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LETTER TO THE EDITOR

A method was developed for correcting the bias in the usual study weights in meta-analyses: comment on Walter and Balakrishnan

The paper byWalter and Balakrishnan [1] notes that the standard inverse-variance weights in meta-analysis can be considered as biased because the sample variance is not equal to the true variance. The authors therefore propose that a bias-corrected weighting scheme should be used in meta-analyses. After careful examination, as indicated below, we think that this is unnecessary. As we show in this response, for most considered small meta-analyses, the proposed bias-corrected approach yields equivalent results to the standard inverse-variance weighted meta-analysis. It differs from standard meta-analysis only where the study effect varies with the study size.

The authors use the fixed-effect approach throughout, and so, although they do not state it explicitly, they make the fixed-effect assumption about study effects, namely:

$$\Delta_i = \Delta + \epsilon_i$$

Where ϵ_i are error terms with an expected value of zero.

If each study is given weight w_i in the meta-analysis (and assuming the weights sum to 1), then the estimate of the overall effect is:

$$\widehat{\Delta} = \sum_i w_i \widehat{\Delta}_i \quad [1]$$

In meta-analysis, it is common to treat the weights as if they were constants. In that case, under the fixed effect model, the meta-analytic estimate $\widehat{\Delta}$ is an unbiased estimator. However, if, as Walter and Balakrishnan propose, the weights are actually estimates of the true inverse variance weights, then the weights and the effect estimates should both be considered to be random variables. Hence, it follows that:

$$E(\widehat{\Delta}) = \Delta \sum_i (E(w_i)) + \sum_i cov(w_i, \widehat{\Delta}_i) \quad [2]$$

Therefore, the meta-analytic estimate $\widehat{\Delta}$ is an unbiased estimate only if:

1. The fixed effect model is valid.
2. The weights and effect estimates across the studies are uncorrelated.

We show that these conditions generally do not hold for the examples given in the paper to justify the bias-corrected approach.

In Table 2 of the paper, the authors create a meta-analysis of two trials, one smaller in size (and hence with a smaller weight) than the other. Then, they arbitrarily assume these two studies have different treatment effects. This violates the fixed effect assumption because the two studies have two distinct, nonrandom, true effects. It also induces a correlation between weights and effect estimates (rather like publication bias).

With only two studies in the meta-analysis, it also follows from [1] that: $\widehat{\Delta} = w\widehat{\Delta}_1 + (1 - w)\widehat{\Delta}_2$. Therefore, any change in the choice of weight will alter the effect estimate, so the bias-corrected approach must give a different effect estimate from the standard approach. However, it cannot be claimed on that basis alone that the bias corrected method produces a "better" estimate of the true effect. Only Example 3 in Table 2 satisfies the fixed effect assumption (and avoids weight-estimate correlation) because both trials have the same treatment effect. In that case, there is no difference between a standard meta-analysis and the bias-corrected method.

To explore this further, we performed a simulation study based on the hypothetical Example 3 in Table 2 by Walter and Balakrishnan [1]. We simulated two trials of 10 and 30 patients, respectively, where patient response followed a standard normal distribution (of mean zero and standard deviation of 1) in all trial arms, repeating this 1000 times. We then analyzed the results in each meta-analysis using the standard and bias-corrected approaches. A summary of the distribution of effect estimates and their variances is shown in Figure 1. We found that both approaches give unbiased estimates of the true treatment effect (and in 95% of simulations, they differ in effect estimates by less than 0.05). The variance of the bias corrected method is maximum 1% larger than that of the standard method. Hence, even in an extremely small meta-analysis that includes two studies with few participants—the scenario in which the two approaches are most likely to diverge—there is no evidence that the bias-corrected method improves the estimation of intervention effect.

The results of this simulation study agree with what is to be expected from theory. We note from equation [2] that, provided weights are not correlated with effect estimates, any choice of weights will give an unbiased estimate of the effect. Hence, both standard and bias-corrected weights

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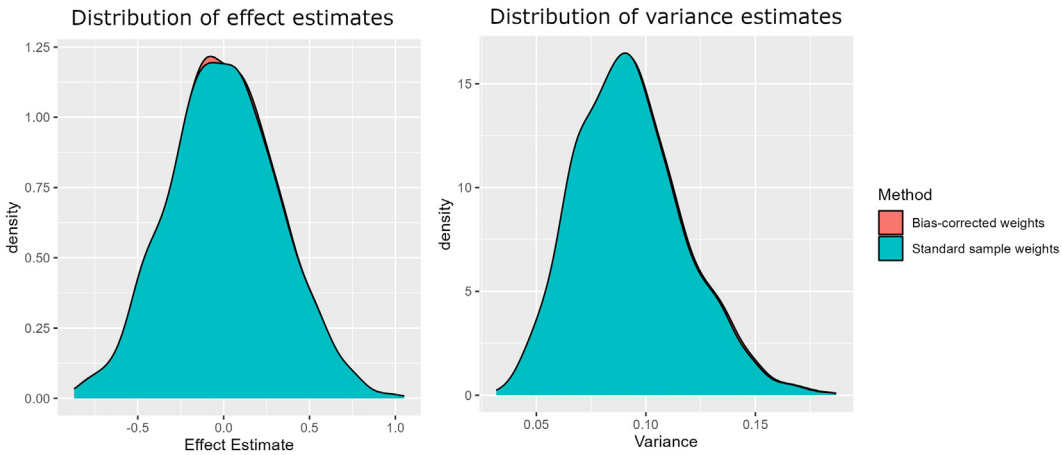

Figure 1. Simulated effect estimates and variance estimates for the standard method (blue) and bias-corrected weighted (red) methods. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

produce an unbiased estimate of the effect. The choice of weighting scheme in a meta-analysis is therefore somewhat arbitrary.

We now consider two of the example meta-analyses in Table 3 of the paper. We report the results of the standard fixed effect, standard random effect, and bias-corrected approaches in Table 1. In the analysis taken from Rietberg et al. [2] (see Fig 2A), there is evidence of heterogeneity across the three included studies ($\tau^2 = 55$, $I^2 = 42\%$), which suggests that a fixed-effect approach is inappropriate. The differences in effect estimate (at most 0.54) are very small when compared to the variance, and particularly when compared to the random effect variance. The differences in effect estimates arise because there is some evidence that effect estimates are correlated with sample size: the smaller two trials have large treatment effects; the larger trial has a treatment effect close to the null.

By contrast, in the analysis taken from Moresco et al. [3] (see Fig 2B), there is still substantial heterogeneity ($\tau^2 = 84.7, I^2 = 72\%$), but the effect estimates are consistent because effect estimates across studies were not correlated with sample size. It appears, therefore, that the bias-corrected meta-analysis effect estimate differs from the standard meta-analysis estimate when the study effect sizes are correlated with the weight. But from equation [2], ie, precisely when an inverse-variance weighted meta-analysis may be invalid, and it is unclear whether the bias-corrected approach leads to a less biased estimate of effect.

Walter and Balakrishnan assume that by using inverse sample variance as weights, we are actually trying to estimate the inverse of the true variances, with inevitable bias. We contend that this is not the case: we can choose any reasonable weighting scheme in a meta-analysis, and inverse sample variances are one sensible choice among many. They provide a simple and explicit way to give larger weight to larger or more informative studies, and any assumption that they are approximations to "true" inverse variance weights is unnecessary. Moreover, our examination highlights the importance of numerical simulation for providing evidence on whether newly derived meta-analysis methods lead to important improvements in estimation.

Table 1
Meta-analyses of two examples given in Table 3 of Walter and Balakrishnan

Cochrane review	Meta-analysis method	Effect estimate	Variance of estimate
Rietberg et al. [2]	Standard fixed effect	8.33	22.32
	Bias-corrected	7.94	22.38
	Standard random effects	8.48	40.55
Moresco et al. [3]	Standard fixed effect	−19.24	5.32
	Bias-corrected	−19.27	5.32
	Standard random effects	−19.84	27.26

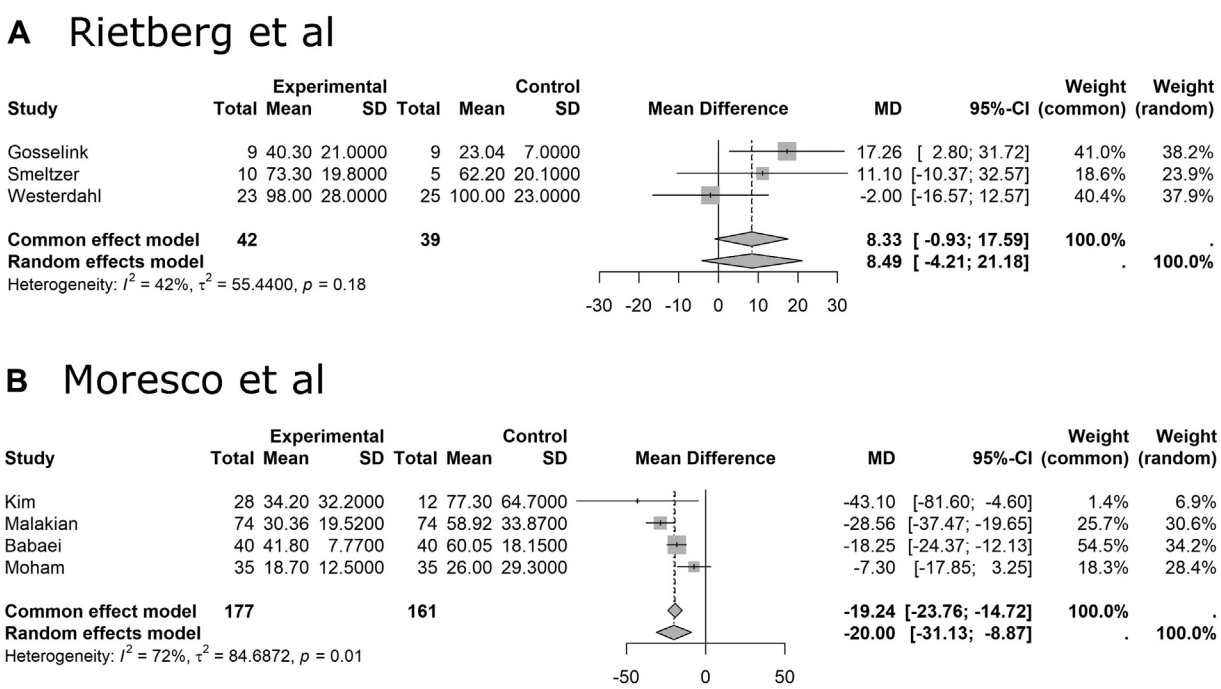

Figure 2. Forest plots for meta-analysis of (A) Rietberg et al. and (B) Moresco et al.

Data availability

Data will be made available on request.

Declaration of competing interest

All authors are co-conveners of the Cochrane Statistical Methods Group. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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