it allows us to see the relationship between sample size and effect size. As we move toward the bottom of the plot the effects shift toward the right, which is what the model would predict if bias is present.

If the analysis includes some studies from peer-reviewed journals and others from the grey literature, we can also group by source and see if the grey papers (which may be representative of any missing studies) tend to have smaller effects than the others.

The funnel plot

Another mechanism for displaying the relationship between study size and effect size is the funnel plot.

Traditionally, the funnel plot was plotted with effect size on the *X* axis and the sample size or variance on the *Y* axis. Large studies appear toward the top of the graph and generally cluster around the mean effect size. Smaller studies appear toward the bottom of the graph, and (since smaller studies have more sampling error variation in effect sizes) tend to be spread across a broad range of values. This pattern resembles a funnel, hence the plot's name (Light and Pillemer, 1984; Light *et al*., 1994).

The use of the standard error (rather than sample size or variance) on the *Y* axis has the advantage of spreading out the points on the *bottom half* of the scale, where the smaller studies are plotted. This could make it easier to identify asymmetry. This affects the display only, and has no impact on the statistics, and this is the route we follow here (Figure 30.2).

IS THERE EVIDENCE OF ANY BIAS?

In the *absence* of publication bias, the studies will be distributed symmetrically about the mean effect size, since the sampling error is random. In the *presence* of publication bias the studies are expected to follow the model, with symmetry at the top, a few studies missing in the middle, and more studies missing near the bottom. If the direction of the effect is toward the right (as in our example), then near the bottom of the plot we expect a gap on the left, where the nonsignificant studies would have been if we had been able to locate them.

In the running example (Figure 30.2) the risk ratio (in log units) is at the bottom and the standard error is on the *Y* axis (which has been reversed, so low values are at

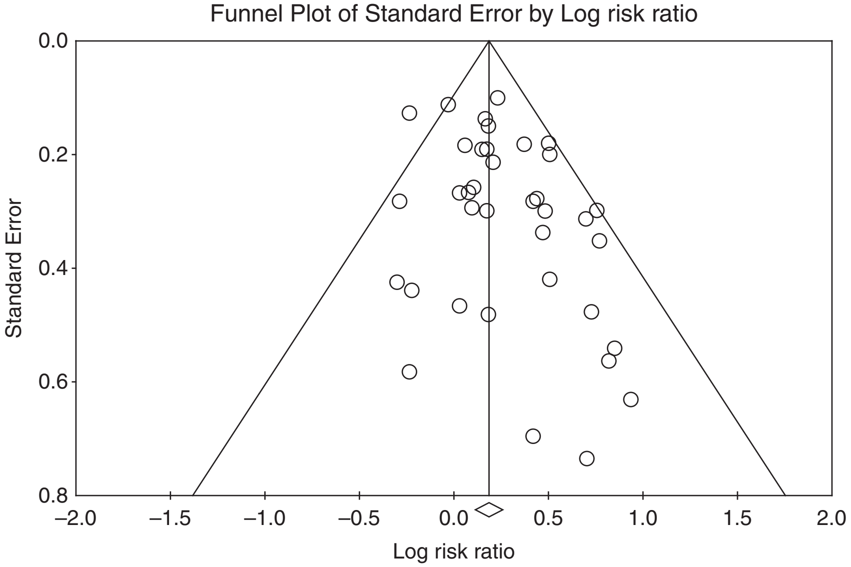


Figure 30.2 Passive smoking and lung cancer – funnel plot.

the top). The subjective impression does support the presence of asymmetry. Toward the bottom of the graph most studies appear toward the right (indicating more risk), which is consistent with the possibility that some studies are missing from the left.

First, we ask if there is evidence of *any* bias. Because the interpretation of a funnel plot is largely subjective, several tests have been proposed to quantify or test the relationship between sample size and effect size. Two early proposals are in common use (Begg and Mazumdar, 1994, Egger *et al*., 1997); a comprehensive review appears in Chapter 10 of Higgins and Green (2008).

While these tests provide useful information, several caveats are in order. First, the tests (like the funnel plot) may yield a very different picture depending on the index used in the analysis (risk difference versus risk ratio, for example). Second, this approach makes sense only if there is a reasonable amount of dispersion in the sample sizes and a reasonable number of studies. Third, even when these criteria are met, the tests tend to have lower power. Therefore, the absence of a significant correlation or regression cannot be taken as evidence of symmetry.

In any event, even if we could somehow solve these problems, the question addressed by the tests (is there evidence of *any* bias) is of limited import. A more interesting question would be *How much bias is there, and what is its impact on our conclusions?*

IS THE ENTIRE EFFECT AN ARTIFACT OF BIAS?

The next question one might ask is whether or not the observed overall effect is robust. In other words, can we be confident that the effect is not solely an artifact of bias?

Rosenthal's *Fail-safe N*

An early approach to dealing with publication bias was Rosenthal's *Fail-safe N*. Suppose a meta-analysis reports a significant p-value based on k studies. We are concerned that studies with smaller effects are missing, and if we were to retrieve all the missing studies and include them in the analysis, the p-value for the summary effect would no longer be significant. Rosenthal (1979) suggested that we actually compute how many missing studies we would need to retrieve and incorporate in the analysis before the p-value became nonsignificant. For purposes of this exercise we would assume that the mean effect in the missing studies was zero. If it should emerge that we needed only a few studies (say, five or ten) to 'nullify' the effect, then we would be concerned that the true effect was indeed zero. However, if it turned out that we needed a large number of studies (say, 20,000) to nullify the effect, there would be less reason for concern.

Rosenthal referred to this as a *File drawer* analysis (file drawers being the presumed location of the missing studies), and Harris Cooper suggested that the number of missing studies needed to nullify the effect should be called the *Fail-safe N* (Rosenthal, 1979; Begg and Mazumdar, 1994).

While Rosenthal's work was critical in focusing attention on publication bias, this approach is of limited utility for a number of reasons. First, it focuses on the question of statistical significance rather than substantive significance. That is, it asks how many hidden studies are required to make the effect not statistically significant, rather than how many hidden studies are required to reduce the effect to the point that it is not of substantive importance. Second, the formula assumes that the mean effect size in the hidden studies is zero, when in fact it could be negative (which would require fewer studies to nullify the effect) or positive but low. Finally, the *Fail-safe N* is based on significance tests that combine *p*-values across studies, as was common at the time that Rosenthal suggested the method. Today, the common practice is to compute a summary effect, and then compute the *p*-value for this effect. The *p*-values computed using the different approaches actually test different null hypotheses, and are not the same. For these reasons this approach is not generally appropriate for analyses that focus on effect sizes. We have addressed it at relative length only because the method is well known and because of its important historical role.

That said, for the passive smoking review the *Fail-safe N* is 398, suggesting that there would need to be nearly 400 studies with a mean risk ratio of 1.0 added to the analysis, before the cumulative effect would become statistically nonsignificant.

Orwin's *Fail-safe N*

As noted, two problems with Rosenthal's approach are that it focuses on statistical significance rather than substantive significance, and that it assumes that the mean effect size in the missing studies is zero. Orwin (1983) proposed a variant on the Rosenthal formula that addresses both of these issues. First, Orwin's method allows the researcher to determine how many missing studies would bring the overall effect to a specified level other than zero. The researcher could therefore select a value that would represent the smallest effect deemed to be of substantive importance, and ask how many missing studies it would take to bring the summary effect below this point. Second, it allows the researcher to specify the mean effect in the missing studies as some value other than zero. This would allow the researcher to model a series of other distributions for the missing studies (Becker, 2005; Begg and Mazumdar, 1994).

In the running example, Orwin's *Fail-safe N* is 103, suggesting that there would need to be over 100 studies with a mean risk ratio of 1.0 added to the analysis before the cumulative effect would become trivial (defined as a risk ratio of 1.05).

HOW MUCH OF AN IMPACT MIGHT THE BIAS HAVE?

The approaches outlined above ask whether bias has had *any* impact on the observed effect (those based on the funnel plot), or whether it might be *entirely* responsible for the observed effect (*Fail-safe N*). As compared with these extreme positions, a third approach attempts to estimate how much impact the bias had, and to estimate what the effect size would have been in the absence of bias. The hope is to classify each meta-analysis into one of three broad groups, as follows.

- The impact of bias is probably trivial. If all relevant studies were included the effect size would probably remain largely unchanged.
- The impact of bias is probably modest. If all relevant studies were included the effect size might shift but the key finding (that the effect is, or is not, of substantive importance) would probably remain unchanged.
- The impact of bias may be substantial. If all relevant studies were included, the key finding (that the effect size is, or is not, of substantive importance) could change.

Duval and Tweedie's *Trim and Fill*

As discussed above, the key idea behind the funnel plot is that publication bias may be expected to lead to asymmetry. If there are more small studies on the right than on the left, our concern is that there may be studies missing from the left. (In the running example we expect suppression of studies on the left, but in other cases we would expect suppression on the right. The algorithm requires the reviewer to specify the expected direction.)

Trim and Fill uses an iterative procedure to remove the most extreme small studies from the positive side of the funnel plot, re-computing the effect size at each iteration until the funnel plot is symmetric about the (new) effect size. In theory, this will yield an unbiased estimate of the effect size. While this *trimming* yields the adjusted effect size, it also reduces the variance of the effects, yielding a too narrow confidence interval. Therefore, the algorithm then adds the original studies back into the analysis, and imputes a mirror image for each. This *fill* has no impact on the point estimate but serves to correct the variance (Duval and Tweedie, 2000a, 2000b).

A major advantage of this approach is that it addresses an important question, *What is our best estimate of the unbiased effect size?* Another nice feature of this approach is that it lends itself to an intuitive visual display. The computer programs that incorporate *Trim and Fill* are able to create a funnel plot that includes both the observed studies and the imputed studies, so the researcher can see how the effect size shifts when the imputed studies are included. If this shift is trivial, then one can have more confidence that the reported effect is valid. A problem with this method is that it depends strongly on the assumptions of the model for why studies are missing, and the algorithm for detecting asymmetry can be influenced by one or two aberrant studies.

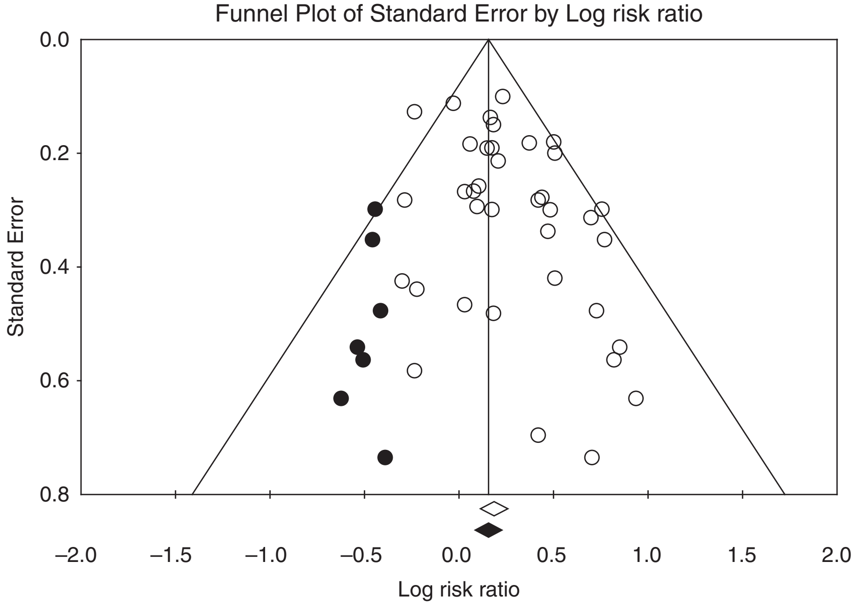


Figure 30.3 Passive smoking and lung cancer – funnel plot with imputed studies.

We can re-display the funnel plot, taking into account the *Trim and Fill* adjustment. In Figure 30.3, the observed studies are shown as open circles, and the observed point estimate in log units is shown as an open diamond at 0.185 (0.113, 0.258), corresponding to a risk ratio of 1.204 (1.120, 1.295). The seven imputed studies are shown as filled circles, and the imputed point estimate in log units is shown as a filled diamond at 0.156 (0.085, 0.227), corresponding to a risk ratio of 1.169 (1.089, 1.254). The 'adjusted' point estimate suggests a lower risk than the original analysis. Perhaps the key point, though, is that the adjusted estimate is fairly close to the original – in this context, a risk ratio of 1.17 has the same substantive implications as a risk ratio of 1.20.

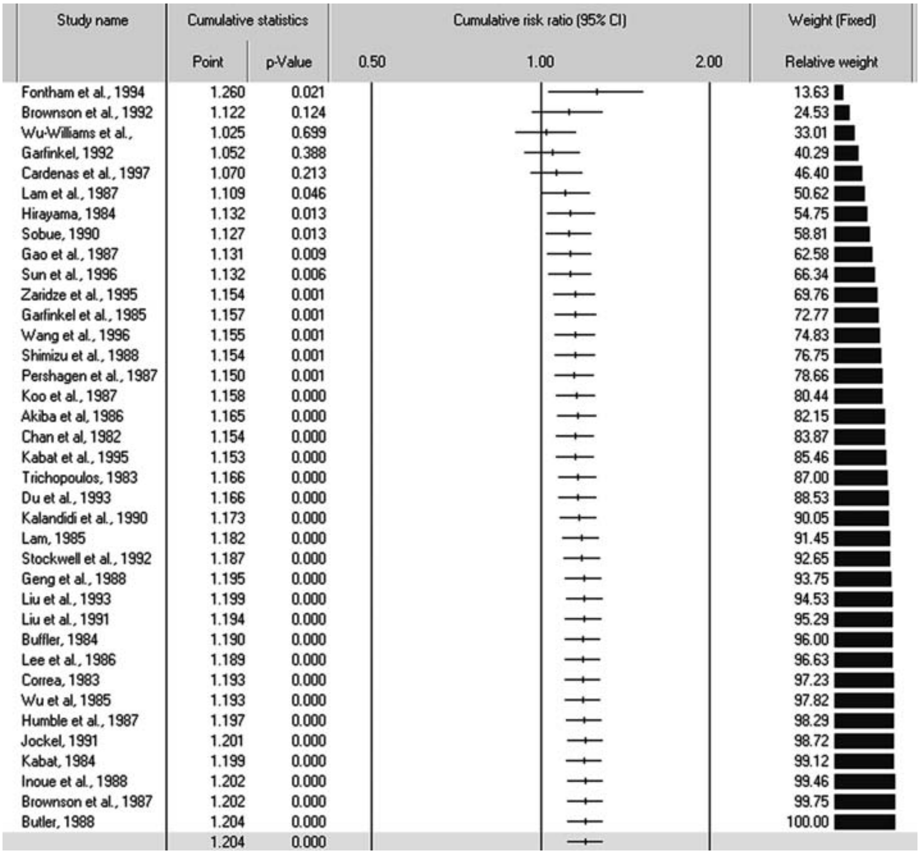
Restricting analysis to the larger studies

If publication bias operates primarily on smaller studies, then restricting the analysis to large studies, which might be expected to be published irrespective of their results, would in theory overcome any problems. The question then arises as to what threshold defines a *large* study. We are unable to offer general guidance on this question. A potentially useful strategy is to illustrate all possible thresholds by drawing a cumulative meta-analysis.

A cumulative meta-analysis is a meta-analysis run first with one study, then repeated with a second study added, then a third, and so on. Similarly, in a cumulative forest plot, the first row shows the effect based on one study, the second row shows the cumulative effect based on two studies, and so on. We discuss cumulative meta-analysis in more detail in Chapter 42.

To examine the effect of different thresholds for study size, the studies are sorted in the sequence of largest to smallest (or of most precise to least precise), and a cumulative meta-analysis performed with the addition of each study. If the point estimate has stabilized with the inclusion of the larger studies and does not shift with the addition of smaller studies, then there is no reason to assume that the inclusion of smaller studies had injected a bias (i.e. since it is the smaller studies in which study selection is likely to be greatest). On the other hand, if the point estimate does shift when the smaller studies are added, then there is at least a *prima facie* case for bias, and one would want to investigate the reason for the shift.

This approach also provides an estimate of the effect size based solely on the larger studies. And, even more so than *Trim and Fill*, this approach is entirely transparent: We compute the effect based on the larger studies and then determine if and how the



Study name	Cumulative statistics		Weight (Fixed)
	Point	p-Value	Relative weight
Fontham et al., 1994	1.260	0.021	13.63
Brownson et al., 1992	1.122	0.124	24.53
Wu-Williams et al.,	1.025	0.699	33.01
Garfinkel, 1992	1.052	0.388	40.29
Cardenas et al., 1997	1.070	0.213	46.40
Lam et al., 1987	1.109	0.046	50.62
Hirayama, 1984	1.132	0.013	54.75
Sobue, 1990	1.127	0.013	58.81
Gao et al., 1987	1.131	0.009	62.58
Sun et al., 1996	1.132	0.006	66.34
Zaridze et al., 1995	1.154	0.001	69.76
Garfinkel et al., 1985	1.157	0.001	72.77
Wang et al., 1996	1.155	0.001	74.83
Shimizu et al., 1988	1.154	0.001	76.75
Pershagen et al., 1987	1.150	0.001	78.66
Koo et al., 1987	1.158	0.000	80.44
Akiba et al, 1986	1.165	0.000	82.15
Chan et al, 1982	1.154	0.000	83.87
Kabat et al., 1995	1.153	0.000	85.46
Trichopoulos, 1983	1.166	0.000	87.00
Du et al., 1993	1.166	0.000	88.53
Kalandidi et al., 1990	1.173	0.000	90.05
Lam, 1985	1.182	0.000	91.45
Stockwell et al., 1992	1.187	0.000	92.65
Geng et al., 1988	1.195	0.000	93.75
Liu et al., 1993	1.199	0.000	94.53
Liu et al., 1991	1.194	0.000	95.29
Buffler, 1984	1.190	0.000	96.00
Lee et al., 1986	1.189	0.000	96.63
Correa, 1983	1.193	0.000	97.23
Wu et al, 1985	1.193	0.000	97.82
Humble et al., 1987	1.197	0.000	98.29
Jockel, 1991	1.201	0.000	98.72
Kabat, 1984	1.199	0.000	99.12
Inoue et al., 1988	1.202	0.000	99.46
Brownson et al., 1987	1.202	0.000	99.75
Butler, 1988	1.204	0.000	100.00
	1.204	0.000	

Figure 30.4 Passive smoking and lung cancer – cumulative forest plot.

effect shifts with the addition of the smaller studies (a clear distinction between larger and smaller studies will not usually exist, but is not needed).

Figure 30.4 shows a cumulative forest plot of the data. Note the difference between the cumulative plot and the standard version shown earlier. Here, the first row is a 'meta' analysis based only on the Fontham *et al.* study. The second row is a meta-analysis based on two studies (Fontham *et al.* and Brownson *et al.*), and so on. The last study to be added is Butler (1988), and so the point estimate and confidence interval shown on the line labeled 'Butler' are identical to that shown for the summary effect on the line labeled 'Fixed'. Note that the scale on this plot is 0.50 to 2.00.

The studies have been sorted from the most precise to the least precise (roughly corresponding to largest to smallest). With the 18 largest studies in the analysis, starting at the top (inclusive of Chan and Fung, 1982) the cumulative relative risk is 1.15. With the addition of another 19 (smaller) studies, the point estimate shifts to the right, and the relative risk is 1.20. As such, our estimate of the relative risk has increased. However, the key point is that even if we had limited the analysis to the 18 larger studies, the relative risk would have been 1.15 (with 95% confidence interval of 1.07, 1.25) and the clinical implications probably would have been the same.

Note also that the analysis that incorporates all 37 studies assigns 83% of its weight to the first 18 (see the bar graph in the right-hand column). In other words, if small studies *are* introducing a bias, we are protected to some extent by the fact that small studies are given less weight. Recall, however, that random-effects meta-analyses award relatively more weight to smaller studies than fixed-effect meta-analyses, so a cumulative meta-analysis based on a random-effects model may not reveal such protection.

A major advantage of this approach is that it provides an estimate of the unbiased effect size (under the strong assumptions of the model) and lends itself to an intuitive visual display. Unlike *Trim and Fill*, this approach will not be thrown by one or two aberrant studies.

SUMMARY OF THE FINDINGS FOR THE ILLUSTRATIVE EXAMPLE

The various statistical procedures approach the problem of bias from a number of directions. One would not expect the results of the different procedures to 'match' each other since the procedures ask different questions. Rather, the goal should be to synthesize the different pieces of information provided by the various procedures.

Getting a sense of the data

There are a substantial number of studies in this analysis. While the vast majority show an increased risk, only a few are statistically significant. This suggests that the mechanism of publication bias based on statistical significance was not a powerful one in this case.

Is there evidence of bias?

The funnel plot is noticeably asymmetric, with a majority of the smaller studies clustering to the right of the mean. This visual impression is confirmed by Egger's test which yields a statistically significant *p*-value. The rank correlation test did not yield a significant *p*-value, but this could be due to the low power of the test. As a whole the smaller studies did tend to report a higher association between passive smoking and lung cancer than did the larger studies.

Is it possible that the observed relationship is entirely an artifact of bias?

Rosenthal's *Fail-safe N* is 398, suggesting that there would need to be nearly 400 studies with a mean risk ratio of 1.0 added to the analysis, before the cumulative effect would become statistically nonsignificant. Similarly, Orwin's *Fail-safe N* is 103, suggesting that there would need to be over 100 studies with a mean risk ratio of 1.0 added to the analysis before the cumulative effect would become trivial (defined as a risk ratio of 1.05). Given that the authors of the meta-analysis were able to identify only 37 studies that looked at the relationship of passive smoking and lung cancer, it is unlikely that nearly 400 studies, or even 103 studies, were missed. While we may have overstated the risk caused by second-hand smoke, it is unlikely that the actual risk is zero.

What impact might the bias have on the risk ratio?

The complete meta-analysis showed that passive smoking was associated with a 20% increase in risk of lung cancer. By contrast, the meta-analysis based on the larger studies reported an increased risk of 16%. Similarly, the *Trim and Fill* method suggested that if we removed the asymmetric studies, the increased risk would be imputed as 15%.

Earlier, we suggested that the goal of a publication bias analysis should be to classify the results into one of three categories (a) where the impact of bias is trivial, (b) where the impact is not trivial but the major finding is still valid, and (c) where the major finding might be called into question. This meta-analysis seems to fall squarely within category *b*. There *is* evidence of larger effects in the smaller studies, which is consistent with our model for publication bias. However, there is no reason to doubt the validity of the core finding, that passive smoking is associated with a clinically important increase in the risk of lung cancer.

SOME IMPORTANT CAVEATS

Most of the approaches discussed in this chapter look for evidence that the effect sizes are larger in the smaller studies, and interpret this as reflecting publication bias. This relationship between effect size and sample size lies at the core of the forest plot, as well as the correlation and regression tests. It also drives the algorithm for *Trim and Fill* and the logic of restricting the analysis to the larger studies.

Therefore, it is important to be aware that these procedures are subject to a number of caveats. They may yield a very different picture depending on the index used in the analysis (e.g. risk difference versus risk ratio). The procedures can easily miss real dispersion. They have the potential to work only if there is a reasonable amount of dispersion in the sample sizes and also a reasonable number of studies. Even when these conditions are met, the tests (correlation and regression) tend to have lower power. Therefore, our failure to find evidence of asymmetry should not lead to a false sense of assurance.

SMALL-STUDY EFFECTS

Equally important, when there is clear evidence of asymmetry, we cannot assume that this reflects publication bias. The effect size *may* be larger in small studies because we retrieved a biased sample of the smaller studies, but it is also possible that the effect size really is larger in smaller studies for entirely unrelated reasons.

For example, the small studies may have been performed using patients who were quite ill, and therefore more likely to benefit from the drug (as is sometimes the case in early trials of a new compound). Or, the small studies may have been performed with better (or worse) quality control than the larger ones. Sterne *et al.* (2001) use the term *small-study effect* to describe a pattern where the effect is larger in small studies, and to highlight the fact that the mechanism for this effect is not known.

Adjustments for publication bias should always be made with this caveat in mind. For example, we should report ‘If the asymmetry is due to bias, our analyses suggest that the adjusted effect would fall in the range of . . .’ rather than asserting ‘the asymmetry is due to bias, and therefore the true effect falls in the range of . . .’

CONCLUDING REMARKS

It is almost always important to include an assessment of publication bias in relation to a meta-analysis. It will either assure the reviewer that the results are robust, or alert them that the results are suspect. This is important to ensure the integrity of the individual meta-analysis. It is also important to ensure the integrity of the field. When a meta-analysis ignores the potential for bias and is later found to be incorrect, the perception is fostered that meta-analyses cannot be trusted.

SUMMARY POINTS

- Publication bias exists when the studies included in the analysis differ systematically from all studies that should have been included. Typically, studies with larger than average effects are more likely to be published, and this can lead to an upward bias in the summary effect.
- Methods have been developed to assess the likely impact of publication bias on any given meta-analysis. Using these methods we report that if we adjusted the

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effect to remove the bias, (a) the resulting effect would be essentially unchanged, or (b) the effect might change but the basic conclusion, that the treatment works (or not) would not be changed, or (c) the basic conclusion would be called into question.

- Methods developed to address publication bias require us to make many assumptions, including the assumption that the pattern of results is due to bias, and that this bias follows a certain model.
- Publication bias is a problem for meta-analysis, but also a problem for narrative reviews or for persons performing any search of the literature.

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