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Quantifying and Adjusting the Effects of Publication Bias in Continuous Meta-Analysis

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Abstract**—**This study uses simulated meta-analysis to assess the effects of publication bias on meta-analysis estimates and to evaluate the efficacy of the trim and fill method in adjusting for these biases. The estimated effect sizes and the standard error were evaluated in terms of the statistical bias and the coverage probability. The results demonstrate that if publication bias is not adjusted it could lead to up to 40% bias in the treatment effect estimates. Utilization of the trim and fill method could reduce the bias in the overall estimate by more than half. The method is optimum in presence of moderate underlying bias but has minimal effects in presence of low and severe publication bias. Additionally, the trim and fill method improves the coverage probability by more than half when subjected to the same level of publication bias as those of the unadjusted data. The method however tends to produce false positive results and will incorrectly adjust the data for publication bias up to 45 % of the time. Nonetheless, the bias introduced into the estimates due to this adjustment is minimal

Keywords**—**Publication bias, Trim and Fill method, percentage relative bias, coverage probability

I. Introduction

PUBLICATION bias may be encountered if a meta-analysis is based on integration of results obtained from studies which have been published. The biases occur when studies which produced large effects or significant results are more likely to get published. A publication bias could produce biased estimates which seem precise and accurate if it operates in the same direction for all studies. The conclusions based on these results will appear convincing although they could be seriously misleading [1].There are a variety of methods available to detect the publication bias in meta analysis, however, only a few could actually adjust for it [2]-[3] . One of the available methods for adjusting the publication bias is the trim and fill method, developed by Duval and Tweedie [4]-[5]. The method assesses whether the publication bias is present and estimates the effect when the bias were to be removed. Although simple, this method is popular due to its practicality and has been shown to have comparable results to its more complex counterparts [6]. The trim and fill method is often utilize as a sensitivity analysis to determine the effects of missing publications on the overall estimates. The method uses an iterative procedure to remove the most extreme small studies from the other side of the funnel plot, i.e. those which do not have the mirror image on the first side. It then re-computes the effect size at each iteration, until the funnel plot is symmetric about the new effect size. The algorithm then adds the removed studies back into the analysis and imputes a mirror image for each of them. The final estimate would be computed from on this data.

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Some of the earlier work which examined the performance of the trim and fill method [7]-[8] were based on dichotomous data utilizing the log-odds ratio as the measure of effect. These studies noted high tendency for this method to conclude false positive results, particularly in heterogeneous data. The aim of the present study is to quantify the effects of publication bias on the overall meta-analysis estimates, and to evaluate the performance of the trim and fill method in continuous data utilizing the absolute mean difference as the measure of effect. The estimates were assessed in terms of statistical bias and the standard errors for point estimates, and confidence band coverage for the interval estimates. A sensitivity analysis were carried out to gauge the effects when the data is incorrectly adjusted for the publication bias when it does not exists.

II. Material And Method

Meta analysis data used in this study were simulated using R statistical software. Simulation of the treatment effects and their corresponding standard error were designed so that no publication bias will be present. This is achieved by combining three randomly generated data sets with the following characteristics ; small-size effects large standard errors , a medium-size effects with small standard errors and a large-size effects with large standard errors [9]. The characteristics and assigned values of the simulated meta-analysis, namely the size of treatment effects, variance and the number of primary studies used, were based on a continuous meta-analyses of patients with benign prostatic hypoplasia [10], where the magnitude of the effect sizes and the corresponding variances ranges from 3.0 to 7.0 and 0.5 to 3.0 , respectively. Publication bias of varying degree were then induced on the simulated meta-analysis based on the assumption that the statistical significance of a study is predictive of publication status [11]. Large studies are likely to achieve statistical significance and therefore more likely to get published, even if their effects are relatively small; small studies, on the other hand, will reach statistical significance only if they yield large effects. Thus small studies with least significant effect size are more likely to be subjected to publication bias. Based partly on the assumptions from earlier work [12]-[13] , three levels of primary studies, N, were used ; small (N = 10), medium (N = 30) and large (N = 50, 100), and three levels of percentage of missing publications, x %, were induced, namely high where 50% of the studies were excluded, and medium and low which corresponds to 30%, and 5% and 10% of the excluded publications, respectively.

Sixteen meta-analysis with different combination of N and x% were generated. Each meta-analysis was replicated 10,000 times. For each meta-analysis, the inverse-variance weighted random effects estimate were computed. The assessment of the effect estimates, including those adjusted for publication bias using the trim and fill method were evaluated in terms of statistical bias and the standard errors for point estimates. The bias is computed using the percentage relative bias as follow:

$$PRB(\hat{\theta}_{x\%}) = \frac{\hat{\theta}_{all} - \hat{\theta}_{x\%}}{\hat{\theta}_{all}} \quad (1)$$

$$PRB(\hat{\theta}_{TF(x\%)}) = \frac{\hat{\theta}_{all} - \hat{\theta}_{TF(x\%)}}{\hat{\theta}_{all}} \quad (2)$$

where $\hat{\theta}_{all}$ is the treatment effect estimate in the absence of publication bias and $\hat{\theta}_{x\%}$ is the corresponding estimate from meta-analysis when x % of the publications were suppressed. $\hat{\theta}_{TF(x\%)}$ is the corresponding adjusted estimate of effect using the trim and fill method. The maximum standard error of estimates for the bias of the treatment effects in the simulation is 2.6%. To estimate the coverage probability, a 95% random interval was computed for each meta-analysis in each simulation run. The coverage probability is estimated as the proportion of the random intervals, out of 10,000 replications, which contains the true estimate.

Finally, a sensitivity analysis were performed to gauge the effects of incorrectly adjusting the data for publication bias when the trim and fill method is used. The PRB of the estimates based on the incorrectly adjusted data were computed against those when no adjustment were made.

III. Results

A. .Percentage Relative Bias

The results show that if the publication bias is not adjusted, a study will produce biased treatment effect estimates (Table 1). The effects were overestimated by an average of 2% in presence of low underlying bias (x = 5%), increasing up to an average of 42 % if there is high degree of publication bias present (x = 50-70%). As expected, the PRB increases with increasing level of publication bias. The number of primary studies included in the meta-analysis has little effect on degree of PRB produced as the publications were excluded based on the percentage of the number of primary studies.

The application of the trim and fill method has substantially reduced the PRB across all N, particularly when the publication bias occur at moderate to high degree (x = 20% - 50%). In this scenario, the PRB in unadjusted meta-analysis, which ranges from approximately 8 % to 25% were reduced by more than half to about an average of 3 % to 14 %. At severe level of underlying bias (x = 70%) however, the PRB of both unadjusted and adjusted estimates are very close at around 42.3% and 41.9 %, respectively, suggesting very little effect trim and fill procedure in this case. Similarly, the trim and fill method has less strong effect in presence of low bias (x < 10%). (Figure 1)

TABLE I
The PRB and the Coverage Probabilities for the Estimates before and After the Adjustment using the Trim and Fill Method

Missing publications, x %	Number of primary studies, N	PRB For $\hat{\theta}_{x\%}$	PRB for $\hat{\theta}_{TF(x\%)}$	Coverage Prob for $\hat{\theta}_{x\%}$	Coverage Prob for $\hat{\theta}_{TF(x\%)}$
5	30	-1.46	-0.77	1.000	1.000
5	50	-1.80	-0.87	1.000	1.000
5	100	-2.17	-0.85	1.000	1.000
10	10	-4.51	-3.30	1.000	1.000
10	30	-4.07	-2.36	1.000	1.000
10	50	-4.22	-1.83	1.000	1.000
10	100	-4.10	-1.24	0.999	1.000
20	10	-8.56	-4.54	0.999	1.000
20	30	-7.56	-2.36	0.948	0.999
20	50	-7.79	-2.05	0.105	0.999
20	100	-7.56	-1.80	0.000	0.993
30	10	-12.07	-3.46	0.947	0.994
30	30	-10.56	-2.92	0.037	0.998
30	50	-10.84	-3.05	0.000	0.994
30	100	-10.51	-2.87	0.000	0.978
50	10	-25.27	-15.98	0.154	0.737
50	30	-19.77	-12.01	0.000	0.274
50	50	-20.79	-13.40	0.000	0.006
50	100	-19.44	-12.63	0.000	0.000
70	30	-41.63	-41.24	0.000	0.000
70	50	-43.12	-42.90	0.000	0.000
70	100	-42.13	-41.75	0.000	0.000

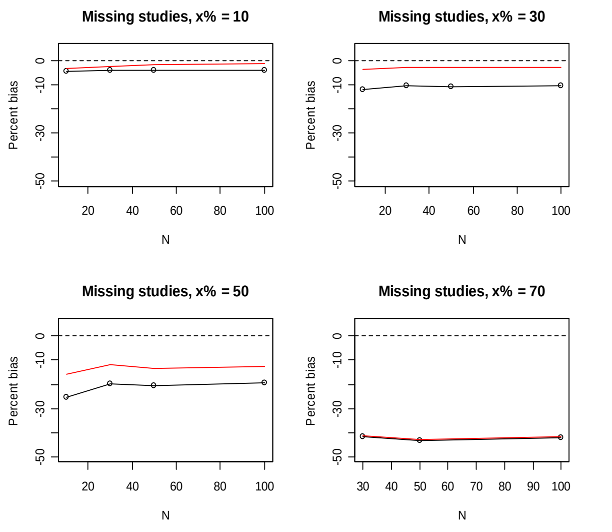

Fig. 1 Percentage relative bias for different levels of missing publications

Note - Red line : Percentage relative bias after the application of Trim and Fill method ; Black line : Percentage relative bias with X% studies missing

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B. Coverage Probability

In general, if publication bias exists and not adjusted, the coverage drops faster as number of primary studies included in meta-analysis increases. For small meta-analysis, the coverage started a sharp slump when about 30% of the publications were missing, while in moderate and large meta-analysis, the slump occur faster at when around 20% of the publications were missing. (Figure 2)

The trim and fill method has substantially improved the coverage. For small meta- analysis (N=10), the coverage remain above 50% even when the degree of publication bias is considered severe (x = 50%).

In medium-size meta-analysis (N = 30), the coverage drops to 0 only when x = 70% compared to x = 30% for unadjusted meta- analysis, while for large meta-analysis the coverage drops to 0 at x = 50% against x = 20% in unadjusted meta analysis. This method is not effective in severe bias as the coverage remain close to zero across all N. (Figure 2)

C. Effects Of Incorrectly Adjusting For Publication Bias

A sensitivity analysis results in Table 2 shows that the proportion that the trim and fill method will incorrectly adjust the data for publication bias is between 10 % to 45 % of the time. The proportion increases with the number of primary studies and the level of heterogeneity, measured by Q.

Even when the data was incorrectly adjusted, it was found that the PRB introduced into the estimates due to this adjustment is minimal, ranging from 0.007% to 0.109 %, with maximum SE for the PRB of 1.7%. The coverage probability for estimates based on this incorrectly adjusted data is not significantly different from those which is correctly not adjusted.

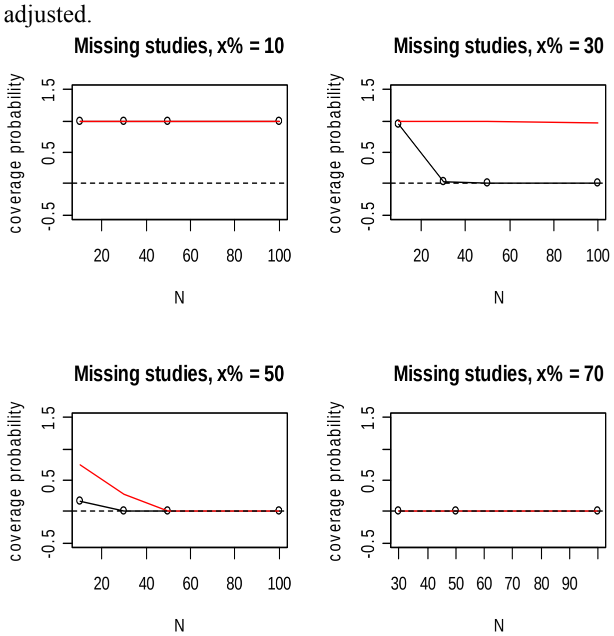

Fig. 2 The coverage probability for different levels of missing publications

Note - Red line : The coverage probability after the application of Trim and Fill method ; Black line : The coverage probability with X% studies missing

TABLE II
THE PRB FOR THE EFFECT ESTIMATES BASED ON THE INCORRECTLY ADJUSTED META-ANALYSIS AND THE RATE OF META-ANALYSIS INCORRECTLY ADJUSTED FOR PUBLICATION BIAS

Number of primary studies, N	10	20	30	50	100
[a] Mean Percentage Relative Bias (PRB)	0.11	0.06	-0.03	0.10	-0.01
SE (PRB)	1.74	1.62	1.42	1.39	1.29
Mean rate of MA incorrectly adjusted for publication bias	9.80	19.90	24.40	31.50	44.70
Heterogeneity level, Q	22.04	45.60	77.39	124.9	257.5
[b] Between-study standard deviation, Tau (τ)	1.13	1.10	1.09	1.08	1.07

a Mean PRB = Mean of ($\hat{\theta}_{unadjusted} - \hat{\theta}_{adjusted}$)
b Tau (τ) = the mean between-study SD

IV. CONCLUSIONS

This study substantiates the relevance of the trim and fill method in dealing with the problem of publication bias in meta-analysis. It demonstrates the effectiveness of the method in reducing the bias in the overall effect estimates attributed by the presence publication bias. Application of this method additionally increases the coverage probability for the true effect sizes.

The results demonstrate that if the publication bias is not adjusted it may lead to up to 42% biased in treatment effect estimates. The application of the trim and fill method has reduced the bias in the overall effect estimate by more than half. The method performs best in presence of moderate to high publication bias (20% < x < 50%). The PRB reduced to an average of 6% compared to about 14% in unadjusted data.

The method improves the coverage probability by more than half when subjected to the same level of publication bias in medium to large meta-analysis. The trim and fill method however is not effective in low underlying bias (x < 10%) and severely bias (x > 50%). The PRB produced by unadjusted data are not significantly different from those that have been adjusted using the imputed trim and fill method. In practice, it is difficult to know the true level of publication bias. However, researchers may consider the number of unpublished studies as a rough estimate for the level of publication bias presence within a meta-analysis.

One limitation of the trim and fill method is it assumes that the sampling error is the key source of variation in a set of studies. This may not be the case in many studies, which are often quite heterogeneous due to both methodological and substantive differences among primary studies. A simulation-based study [14] showed that when trim and fill is applied to heterogeneous data sets, it can adjust for publication bias when none actually exists.

Our simulation study reveals that the trim and fill method will incorrectly adjust the data for publication bias between 10 % to 45% of the time (for the 5% nominal level), increasing with the number of primary studies. This is expected as the level of heterogeneity increases with the number of primary studies, resulting in the meta-analysis being more likely to be adjusted for publication bias.

However, even when the data was incorrectly adjusted, it was found that the percentage relative bias (PRB) introduced into the estimates due to this adjustment is minimal (min : 0.007% , max: 0.109 %), and coverage probability for estimates based on this incorrectly adjusted data is not significantly different from those of which is correctly not adjusted. Nonetheless, reasonable steps must be taken to eliminate any factor which may increase the heterogeneity level in effect sizes.

Researchers may alternatively view the degree of divergence between the original mean effect and the adjusted mean effect as a useful sensitivity analysis to gauge the robustness of meta-analytic results to the risk posed by the publication bias. The trim and fill method is therefore recommended be routinely used when conducting meta-analysis as its benefit far outweigh its harm.

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