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Journal of Clinical Epidemiology 64 (2011) 1230−1241

Journal of Clinical Epidemiology

Adjusting for publication biases across similar interventions performed well when compared with gold standard data

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Accepted 28 January 2011; Published online 6 May 2011

Abstract

Objective: To extend, apply, and evaluate a regression-based approach to adjusting meta-analysis for publication and related biases. The approach uses related meta-analyses to improve estimation by borrowing strength on the degree of bias.

Study Design and Setting: The proposed adjustment approach is described. Adjustments are applied both independently and by borrowing strength across journal-extracted data on the effectiveness of 12 antidepressant drugs from placebo-controlled trials. The methods are also applied to Food and Drug Administration (FDA) data obtained on the same 12 drugs. Results are compared, viewing the FDA observed data as gold standard.

Results: Estimates adjusted for publication biases made independently for each drug were very uncertain using both the journal and FDA data. Adjusted estimates were much more precise when borrowing strength across meta-analyses. Reassuringly, adjustments in this way made to the journal data agreed closely with the observed estimates from the FDA data, while the adjusted FDA results changed only minimally from those observed from the FDA data.

Conclusion: The method worked well in the case study considered and therefore further evaluation is encouraged. It is suggested that this approach may be especially useful when adjusting several meta-analyses on similar interventions and outcomes, particularly when there are small numbers of studies.

Keywords: Publication bias; Adjustment; Meta-analysis; Antidepressant; Meta-regression; Small-study effects

1. Introduction

In medicine, meta-analyses of randomized controlled trials are regarded as the highest level of evidence for evaluating interventions [1]. Standard approaches to meta-analysis consider the individual studies to be free from selection biases (and from internal and external quality/validity biases [2,3]). However, substantial empirical evidence is amassing suggesting that publication and related biases (e.g., outcome reporting bias [4], selection of the most favorable of a number of alternative analyses) exist [5], and that smaller studies are more influenced by such biases [6−13]. Because of this, it has even been suggested that standard meta-analysis could be considered to offer a naïve synthesis of the evidence [14].

Although it is widely acknowledged that prevention of publication biases is better than any cure, the evidence suggests that alleviation of the problem is still some way off. This has motivated numerous approaches to detect the presence of, and adjust for, publication and related biases; detailed accounts of which can be found elsewhere [15−18]. Adjusting a meta-analysis for publication biases is challenging because the underlying mechanisms causing the bias are usually unknown. Adjustment methods assuming study suppression based on (1) significance of the study [19], (2) study size and significance [20], and (3) magnitude and direction of the treatment effect [21] have all been developed. However, none of the assumed selection models are probably as complex as reality because reporting biases such as changing primary endpoints, or other data ‘‘massaging’’ exploits (e.g., such as choosing between intention to treat and per protocol analyses based on the significance of the results) are not explicitly considered by any of these approaches. This is not surprising given that most of the meta-analyses (particularly of randomized controlled trials [RCTs]) contain modest numbers of studies. Schmid et al. [22] found the median number of studies of seven major medical journals to be 11.5, whereas this was lower still

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0895-4356/$ - see front matter
doi: 10.1016/j.jclinepi.2011.01.009

at eight in Cochrane meta-analyses. Hence, estimating multiple complex selection processes from such data sets is futile [23] (and this is before biases caused by other study "quality"-related factors [24] are considered [25–27]).

A recently developed and evaluated adjustment method [16] took a different approach to the problem of adjustment for publication biases. This approach exploits the fact that smaller studies tend to show a greater effect than larger studies. This phenomenon has been called small-study effects [28] and is observable on a funnel plot (a scatter plot of effect size vs. associated standard error) (see Fig. 1 for an example adapted from Moreno et al. [6] discussed later with contours of statistical significance added to aid interpretation [18,29]). Indeed, the presence of publication bias is usually assessed by means of investigating the existence of small-study effects exposed by funnel-plot asymmetry [23,30]. Although traditionally publication biases have been seen as the main reason for the observed small-study effects in most meta-analyses [9,31,32], the small-study effects phenomenon can be induced by a variety of factors besides publication biases [23,33,34].

Moreno et al. [6,16] have argued that adjusting for small-study effects (which may be induced simultaneously by suppression of whole studies, outcome reporting bias, or any of the other related biases) can be achieved by modeling the relationship between effect size and a measure of its precision using regression to extrapolate to a hypothetical study of infinite size; that is, which has an effect size with an associated standard error of zero (adjusted effect given where standard error = 0). Such a regression can be visualized directly on a funnel plot (e.g., see Fig. 1). The proposed regression model is described in Equation (1), which assumes a linear association between the effect size and its variance (rather than its standard error, as assumed in the original Egger's test [16]).

$$y_i = \alpha + \beta \times se_i^2 + \varepsilon_i \text{ weighted by } \frac{1}{se_i^2} \quad \text{with } \varepsilon_i \sim N(0, se_i^2 \times \varphi) \tag{1}$$

where y_i and se_i^2 are the treatment effect and associated variance for the ith trial. The adjusted pooled effect size is α and the regression slope β. Each trial has an error term ε_i. The between-study heterogeneity is modeled using a multiplicative dispersion component [35] originally proposed by Egger et al. [30].

The justification for this regression-based approach is based on the argument that the larger studies are less influenced by publication biases and more accurately reflect routine clinical care received by the general population (with the condition of interest). Hence, a hypothetical study of infinite size is viewed as an "ideal" study unaffected by publication biases (and other small-study effects). If no such biases exist, no underlying relationship between effect size and study precision will exist and the regression line will be (close to) vertical on the funnel plot implying the extrapolated estimate will not deviate (markedly) from the standard meta-analysis estimate. Note that because study quality is known to induce small-study effects [28], such adjustment may be beneficial even if publication biases are not the cause of any funnel plot asymmetry (i.e., the proposed adjustment approach does not intend to attribute the small-study effects to any particular cause).

Use of a function of effect size variance as a covariate is commonly used to test for the presence of publication bias [36], and it has been seen to dominate other covariates when attempting to explain heterogeneity [33,34,37,38]. Hence, study precision could be considered to be the best single proxy for the cumulative effect of the different sources of bias in meta-analysis [7]. Reassuringly, this regression adjustment approach compared favorably with alternative adjustment methods (including the popular Trim and Fill [21]) in an extensive simulation study [16]. Further, this empirical result, to some extent, agrees with recent findings from Copas and Malley [39], who advocates a permutation test [40] as a novel way of obtaining a robust P-value for effect in a meta-analysis affected by publication bias. Interestingly, the permutation test is shown to be closely related to the radial plot [41], which in turn is closely related to a funnel plot-related regression [16]. Note that because our primary interest is adjustment for biases to facilitate decision making, and P-values have limited utility for this, we pursue our effect size adjustment method in favor of this elegant-related P-value adjustment approach. The regression adjustment approach has also commonalities with the so-called limit meta-analysis method recently proposed by Rücker et al. [17]. In addition to providing a measure of heterogeneity after accounting for small-study effects, the "limit meta-analysis" method can be

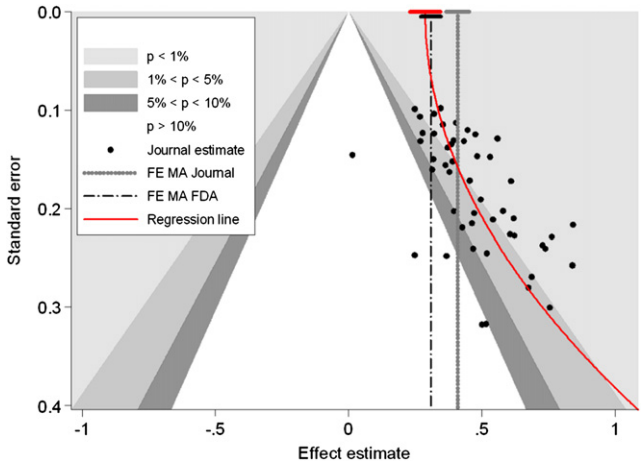

Fig. 1. Contour-enhanced funnel plot of placebo-controlled trials of antidepressants published in medical journals. The fixed-effect (FE) meta-analysis (MA) pooled estimate and the regression adjustment line are displayed with its 95% confidence interval at the top. The pooled estimate of the same studies submitted to the Food and Drug Administration (FDA) is also included.