

Approaches for identifying and managing publication bias in meta-analysis

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ABSTRACT

The consequences of publication bias in meta-analysis pose significant risks, potentially leading to erroneous conclusions within the meta-analytic framework. The objective of this article was to explore the methodologies for identifying publication bias and approaches for mitigating its effects. The techniques employed to detect publication bias can generally be distinguished into two major categories: graphical and statistical methodologies. Graphical approaches utilize techniques such as funnel plots and meta-plots, which visually depict the distribution of effect sizes and standard errors across studies. Statistical methods encompass various computations, including Fail-Safe N, rank correlation, Egger regression, tests for excess significance (TES), and selection models tailored for evaluating publication bias through quantitative analyses. The combination of these methods is recommended for a more comprehensive assessment, rather than relying on individual approaches. Methods for addressing publication bias include the trim and fill (T&F) method, Publication Error and True Effect Size Estimation (PET-PEESE) method, and the Weight-Function Model, each offering unique strategies for adjusting effect size estimates. The selection of these methods should consider the specific characteristics of the meta-analysis under consideration, ensuring the most appropriate approach is employed. Publication bias poses a significant risk in the field of meta-analysis, and selecting methods for its identification and mitigation requires comprehensive consideration.

KEYWORDS: Publication bias; meta-analysis; systematic review; statistical techniques.

INTRODUCTION

Meta-analysis serves as a quantitative and formal epidemiological research design aimed at systematically evaluating prior studies to draw conclusions regarding the collective body of research.¹ Over the past decade, meta-analysis has undergone numerous advancements, including improvements in methodology, addressing bias both within individual studies and across multiple studies, extension of concepts to complex evidence synthesis, adoption of Bayesian methods, enhancement of transparency and reporting, and the emergence of network meta-analysis.² It is anticipated that in the future, meta-analysis studies will increase both in quantity and quality. The convenience of conducting meta-analysis extends to data acquisition, which can be accomplished through straightforward browsing without the necessity for fieldwork. In the future, formulating high-quality evidence is expected to become even easier due to the support provided by meta-analysis studies. However, meta-analysis encounters challenges such as identifying relevant studies, poor reporting, handling heterogeneity,³ methodological complexities, language bias, and publication bias.⁴ Among these factors, publication bias poses a notable challenge, demanding additional efforts for resolution.

Publication bias in meta-analysis refers to the systematic distortion of research findings resulting from the selective publication of studies with statistically significant results, while often excluding those with non-significant or null findings. This phenomenon introduces a skew in the representation of research outcomes, leading to an overestimation of effect sizes and potentially suggesting the presence of effects that may not truly exist. Such bias poses a significant threat to the validity and generalizability of conclusions drawn from meta-analyses, as it distorts the overall picture of the underlying population of studies.⁴ This issue is particularly concerning as it undermines the reliability of data interpretations, even when seemingly positive conclusions are drawn. Failure to address publication bias in meta-analysis can lead to significant consequences, potentially culminating in inaccurate conclusions and misguided decision-making founded on flawed evidence. Therefore, it is imperative for researchers to be cognizant of methods for identifying and mitigating publication bias in meta-analysis. This article aimed to provide an in-depth exploration of these methods to equip researchers with the tools necessary to tackle this challenge effectively and ensure the integrity of meta-analytic findings.

SOURCES OF PUBLICATION BIAS IN META-ANALYSIS

In the context of meta-analysis, publication bias emerges as a consequence of inconsistencies in data presentation, which may incline towards either positive or negative skewness. This phenomenon can be triggered by a multitude of factors, whether intentional or unintentional. Intentional factors include selective reporting, outcomes arising from selective reporting, editorial bias, and selective publication.⁵ Selective reporting, the notion that solely statistically significant outcomes warrant attention and subsequent publication, emerges as the primary catalyst of publication bias. This practice proliferates as researchers strive for funding acquisition and reputation enhancement, with the dissemination of null findings often viewed as unfavorable. In the context of meta-analysis, where studies accumulate, this bias is exacerbated. Consequently, while the underlying risk persists, its impact is potentially amplified.⁶

Another cause of publication bias is outcome reporting bias, where researchers selectively report or alter specific outcomes or analyses in a study that yield statistically significant results.⁵ Additionally, editorial bias also plays a role, as journal editors or reviewers may exhibit bias towards statistically significant findings due to pressure to publish "novel" and "exciting" research, expecting these papers to attract a larger readership and make a greater impact on the scientific community. However, this selective publication can distort the overall findings of a meta-analysis, resulting in an overrepresentation of positive results and potentially biased conclusions.⁶

STRATEGIES FOR RECOGNIZING PUBLICATION BIAS IN META-ANALYSIS

There are various methodologies available for determining the potential presence of publication bias in meta-analytical investigations. These methodologies can be broadly classified into two categories: graphical and statistical methods. Graphical approaches employ techniques such as funnel plots and meta-plots, while statistical methods encompass computations such as Fail-Safe N, rank correlation, Egger regression, tests for excess significance (TES), and selection models specifically designed for evaluating publication bias (Table 1).

Funnel plot

Publication bias can be evaluated using a funnel plot, which assesses whether the distribution of studies resembles the shape of an inverted funnel. Funnel plots are constructed as scatterplots, with each study's effect size plotted on the x-axis against its standard error on the y-axis.⁷ In the absence of publication bias, the data points form a symmetrical upside-down funnel, with smaller studies positioned at the top and larger studies at the bottom, indicating an even distribution of effect sizes. However, in the presence of publication bias, the points may exhibit skewness. For instance, some studies may be absent from the left bottom corner of the funnel plot, implying suppression of studies with negative observed effect sizes from publication. It's essential to note that funnel plots deviating from an inverted funnel shape can also result from factors other than publication bias. An asymmetric funnel plot, indicating larger observed effect sizes coupled with larger imprecision (i.e., larger standard errors) of studies, may suggest small-study effects attributable to publication bias or other factors like heterogeneity in true effect size. In this context, publication bias may occur unintentionally. Given the common occurrence of heterogeneity in meta-analyses, caution is warranted in concluding the presence of publication bias solely based on visual inspection of a funnel plot.⁸

Funnel plots possess several merits. They serve primarily as visual aids for the identification of publication bias or systematic heterogeneity in meta-analyses. The construction and interpretation of funnel plots are straightforward, necessitating only basic statistical software proficiency and graphical comprehension. They are applicable to various effect sizes and outcome measures, provided they are standardized and comparable across studies.⁹ Additionally, funnel plots may be complemented by statistical tests and methodologies to address publication bias, such as the trim-and-fill technique, Egger's test, or contour-enhanced funnel plot. A rudimentary triangular region can be delineated, within which 95% of studies would be anticipated to reside in the absence of both biases and heterogeneity. Furthermore, funnel plots can facilitate the identification of studies within distinct subgroups, utilizing disparate plotting symbols for each subgroup.¹⁰

Nevertheless, funnel plots exhibit certain drawbacks, including interpretational subjectivity, susceptibility to the selection of precision or sample size metrics, and diminished reliability in instances where the number of studies is limited. Meta-analysts are advised to approach the interpretation of funnel plots with caution due to their potential for misinterpretation.¹¹ Studies have shown that only 52.5% of funnel plots effectively identify publication bias within a diverse and extensive sample. Furthermore, adjustments made to the precision of studies along the y-axis can significantly alter the overall shape and structure of the funnel plot.¹² In response to these limitations, innovative methodologies such as the contour-enhanced funnel plot have been introduced to improve accuracy in detecting publication bias. However, it is essential to recognize the subjective nature of individuals' interpretations of symmetry, as this can introduce further complexity and potential for misinterpretation.¹⁰ Therefore, meta-analysts are encouraged to adopt a comprehensive approach that considers these multifaceted factors when utilizing funnel plots in their analytical assessments.

Meta-plot

The meta-plot constitutes a graphical instrument employed in meta-analytical investigations to visually elucidate and interpret findings, elucidating details

concerning primary studies and the overarching meta-analysis. It delineates aspects such as precision, statistical robustness, estimates, and confidence intervals pertaining to random-effects meta-analyses, in addition to portraying cumulative outcomes and indicators of potential publication bias. Diverging from conventional forest plots, which predominantly spotlight observed effects, confidence intervals, and study weights, meta-plots offer a more exhaustive portrayal of meta-analytical results.¹³ Furthermore, the meta-plot functions as a tool for scrutinizing small study effects and publication bias, presenting an evolution beyond conventional funnel plot methodologies.¹⁴ Originating from the conceptualization by Poorolajal et al. in 2010,¹⁵ the meta-plot facilitates the identification of potential publication bias, with asymmetry or skewness in data points suggestive of its presence.¹⁶

Meta-plot offers several advantages. It provides a holistic perspective of the primary studies encompassed within the meta-analysis, presenting their effect sizes, confidence intervals, and weights. This enables the evaluation of the precision of primary studies, crucial for gauging the reliability of meta-analysis outcomes. Moreover, meta-plot aids in identifying potential publication bias by illustrating the distribution of studies and their effect sizes. It also furnishes insights into the cumulative results of the meta-analysis, facilitating a more thorough comprehension of the overall impact of the independent variable on the outcome.¹³ Comparisons with forest plots, a more prevalent visualization tool for meta-analysis, allow for a more comprehensive understanding of results.¹⁶ Ultimately, meta-plot enhances the interpretation of meta-analysis findings by furnishing a detailed and comprehensive portrayal of the data.¹³

Meta-plot presents several limitations. It is not as widely utilized as alternative visualization tools, such as forest plots, potentially leading to unfamiliarity among researchers. Its interpretation complexity relative to other tools, like forest plots, may impede accessibility for certain researchers. Moreover, the availability and user-friendliness of software for creating meta-plots may not match those of other visualization tools, thus restricting their application.¹³ Furthermore, meta-plots may not offer additional benefits compared to alternative visualization tools, such as forest plots, in effectively conveying meta-analytic findings.¹⁵ Despite these constraints, meta-plot remains a valuable instrument for comprehending meta-analysis results, particularly with regard to primary studies and the assessment of precision and publication bias.¹⁶

Fail-safe N

Fail-safe N, initially introduced by Rosenthal in 1979, serves as a pivotal metric in meta-analysis for assessing potential publication bias.^{17,18} It is determined by the number of additional 'negative' studies needed to raise the meta-analysis's P value above 0.05. Its computation heavily relies on the assumed mean intervention effect for unpublished studies, resulting in widely varied estimates.^{19,20} Criticisms have been levied against its emphasis on P values over the magnitude of intervention effects and associated confidence intervals. Despite its widespread adoption, the utility of fail-safe N has come under scrutiny, leading to its exclusion from Cochrane reviews.^{21,22} Computed by summing z-scores and dividing by the study count, fail-safe N often yields substantial values, even with seemingly minor effect sizes, and is susceptible to distortion by publication bias, potentially inflating effect size estimates. While not a direct measure of publication bias, fail-safe N offers insights into the tolerance for null results in meta-analyses.¹⁷

Fail-safe N exhibits several merits within the context of meta-analysis. It furnishes an approximation of the requisite number of studies showcasing zero effect sizes essential for modifying result significance to non-significant, thereby assisting in the scrutiny of result robustness.²¹ Additionally, this statistical metric computes the quantity of supplementary 'negative' studies, characterized by zero intervention effects, needed for altering result significance, thereby aiding in the evaluation of potential publication bias. Moreover, Fail-safe N offers precise mathematical quantification, augmenting the capacity to assess result stability within a meta-analytical framework.²³

Table 1. The methodologies employed to assess the potential presence of publication bias in meta-analysis.

| Methods | Description | Recommendations |
|----------------------------|---|---|
| Graphical | | |
| Funnel plot | A graphical representation illustrating the association between effect size and precision. | Small study effects may originate from publication bias as well as additional contributing factors. |
| Meta-plot | A graphical depiction presenting the outcomes of cumulative meta-analysis, where studies are arranged based on their precision. | The meta-plot serves as a tool for evaluating small study effects and publication bias, representing an enhancement over the conventional funnel plot method. |
| Assessment | | |
| Fail-safe N | Determines the quantity of studies necessary to render the null hypothesis of no meta-analytic effect non-significant. | The method is discouraged for use primarily because of assumptions such as the absence of heterogeneity and the presumption that missing studies have no impact. |
| Funnel plot asymmetry test | Rank correlation and the Egger regression test are employed to identify small study effects within funnel plots. | The tests aim to detect small-study effects rather than publication bias. It is recommended that these methods be applied when there are a minimum of 10 studies included in the meta-analysis. |
| TES | The test assesses whether a higher number of statistically significant studies is observed compared to what would be expected based on their statistical power. | The method is not recommended for application in scenarios involving heterogeneity and is acknowledged to be conservative. |
| The p-uniform test | The p-uniform and weight function model assess the distinction between models that are corrected and those that are not corrected for publication bias. | The p-uniform test exhibits conservative behavior when the true effect size is substantial. The characteristics of the weight-function model test are presently undetermined. |

Note, TES, Test of excess significance.

Fail-safe N presents several limitations that warrant consideration. Firstly, it presupposes that the absent studies' outcomes conform to the null hypothesis, a presumption that may not universally hold true. Moreover, while Fail-safe N adeptly estimates the threshold for null outcomes, its primary function isn't geared towards detecting bias within meta-analytic frameworks.¹⁸ Additionally, as additional significant findings accumulate, Fail-safe N tends to inflate, even in cases where studies

exhibit marginal significance, potentially yielding inflated values that don't conclusively signify the absence of bias.²³ These constraints underscore the necessity of employing Fail-safe N judiciously and in conjunction with complementary methodologies to mitigate their impact on meta-analytic outcomes.

Egger's test

Egger's test, initially proposed by Egger et al. in 1997, constitutes a pivotal statistical tool within meta-analytical frameworks, designed to evaluate potential publication bias via the assessment of funnel plot asymmetry.²⁴ This methodological approach involves conducting a linear regression analysis wherein intervention effect estimates are regressed against their corresponding standard errors, weighted proportionally by their inverse variance. While predominantly employed in meta-analyses dealing with continuous outcome measures, its utility has been extensively scrutinized concerning studies involving binary outcomes. In the absence of publication bias, the expected regression intercept ideally converges to zero, indicating a balanced distribution within the funnel plot.⁴ However, critical appraisals have surfaced regarding its statistical power and susceptibility to type I errors, particularly in scenarios characterized by significant discrepancies in study sizes or pronounced treatment effects.²⁵ The interpretation of Egger's test hinges upon the examination of the regression intercept (β^0), whereby a statistically significant deviation from zero signifies the presence of asymmetry in the funnel plot, potentially indicative of publication bias. Furthermore, a substantial intercept magnitude implies an anticipated z-score under conditions of null precision, suggestive of asymmetrical funnel plots attributed to the inclusion of small-scale studies exhibiting disproportionately elevated effect sizes.⁴

The Egger test possesses several merits. It is widely utilized in meta-analysis to evaluate potential publication bias by scrutinizing the asymmetry of funnel plots, aiding in the detection of potential bias stemming from small studies with notably high effect sizes. This statistical procedure relies on a linear regression model where intervention effect estimates are regressed against their standard errors, with weights derived from their inverse variance. Such methodology facilitates a more accessible interpretation of findings compared to alternative approaches.⁴ Notably, the Egger test demonstrates applicability to both continuous and binary outcome measures, rendering it a versatile instrument within the realm of meta-analysis.²⁶

The Egger test exhibits several drawbacks. It has been subject to criticism due to its diminished statistical power, notably in instances characterized by significant dissimilarities in study sizes or notable treatment effects.⁴ Furthermore, its effectiveness in detecting publication bias may be compromised when substantial heterogeneity exists in effect estimates across studies. In such contexts, visual inspection of funnel plots may offer a more effective means of identifying publication bias, particularly in cases of pronounced heterogeneity. Importantly, it is advisable to employ the Egger test in conjunction with other methodologies, such as visual examination of funnel plots and alternative statistical tests for publication bias, to ensure a comprehensive assessment of potential biases in meta-analytical investigations.¹⁰

Begg and Mazumdar test

The classic manifestation of publication bias is exemplified through the funnel plot, where larger studies tend to be incorporated into analyses regardless of their treatment

effects, while smaller studies are more likely to be included when they exhibit comparatively substantial treatment effects. Consequently, an inverse correlation between study size and effect size emerges under such circumstances.⁷ Begg and Mazumdar proposed utilizing this correlation as a means to test for publication bias, introducing their test in 1994. Specifically, they advocate computing the rank-order correlation (Kendall's tau b) between treatment effect and standard error, predominantly influenced by sample size.²⁷ However, this method is subject to limitations. While a significant correlation suggests the presence of bias, it does not directly address its implications. Conversely, a non-significant correlation may result from low statistical power and does not conclusively indicate the absence of bias. Interpretation of the Begg and Mazumdar test hinges upon the significance level, where a significant outcome signifies evidence of publication bias in the meta-analysis, as the standardized treatment effect correlates with its variance.²⁸ Nonetheless, criticism has been directed at the test regarding its statistical power and susceptibility to false positives, particularly in scenarios involving binary outcomes and expressions of intervention effects as odds ratios or relative risks.²⁹

Begg and Mazumdar test presents several advantages. Their test, rooted in a rank correlation between the standardized treatment effect and its variance, employs Kendall's tau as the correlation coefficient, enhancing its accessibility and interpretability relative to alternative approaches. This methodological simplicity facilitates comprehension and application across various contexts.²⁹ Moreover, its versatility extends to both continuous and binary outcomes, rendering it a flexible instrument for meta-analysis. Widely utilized in the field, the Begg and Mazumdar test has garnered substantial recognition, as evidenced by its significant citation count in databases such as Web of Science, affirming its utility in discerning publication bias within meta-analytical investigations.²⁸

Begg and Mazumdar test exhibits several limitations. Critiques have been directed towards the test for its diminished statistical power, particularly evident when there exists a significant imbalance in study sizes or substantial treatment effects.²⁸ Additionally, concerns have been raised regarding its potential for yielding false positives, notably in instances involving binary outcomes where the intervention effect is expressed as an odds ratio or relative risk. The test's foundation lies in a rank correlation between the standardized treatment effect and its variance, employing Kendall's tau as the correlation coefficient. However, this approach may not consistently provide an accurate depiction of the relationship between variables, with alternative correlation measures potentially proving more suitable in certain contexts. It is essential to recognize that the Begg and Mazumdar test should be utilized in conjunction with supplementary methodologies, such as visual scrutiny of funnel plots and alternative statistical tests for publication bias, to furnish a more comprehensive assessment of the dataset under analysis.²⁹

Test of Excess Significance

TES serves as a statistical tool within meta-analysis, aiming to discern the presence of publication bias by scrutinizing whether there exists an overabundance of statistically significant findings compared to what would be anticipated under the null hypothesis of no effect. This exploratory test evaluates the prevalence of studies yielding statistically significant results and contrasts it with the anticipated number derived from the null hypothesis. Introduced in 2007 by Ioannidis and Trikalinos, the TES offers insight into potential biases within meta-analytical studies.³⁰ Interpretation of

TES results involves assessing the significance level of the test. A significant outcome suggests an overrepresentation of significant studies in the meta-analysis, potentially indicative of publication bias, selective analyses, or other biases. The versatility of the test extends to both continuous and binary outcomes, rendering it applicable across various research domains. Particularly in fields susceptible to publication bias, such as clinical trials, the TES may serve as a valuable analytical tool.³¹

The TES presents several strengths. Functioning as an exploratory test, it scrutinizes whether there is an apparent surplus of formally significant findings within published literature, facilitating the identification of potential biases stemming from the pursuit of nominal statistical significance. Furthermore, the TES exhibits versatility by being adaptable to meta-analyses encompassing both continuous and binary outcomes, thereby establishing itself as a versatile tool for evaluating publication bias.³⁰ Although the TES may demonstrate limited power when employed in single meta-analyses featuring a restricted number of studies, its effectiveness can be augmented when applied across multiple meta-analyses that share common characteristics. This collective approach enhances the TES's sensitivity to detect biases, thereby enhancing its utility in meta-analytical research endeavors.³¹

The TES exhibits several limitations. Notably, it may possess low power to detect bias in single meta-analyses characterized by a limited number of studies.³¹ Additionally, the test relies on certain assumptions regarding plausible effect size, potential miscalculations of p values within original datasets, and power miscalculations, all of which can potentially influence its outcomes.³² Given its exploratory nature, the TES may also be susceptible to dependence on prior assumptions, necessitating cautious application. It is imperative to underscore that the TES should be employed alongside other methodologies, such as visual examination of funnel plots and alternative statistical tests for publication bias, to furnish a more comprehensive assessment of the dataset under scrutiny.³⁰

The p-uniform test

The p-uniform method, devised by van Assen et al.³³ and Simonsohn et al.,³⁴ represents a meta-analytical approach developed to address the challenge of publication bias. This methodological strategy hinges on the assumption that p-values distribute uniformly around the true effect size.^{33,34} In circumstances where publication bias is present, statistically nonsignificant effect sizes may not all be published. Thus, the p-uniform method excludes nonsignificant effect sizes and calculates conditional p-values assuming uniform distribution centered on the meta-analytic effect size estimate.³⁵ Interpretation of the p-uniform method entails examining the distribution of conditional p-values at the meta-analytic effect size estimate, with deviations from uniformity indicating potential publication bias. This analytical framework offers insight into the reliability of meta-analytical outcomes in the presence of publication bias.³⁶

The p-uniform test exhibits several strengths. It yields more accurate estimations relative to traditional meta-analytical techniques in instances where p-hacking has not been practiced.³⁵ Its applicability spans across meta-analyses involving continuous and binary outcomes, underscoring its versatility as a tool for discerning publication bias within various research contexts. Furthermore, the p-uniform method incorporates a structured assessment for publication bias and possesses the capacity to compute

corrected meta-analytical effect sizes. These features highlight its efficacy as a rigorous and comprehensive approach for conducting meta-analytical inquiries.³⁷

The p-uniform test exhibits certain limitations. It is predicated on the assumption of homogeneity in the true effect size, a premise that may not universally apply in all meta-analytical contexts.³⁶ Furthermore, both the p-uniform and p-curve methodologies have the potential to produce unrealistic negative estimates or inaccuracies in meta-analytical outcomes, particularly in situations marked by p-hacking or significant heterogeneity. Moreover, the p-uniform test may not always effectively address instances of p-hacking, leading to potential inaccuracies in effect size estimates. These constraints underscore the necessity for cautious interpretation and supplementation with complementary methodologies when employing the p-uniform test in meta-analytical research endeavors.³⁵ It is crucial to approach the implementation of the p-uniform test judiciously, considering its potential limitations and employing it alongside complementary methods for a comprehensive analysis. Furthermore, the test should be used in conjunction with visual inspection of funnel plots and other statistical tools aimed at detecting publication bias. These precautions are essential to ensure a robust and accurate assessment of the data.

MANAGING PUBLICATION BIAS IN META-ANALYSIS

Publication bias in meta-analysis is a concerning issue that requires concrete measures for mitigation. Numerous methods are available to address this problem, among which the most commonly utilized ones include the trim and fill (T&F) method, Publication Error and True Effect Size Estimation (PET-PEESE) method, and the Weight-Function Model. These approaches offer distinct strategies for adjusting effect size estimates and improving the accuracy and reliability of meta-analytical outcomes.

Trim and Fill

The "trim-and-fill" method, also referred to as the "Trim and Fill" (T&F) method, serves as a statistical tool in meta-analysis for assessing the influence of publication bias on the final inference. Introduced by Duval and Tweedie in 2000, this approach aims to detect and rectify funnel plot asymmetry resulting from publication bias. The method operates by first "trimming" smaller studies responsible for funnel plot asymmetry, utilizing the trimmed funnel plot to estimate the true "centre" of the funnel, and subsequently replacing the omitted studies and their missing "counterparts" around this centre (filling).³⁸ By performing a meta-analysis inclusive of the filled studies, the T&F method furnishes an estimate of the number of absent studies and derives an adjusted intervention effect. Remarkably, this method does not rely on assumptions about the underlying mechanism of publication bias and provides an estimate of missing studies. However, it is predicated on the assumption of a symmetric funnel plot, with no guarantee that the adjusted intervention effect aligns with what would have been observed in the absence of publication bias.³⁹

The T&F method exhibits several strengths. Widely adopted as a prominent technique, the T&F method is commonly employed to assess the influence of publication bias on the outcomes of meta-analyses. Its utility extends to adjusting for publication bias by estimating the quantity of absent studies and deriving an adjusted intervention effect.³⁹ Additionally, the T&F method demonstrates versatility in its application to meta-regression analyses, where it can estimate the number of missing studies utilizing different models, such as common effect or random effects models. This versatility

enhances its applicability across various research contexts within the realm of meta-analytical investigations.⁴⁰

The T&F method exhibits several limitations. The method's efficacy hinges on the assumption of a symmetric funnel plot, which may not always hold true, as funnel plot asymmetry can stem from factors beyond publication bias, such as heterogeneity or measurement error.³⁹ Moreover, the T&F method tends to perform inadequately in the presence of substantial between-study heterogeneity, and its estimations and inferences rely on a dataset containing imputed intervention effect estimates, potentially introducing inappropriate information that could reduce uncertainty in the summary intervention effect. Empirical comparisons with the Copas selection model indicate that the T&F method tends to yield overly conservative inferences in practical applications. Therefore, it is imperative to utilize the T&F method cautiously and in conjunction with other methodologies, including visual inspection of the funnel plot and additional statistical tests for publication bias, to ensure a comprehensive evaluation of the data. Additionally, the method should be applied judiciously, considering its potential limitations and reservations.⁴⁰

Publication error and true effect size estimation

PET-PEESE represents a conditional regression-based meta-analytic approach utilized for evaluating the presence of publication bias within meta-analyses. Developed with the objective of estimating the true effect size while accounting for potential publication bias, PET-PEESE was originally introduced by Moreno et al. in 2006.⁴¹ This method operates under the assumption of a homogeneous underlying effect size and is specifically designed to discern the association between the effect size and the standard error, often indicative of publication bias. However, PET-PEESE has been subject to critique regarding its assumptions, performance, and biases, particularly when confronted with heterogeneity within the analyzed data.³⁶

PET-PEESE offers several advantages. Primarily, it is tailored to identify the association between the effect size and the standard error, a relationship commonly indicative of publication bias. Additionally, the method's versatility allows for its extension to meta-analytic regressions, facilitating the analysis of multiple effect sizes nested within samples.⁴² Furthermore, PET-PEESE can be seamlessly integrated into random-effects or mixed-effects meta-analytic models, which inherently possess greater robustness to heterogeneity compared to fixed-effects models. These attributes collectively enhance PET-PEESE's utility and applicability in meta-analytical research, contributing to a more comprehensive understanding of the underlying data.³⁶

PET-PEESE exhibits several drawbacks. Its ability to detect small effects in small meta-analysis samples is notably limited, with a power of less than 50%, rendering it less effective in such instances. Moreover, PET-PEESE's performance deteriorates under high levels of heterogeneity. At extreme heterogeneity levels, characterized by $h \leq 50$, PET-PEESE has been observed to inflate effect sizes by up to 0.17, contributing to type I error inflation.⁴² Additionally, PET-PEESE may lack accuracy, frequently failing to identify numerous true effect sizes, particularly in realistic contexts. Hence, cautious utilization of the PET-PEESE method, preferably complemented by other methodologies like visual inspection of funnel plots and additional statistical tests for publication bias, is essential to ensure a thorough assessment of the data. Moreover, its application should be exercised with care, considering its inherent limitations and reservations.³⁶

The weight-function model

The weight-function model in meta-analysis is a method utilized to rectify publication bias by allotting weights to individual effect size estimates contingent on their standard errors. Particularly advantageous in multivariate meta-analysis scenarios involving multiple predictors, this model was initially introduced by Iyengar & Greenhouse to depict the likelihood of publication for studies with non-significant findings.⁴³ Subsequent refinement and assessment of this model were conducted by Silliman, who introduced distinct classes of weight functions tailored to modeling publication bias in meta-analytical contexts.⁴⁴ Within the meta-analysis framework, the weight function delineates the relative probability of a study's publication based on its one-sided p-value. In instances where the direction of the effect is discernible, the weight function proves efficacious in adjusting for publication bias in the analysis. The weight-function model is particularly beneficial for ameliorating publication bias as it enables the adjustment of effect size estimates predicated on their precision. This feature is pivotal as it accords greater weight to more precise estimates while assigning less weight to those less precise, thus ensuring a more accurate synthesis of evidence in meta-analytic investigations.⁴⁵

The weight-function model exhibits several strengths. Notably, it facilitates the adjustment of effect size estimates based on their precision, which is crucial for mitigating publication bias. Moreover, the model's adaptability allows for the customization of the weight function's complexity according to the available dataset size. In situations with ample data, employing a more intricate weight function is viable, whereas simpler functions are preferable for smaller datasets.⁴⁵ Furthermore, the weight-function model enhances the accuracy of effect size estimates by prioritizing studies with smaller standard errors while reducing the influence of studies with larger standard errors. This approach contributes to a more refined estimation of effect sizes, thereby bolstering the reliability and robustness of meta-analytical outcomes.⁴⁴

The weight-function model is subject to several drawbacks. Firstly, it may pose complexity due to the necessity of specifying a weight function that captures the relationship between standard error and the likelihood of publication. This intricacy adds to the challenge of its application.⁴⁶ Furthermore, the method relies on assumptions regarding the distribution of effect sizes and the association between effect size and standard error, assumptions that may not consistently hold true in practical scenarios.⁴⁷ Additionally, the computational complexity associated with the weight-function model necessitates specialized software or programming skills for implementation. Given these limitations, it is imperative to exercise caution when employing the weight-function model and to supplement it with other methodologies, such as visual inspection of funnel plots and additional statistical tests for publication bias, to ensure a comprehensive evaluation of the data. Moreover, its utilization should be approached judiciously, taking into account the potential limitations and reservations inherent in its application.⁴⁶

CONCLUSION

Publication bias in meta-analysis poses a significant concern. Various methods are available for identifying publication bias in meta-analysis, including funnel plots, meta-plot, Fail-safe N, Egger's test, Begg and Mazumdar test, TES, and the p-uniform test. Concrete steps are essential to address this issue, encompassing methodologies

such as the T&F method, PET-PEESE method, and the Weight-Function Model. This article may help to enhance understanding of publication bias and its mitigation strategies in meta-analysis, thus contributing to broader knowledge in this field.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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We have no conflict of interest

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REFERENCES

1. Haidich AB. Meta-analysis in medical research. *Hippokratia* 2010;14(1):29-37.doi. PMID: 21487488
2. Sutton AJ, Higgins JP. Recent developments in meta-analysis. *Stat Med* 2008;27(5):625-650.doi: 10.1002/sim.2934. PMID: 17590884
3. Metelli S, Chaimani A. Challenges in meta-analyses with observational studies. *Evid Based Ment Health* 2020;23(2):83-87.doi: 10.1136/ebmental-2019-300129. PMID: 32139442
4. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics* 2018;74(3):785-794.doi: 10.1111/biom.12817. PMID: 29141096
5. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol* 2000;53(2):207-216.doi: 10.1016/s0895-4356(99)00161-4. PMID: 10729693
6. Mueller KF, Meerpohl JJ, Briel M, et al. Methods for detecting, quantifying, and adjusting for dissemination bias in meta-analysis are described. *J Clin Epidemiol* 2016;80(1):25-33.doi: 10.1016/j.jclinepi.2016.04.015. PMID: 27502970
7. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol* 2001;54(10):1046-1055.doi: 10.1016/s0895-4356(01)00377-8. PMID: 11576817
8. Godavitarne C, Robertson A, Ricketts DM, et al. Understanding and interpreting funnel plots for the clinician. *Br J Hosp Med (Lond)* 2018;79(10):578-583.doi: 10.12968/hmed.2018.79.10.578. PMID: 30290744
9. Mayer EK, Bottle A, Rao C, et al. Funnel plots and their emerging application in surgery. *Ann Surg* 2009;249(3):376-383.doi: 10.1097/SLA.0b013e31819a47b1. PMID: 19247021
10. Simmonds M. Quantifying the risk of error when interpreting funnel plots. *Syst Rev* 2015;4(1):24.doi: 10.1186/s13643-015-0004-8. PMID: 25875027
11. Tang JL, Liu JL. Misleading funnel plot for detection of bias in meta-analysis. *J Clin Epidemiol* 2000;53(5):477-484.doi: 10.1016/s0895-4356(99)00204-8. PMID: 10812319
12. Terrin N, Schmid CH, Lau J, et al. Adjusting for publication bias in the presence of heterogeneity. *Stat Med* 2003;22(13):2113-2126.doi: 10.1002/sim.1461. PMID: 12820277
13. van Aert R, van Assen MALM, van den Akker OR, et al. The meta-plot: A graphical tool for interpreting the results of a meta-analysis. *Zeitschrift für Psychologie* 2023;23(1):65-78.doi: 10.1027/2151-2604/a000513. PMID:
14. Lin L. Graphical augmentations to sample-size-based funnel plot in meta-analysis. *Res Synth Methods* 2019;10(3):376-388.doi: 10.1002/jrsm.1340. PMID: 30664834
15. Poorolajal J, Mahmoodi M, Majdzadeh R, et al. Metaplot: a novel stata graph for assessing heterogeneity at a glance. *Iran J Public Health* 2010;39(2):102-104.doi. PMID: 23113013

16. Poorolajal J, Noornejad S. Metaplot: A new Stata module for assessing heterogeneity in a meta-analysis. *PLoS One* 2021;16(6):e0253341. doi: 10.1371/journal.pone.0253341. PMID: 34181682
17. Ferguson CJ, Brannick MT. Publication bias in psychological science: prevalence, methods for identifying and controlling, and implications for the use of meta-analyses. *Psychol Methods* 2012;17(1):120-128. doi: 10.1037/a0024445. PMID: 21787082
18. Rosenthal R. The file drawer problem and tolerance for null results. *Psychological bulletin* 1979;86(3):638. doi. PMID:
19. Rosenberg MS. The file-drawer problem revisited: a general weighted method for calculating fail-safe numbers in meta-analysis. *Evolution* 2005;59(2):464-468. doi. PMID: 15807430
20. Fragkos KC, Tsagris M, Frangos CC. Publication bias in meta-analysis: Confidence intervals for rosenthal's fail-safe number. *Int Sch Res Notices* 2014;2014(1):825383. doi: 10.1155/2014/825383. PMID: 27437470
21. Dowdy A, Hantula DA, Travers JC, et al. Meta-analytic methods to detect publication bias in behavior science research. *Perspect Behav Sci* 2022;45(1):37-52. doi: 10.1007/s40614-021-00303-0. PMID: 35342865
22. Higgins JPT, Green S. *Cochrane handbook for systematic reviews of interventions*. Online Library: Wiley; 2008.
23. Persaud R. Misleading meta-analysis. "Fail safe N" is a useful mathematical measure of the stability of results. *BMJ* 1996;312(7023):125. doi: 10.1136/bmj.312.7023.125. PMID: 8555918
24. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-634. doi: 10.1136/bmj.315.7109.629. PMID: 9310563
25. Peters JL, Sutton AJ, Jones DR, et al. Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006;295(6):676-680. doi: 10.1001/jama.295.6.676. PMID: 16467236
26. Schwab S, Kreiliger G, Held L. Assessing treatment effects and publication bias across different specialties in medicine: a meta-epidemiological study. *BMJ Open* 2021;11(9):e045942. doi: 10.1136/bmjopen-2020-045942. PMID: 34521659
27. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(4):1088-1101. doi. PMID: 7786990
28. Gjerdevik M, Heuch I. Improving the error rates of the Begg and Mazumdar test for publication bias in fixed effects meta-analysis. *BMC Med Res Methodol* 2014;14(1):109. doi: 10.1186/1471-2288-14-109. PMID: 25245217
29. Lin L, Chu H, Murad MH, et al. Empirical comparison of publication bias tests in meta-analysis. *J Gen Intern Med* 2018;33(8):1260-1267. doi: 10.1007/s11606-018-4425-7. PMID: 29663281
30. Ioannidis JP, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials* 2007;4(3):245-253. doi: 10.1177/1740774507079441. PMID: 17715249
31. Tsilidis KK, Panagiotou OA, Sena ES, et al. Evaluation of excess significance bias in animal studies of neurological diseases. *PLoS Biol* 2013;11(7):e1001609. doi: 10.1371/journal.pbio.1001609. PMID: 23874156
32. Ioannidis JP. Excess significance bias in the literature on brain volume abnormalities. *Arch Gen Psychiatry* 2011;68(8):773-780. doi: 10.1001/archgenpsychiatry.2011.28. PMID: 21464342
33. van Assen MA, van Aert RC, Wicherts JM. Meta-analysis using effect size distributions of only statistically significant studies. *Psychol Methods* 2015;20(3):293-309. doi: 10.1037/met0000025. PMID: 25401773
34. Simonsohn U, Nelson LD, Simmons JP. p-curve and effect size: Correcting for publication bias using only significant results. *Perspect Psychol Sci* 2014;9(6):666-681. doi: 10.1177/1745691614553988. PMID: 26186117
35. van Aert RC, Wicherts JM, van Assen MA. Conducting meta-analyses based on p values: Reservations and recommendations for applying p-uniform and p-curve. *Perspect Psychol Sci* 2016;11(5):713-729. doi: 10.1177/1745691616650874. PMID: 27694466
36. van Aert RCM, Wicherts JM, van Assen M. Publication bias examined in meta-analyses from psychology and medicine: A meta-meta-analysis. *PLoS One* 2019;14(4):e0215052. doi: 10.1371/journal.pone.0215052. PMID: 30978228
37. Scofield JE, Buchanan EM, Kostic B. A meta-analysis of the survival-processing advantage in memory. *Psychon Bull Rev* 2018;25(3):997-1012. doi: 10.3758/s13423-017-1346-0. PMID: 28744766
38. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56(2):455-463. doi: 10.1111/j.0006-341x.2000.00455.x. PMID: 10877304
39. Weinhandl ED, Duval S. Generalization of trim and fill for application in meta-regression. *Res Synth Methods* 2012;3(1):51-67. doi: 10.1002/jrsm.1042. PMID: 26061999
40. Shi L, Lin L. The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses. *Medicine (Baltimore)* 2019;98(23):e15987. doi: 10.1097/MD.00000000000015987. PMID: 31169736
41. Cano G, Suarez-Roca H, Bonilla E. Alterations of excitatory amino acid receptors in the brain of manganese-treated mice. *Mol Chem Neuropathol* 1997;30(1):41-52. doi: 10.1007/BF02815149. PMID: 9138428
42. Stanley TD. Limitations of PET-PEESE and Other Meta-Analysis Methods. *Social Psychological and Personality Science* 2017;8(5):581-591. doi: 10.1177/1948550617693062. PMID:
43. Iyengar S, Greenhouse JB. Selection models and the file drawer problem. *Statist Sci* 1988;3(1):109-117. doi: 10.1214/ss/1177013012. PMID:
44. Silliman NP. Nonparametric classes of weight functions to model publication bias. *Biometrika* 1997;84(4):909-918. doi. PMID:
45. McShane BB, Bockenholt U, Hansen KT. Adjusting for publication bias in meta-analysis: An evaluation of selection methods and some cautionary notes. *Perspect Psychol Sci* 2016;11(5):730-749. doi: 10.1177/1745691616662243. PMID: 27694467

46. Rufibach K. Selection models with monotone weight functions in meta analysis. *Biom J* 2011;53(4):689-704.doi: 10.1002/bimj.201000240. PMID: 21567443
47. Citkowicz M, Vevea JL. A parsimonious weight function for modeling publication bias. *Psychol Methods* 2017;22(1):28-41.doi: 10.1037/met0000119. PMID: 28252998