

Copas-Heckman-type sensitivity analysis for publication bias in rare-event meta-analysis under the framework of the generalized linear mixed model

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Summary

Publication bias (PB) is one of the serious issues in meta-analysis. Many existing methods dealing with PB are based on the normal-normal (NN) random-effects model assuming normal models in both the within-study and the between-study levels. For rare-event meta-analysis where the data contain rare occurrences of event, the standard NN random-effects model may perform poorly. Instead, the generalized linear mixed effects model (GLMM) using the exact within-study model is recommended. However, no method has been proposed for dealing with PB in rare-event meta-analysis using the GLMM. In this paper, we propose sensitivity analysis methods for evaluating the impact of PB on the GLMM based on the famous Copas-Heckman-type selection model. The proposed methods can be easily implemented with the standard software coring the nonlinear mixed-effects model. We use a real-word example to show how the usefulness of the proposed methods in evaluating the potential impact of PB in meta-analysis of the log-transformed odds ratio based on the GLMM using the non-central hypergeometric or binomial distribution as the within-study model. An extension of the proposed method is also introduced for evaluating PB in meta-analysis of proportion based on the GLMM with the binomial within-study model.

KEYWORDS

generalized linear mixed model, publication bias, sensitivity analysis, rare-event meta-analysis

1 | INTRODUCTION

In meta-analyses comparing two groups, it is often of interest whether the events (e.g., adverse events) are more or less possible to occur in the treatment group. This treatment effect is commonly quantified by the odds ratio (OR) or the log-transformed OR (lnOR). When events are rare or sample sizes of studies are small, it frequently happens that the observed numbers of events are zero, making the OR and its standard error (SE) to be zero or undefined. To address these issues, the continuity correction (CC) methods¹ are widely applied. However, the CC methods are not on sound rationale; among different CC methods, no single method is consistently recommended.²

Despite the inconsistency of the CC methods, the standard meta-analytical methods, such as the inverse-variance methods including the normal-normal random-effects model³ (hereinafter, the NN model), can be problematic. The NN model³ comprises a two-level model. The within-study model assumes the reported outcome to be normally distributed with the study-specific mean and the variance of outcome. The between-study model assumes that the treatment effect of each study is normally distributed with a common value and between-study variance. For meta-analysis with binary outcomes (e.g., the occurrence of event), the lnORs are often modeled using the NN model. In situations with small study sizes or rare events, the normal

approximation in the within-study model is questionable. Additionally, the NN model assumes the independence between InOR estimates and their SEs, which may not be satisfied practically and introduce bias.^{4,5} Alternative to the NN model,³ the generalized linear mixed model (GLMM) with exact within-study likelihood can be promising.^{4,5,6}

Meta-analytical results are often threatened by publication bias (PB), a phenomenon where studies with significant results are more likely to be published. Combining only those selectively published studies may lead to over-optimistic conclusions in meta-analyses.⁷ In recent decades, many sophisticated selection-model-based methods have been proposed to quantitatively evaluate the potential impact of PB.^{7,8} Famous ones include the sensitivity analysis methods by Copas and colleagues, such as the Copas-Heckman-type selection model,^{9,10,11} also known as the Heckman model^{12,13} in the field of econometrics; Others include the *t*-statistic-based selection model¹⁴ and the non-parametric worst-case bounds.¹⁵ Among them, the Copas-Heckman-type selection model has been extensively developed^{16,17,18} and further extended to address PB in multivariate meta-analyses.^{19,20,21,22} Most of these developments rely on the NN model or its multivariate versions. The Copas-Heckman-type selection model could avoid the correction of zero entries in data during the inference; Hattori and Zhou¹⁹ extended the Copas-Heckman-type selection model for diagnostic meta-analysis using the bivariate exact likelihood.

In rare-event meta-analysis, existing methods for PB inherit limitations of the CC methods or the NN model. While the GLMM with the exact likelihood can outperform the NN model, no methods are currently available for evaluating PB in the meta-analytical results of the GLMM. With the success of Hattori and Zhou,¹⁹ we aim to develop new methods for evaluating the impact of PB in rare-event meta-analysis using the GLMM.

2 | GLMM FOR META-ANALYSIS OF ODDS RATIOS WITHOUT PUBLICATION BIAS

Suppose that a meta-analysis contains N studies with binary outcomes. Each study has treatment and control groups; the numbers of events and subjects are accessible. Let y_{i0} and n_{i0} be the number of events and subjects in the control group, respectively; y_{i1} and n_{i1} are defined similarly in the treatment group. The data of study i are formulated by the contingency matrix in Table 1. The common practice of meta-analysis is based on the NN model, where the summary statistic such as the InOR calculated from Table 1 is used and the likelihood is constructed based on the normal approximation. (The details are outlined in Appendix A.)

Exact likelihoods based on the observations (y_{i0}, y_{i1}) are recommended and constructed as follows. The non-central hypergeometric distribution is proposed for the within-study likelihood, i.e., $y_{i1} | y_i$ follows the non-central hypergeometric distribution.⁴ The between-study model is assumed to be normally distributed, i.e., $\theta_i \sim N(\theta, \tau^2)$, where θ_i is the true InOR in each study, θ the overall InOR of interest, and τ^2 the between-study variance. This model is called the hypergeometric-normal (HN)-GLMM with parameters (θ, τ) estimated from the likelihood:

$$\prod_{i=1}^N \int_{-\infty}^{\infty} L_i(\theta_i) \frac{1}{\tau} \phi\left(\frac{\theta_i - \theta}{\tau}\right) d\theta_i \text{ with } L_i(\theta_i) = \frac{\binom{n_{i1}}{y_{i1}} \binom{n_{i0}}{y_{i0}} \exp(\theta_i y_{i1})}{\sum_{k \in K} \binom{n_{i1}}{k} \binom{n_{i0}}{y_{i0}-k} \exp(\theta_i k)}, \quad (1)$$

where $\phi(\cdot)$ denotes the density of standard normal distribution, and K is the set of all possible values of y_{i1} constrained by the marginal totals in Table 1.

When many studies are involved in meta-analysis, the estimation of HN-GLMM can be computationally demanding.⁵ The following binomial distribution: $y_{i1} | y_i \sim \text{Bin}\left(y_i, \frac{\exp\{\log(n_{i1}/n_{i0}) + \theta_i\}}{1 + \exp\{\log(n_{i1}/n_{i0}) + \theta_i\}}\right)$ can approximate to the non-central hypergeometric distribution in the HN-GLMM when the total number of events is much smaller than the sample sizes;⁴ we call this the binomial-normal (BN)-GLMM with the likelihood:

$$\prod_{i=1}^N \int_{-\infty}^{\infty} L_i(\theta_i) \frac{1}{\tau} \phi\left(\frac{\theta_i - \theta}{\tau}\right) d\theta_i \text{ with } L_i(\theta_i) = \binom{y_i}{y_{i1}} \frac{\exp\{\log(n_{i1}/n_{i0}) + \theta_i\}^{y_{i1}}}{[1 + \exp\{\log(n_{i1}/n_{i0}) + \theta_i\}]^{y_i}}. \quad (2)$$

3 | NEW SENSITIVITY ANALYSIS METHODS FOR PB IN THE GLMM

In the presence of selective publication of studies, the data of N studies may be biased sample from the population, possibly leading to biased estimates of parameters. Along with the idea by Copas and Shi¹⁰ for the NN model, we construct a sensitivity

analysis method, where a latent Gaussian variable responsible for selective publication is introduced, and a conditional likelihood given the published is constructed. For the NN model, the conditional likelihood is obtained on the property of the joint normal distribution of the outcome and the latent variable as summarized in Appendix B.

For binary outcomes, an alternative construction is needed. We consider a latent variable Z_i with the selection equation on the samples sizes:⁹

$$Z_i = a_0 + a_1 \sqrt{n_i} + \delta_i \quad (3)$$

where a_0 and a_1 are constants, n_i the total number of subjects in Table 1, and $\delta_i \sim N(0, 1)$; study i is published if and only if $Z_i > 0$. As explained in Appendix B, the latent variable (B3) is often used for the NN model. One application of the latent variable (3) was for PB in diagnostic meta-analysis.¹⁹

The probability of publishing study i is modeled by:

$$P(Z_i > 0 \mid n_i) = \Phi(a_0 + a_1 \sqrt{n_i}), \quad (4)$$

where $\Phi(\cdot)$ is the standard normal cumulative distribution function. Model (4) indicates that larger studies are more likely to be published. We then employ bivariate normal distribution with correlation coefficient ρ to present the dependence between δ_i and θ_i in the HN-GLMM (1) or BN-GLMM (2):

$$\begin{pmatrix} \theta_i \\ \delta_i \end{pmatrix} \sim N \left(\begin{pmatrix} \theta \\ 0 \end{pmatrix}, \begin{bmatrix} \tau^2 & \rho\tau \\ \rho\tau & 1 \end{bmatrix} \right).$$

Considering PB, the likelihood conditional on the published is constructed as

$$\prod_{i=1}^N \int L_i(\theta_i \mid Z_i > 0, n_i) \frac{1}{\tau} \phi \left(\frac{\theta_i - \theta}{\tau} \right) d\theta_i \quad (5)$$

with

$$\begin{aligned} L_i(\theta_i \mid Z_i > 0, n_i) &= \frac{P(Z_i > 0 \mid \theta_i, n_i) L_i(\theta_i)}{P(Z_i > 0 \mid n_i)} \\ &= \frac{P(a_0 + a_1 \sqrt{n_i} + \delta_i > 0 \mid \theta_i, n_i) L_i(\theta_i)}{P(Z_i > 0 \mid n_i)} \\ &= \frac{\Phi \left\{ \frac{a_0 + a_1 \sqrt{n_i} + \rho(\theta_i - \theta)/\tau}{\sqrt{1 - \rho^2}} \right\} L_i(\theta_i)}{\Phi(a_0 + a_1 \sqrt{n_i})}, \end{aligned}$$

where $L_i(\theta_i)$ is defined in likelihood (1) or (2). The parameters in (5) can be estimated by the maximum likelihood method. One concern is that parameters in (5) may not be fully identified; then, a sensitivity analysis approach can be taken as follows. Let $n_{\min}$ and $n_{\max}$ be the minimum and maximum numbers of subjects among the published studies; $P_{\min}$ and $P_{\max}$ denotes the probabilities of publishing a study with $n_{\min}$ and $n_{\max}$ subjects (practically, $P_{\min} \leq P_{\max}$). With model (4), $P_{\min} = \Phi(a_0 + a_1 \sqrt{n_{\min}})$ and $P_{\max} = \Phi(a_0 + a_1 \sqrt{n_{\max}})$ hold. Given the values of $(P_{\min}, P_{\max})$, the constants (a_0, a_1) are derived by

$$a_1 = \frac{\Phi^{-1}(P_{\max}) - \Phi^{-1}(P_{\min})}{\sqrt{n_{\max}} - \sqrt{n_{\min}}} \text{ and } a_0 = \Phi^{-1}(P_{\max}) - a_1 \sqrt{n_{\max}}.$$

Then, the parameters (θ, τ, ρ) in the likelihood conditional on the published (e.g., likelihood (5)) can be estimated by the ML method. On the other hand, the number of unpublished studies is estimated by $\sum_{i=1}^N \{1 - P(Z_i > 0 \mid n_i)\} / P(Z_i > 0 \mid n_i)$.

4 | APPLICATION

We revisit the meta-analysis of lnORs⁴ with the background and estimates without PB summarized in Box 1. We employed the proposed methods and the original Copas-Heckman-type selection model¹⁰ to evaluate the potential PB on the lnOR estimated by the HN/BN-GLMM and the NN model, respectively. The sensitivity analysis approach was used for all the methods to

estimate (θ, τ, ρ) by the ML method, where some reasonable values, $(P_{\min}, P_{\max}) = \{(0.9, 0.99), (0.8, 0.99), \dots, (0.1, 0.99)\}$, were fixed. The impact of PB was assessed via the changes of the estimated lnOR. Since the Copas-Heckman-type selection model adopted selection equation on the precision (i.e., $1/s_i$) of the lnOR,¹⁰ the parameter $P_{\min}$, for example, then indicates the probabilities of publishing study with *maximum* SE (*minimum* subjects).

Figure 1 presents the sensitivity analysis results on the lnOR estimated by different methods with the detailed estimates of parameters in Table A1. Given $P_{\max} = 0.99$ and decreasing $P_{\min}$, the lnOR increased with increasing number of unpublished studies. According to the results of the proposed methods, the lnOR considering PB and estimated by the HN/BN-GLMM remained significant, indicating that the meta-analytical results by the HN/BN-GLMM were robust against potential PB. For the HN/BN-GLMM model, there was little change of the lnOR over $P_{\min}$ (x-axis in Figure 1). On the other hand, for the NN model, certain change was observed possibly due to the influence of sparsity of data.

5 | DISCUSSION

Publication bias has been recognized as an inevitable problem in meta-analysis. Although many advanced selection-model-based methods are proposed for evaluating the impact of PB on the meta-analytical results, implementing these methods on rare-event meta-analysis can be problematic since they are based on the NN model. The GLMM with the exact within-study likelihood is recommended for rare-event meta-analysis;^{4,5,6} we proposed sensitivity analysis methods to fill missingness of methods for evaluating the potential PB in the GLMM, and the proposed methods can be easily implemented by the standard statistical software. With the simple implementation, the proposed methods could have wide applicability in rare-event meta-analysis. As demonstrated in likelihood (5), our development can handle the exact likelihoods in a unified way by setting a relevant likelihood function. We present the additional case of rare-event meta-analysis of proportions in single group with a real example in Appendix D. In summary, our proposal provides practical tools for evaluating PB in rare-event meta-analysis using the GLMM.

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DATA AVAILABILITY STATEMENT

R codes together with a sample application data set are available at <https://github.com/meta2020/metaeventsa-r>

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

HIGHLIGHTS

What is already known

- For rare-event meta-analysis, the generalized linear mixed effects model (GLMM) adopting the exact within-study likelihood, such as the hypergeometric or the binomial distributions, are recommended than the standard normal-normal random-effects model using the approximately normal likelihood.
- Publication bias (PB), also known as small study effects, is one of the major issues in meta-analysis; the existing methods for PB are developed for the NN model and can be problematic for rare-event meta-analysis.
- The Copas-Heckman-type selection model is one of the famous sensitivity analysis methods for PB and has been widely developed for various meta-analyses; however, this model cannot be used directly for PB in rare-event meta-analysis using the GLMM.

What is new

- We successfully extended the Copas-Heckman-type selection model to deal with PB in rare-event meta-analysis based on the GLMM.
- This work is the first development of the Copas-Heckman-type selection model for evaluating the impact of PB in rare-event meta-analysis using the exact likelihood.

Potential impact for Research Synthesis Methods readers outside the authors' field

- The proposed methods help researchers analyze the impact of PB on the meta-analytical estimates (e.g., the log-transformed odds ratio, the logit-proportion) using the GLMM, and then robust conclusions can be drawn from rare-event meta-analysis.
- The proposed methods provide simple tools for evaluating PB in rare-event meta-analysis based on the GLMM, and we provided the open-source R codes for researchers to implement the methods in practice.

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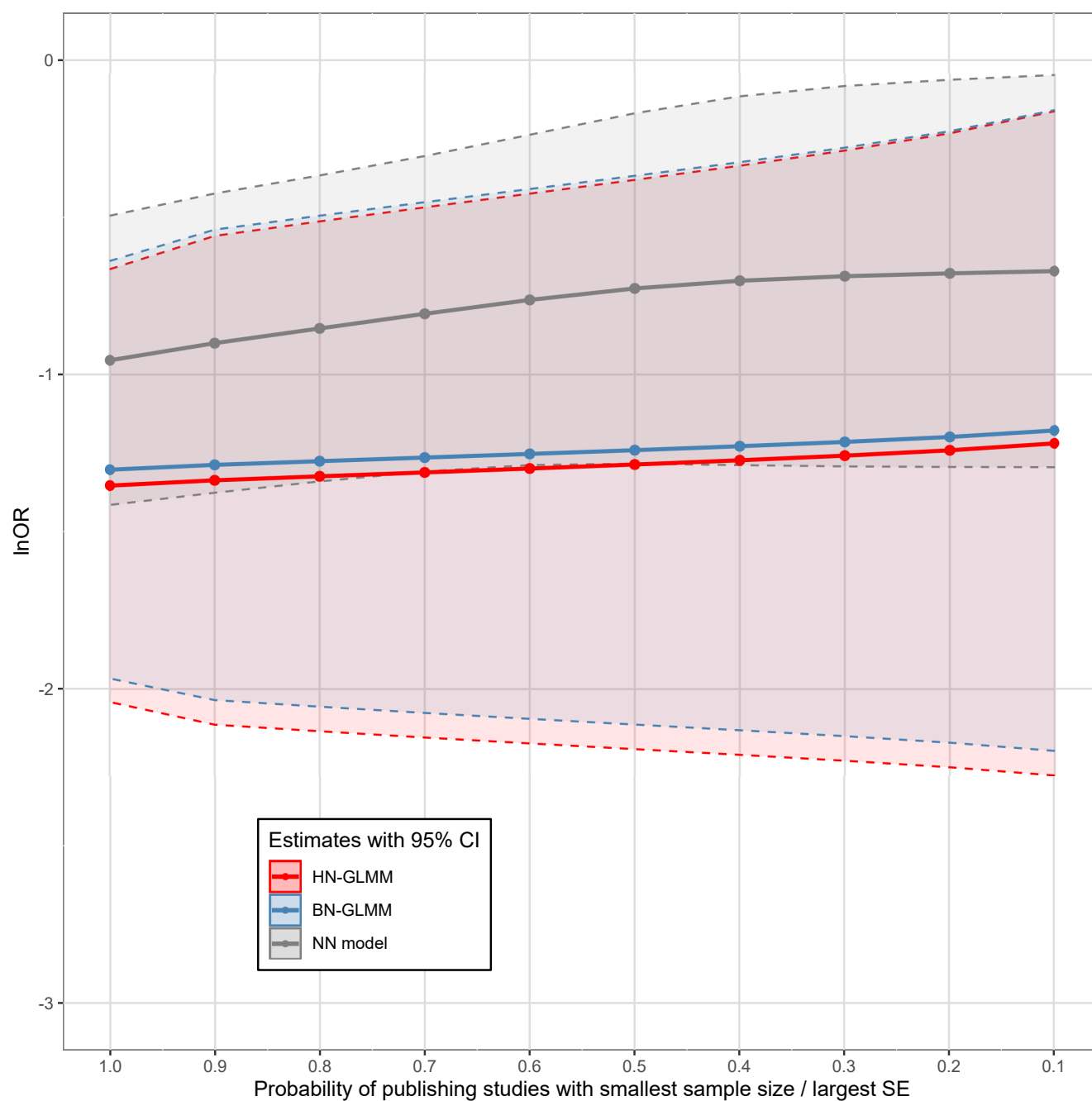


FIGURE 1 Application: Comparison of sensitivity analysis methods for PB in meta-analysis of InORs.

TABLE 1 Example of the contingency table for data of study i

	Event	Non-event	Total
Treatment	y_{i1}	$n_{i1} - y_{i1}$	n_{i1}
Control	y_{i0}	$n_{i0} - y_{i0}$	n_{i0}
Total	y_i	$n_i - y_i$	n_i

BOX 1 Meta-analysis in the application without considering PB

Background: This is the meta-analysis of lnORs of catheter-related bloodstream infection (CRBSI) between anti-infective-treated (AIT) central venous catheters and the standard catheter.²³ The data of this meta-analysis are presented below.

Study	AIT catheter		Standard catheter	
	CRBSI (y_{i1})	Patients (n_{i1})	CRBSI (y_{i0})	Patients (n_{i0})
1	3	117	0	116
2	3	35	1	44
3	9	195	2	208
4	7	136	0	130
5	6	157	5	151
6	4	139	1	98
7	3	177	1	174
8	2	39	1	74
9	19	103	1	97
10	2	122	1	113
11	7	64	0	66
12	1	58	0	70
13	5	175	3	188
14	11	180	6	187
15	0	105	0	118
16	1	262	0	252
17	3	362	1	345
18	1	69	4	64

Methods: In Stijnen et al,⁴ the meta-analytical results by the NN model and the HN/BN-GLMM were compared without considering selective publication of studies. We reproduced the results and estimated the parameters by the ML method. The optimization was implemented by the R function `nlminb()`; the SEs of the parameters were estimated by the inverse of the empirical Fisher information matrix following the ML theory. R function `hcubature()` was used to calculate the integrals in the likelihoods of HN/BN-GLMM.

Results: The HN-GLMM and the BN-GLMM gained similar results with the lnOR estimated as -1.353 (-2.041 to -0.665) and -1.303 (-1.966 to -0.639), respectively, since the total number of CRBSI was relatively small to the total number of subjects. The NN model estimated the meta-analytical lnOR to be -0.955 (95%CI, -1.501 to -0.408), which was biased towards zero.⁴ Without accounting for selective publication, there are certain discrepancies between the NN model and the HN/BN-GLMM model, indicating that normal approximation in the NN model was questionable.

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APPENDIX

A REVIEW OF THE NORMAL-NORMAL RANDOM-EFFECTS MODEL WITHOUT PUBLICATION BIAS

As mentioned in Section 2 of the main text, we present the likelihood of the normal-normal random-effects model (hereinafter, the NN model) without considering publication bias (PB).

Based on the data in Table 1 of the main text, to evaluate the occurrence of events between two groups, the measurement of log-transformed odds ratio (lnOR) is often reported and estimated by

$$\hat{\theta}_i = \log \frac{y_{i1}/(n_{i1} - y_{i1})}{y_{i0}/(n_{i0} - y_{i0})},$$

with its SE estimated by

$$s_i = \sqrt{\frac{1}{y_{i1}} + \frac{1}{n_{i1} - y_{i1}} + \frac{1}{y_{i0}} + \frac{1}{n_{i0} - y_{i0}}}.$$

If there are zero entries in the data, the continuity correction method is usually conducted by adding 0.5 to the numbers of events and non-events before estimating the lnOR and its SE.

In the absence of PB, the NN model³ assumes that, in the within-study level, the distribution of the estimated lnOR $\hat{\theta}_i$ is modeled by

$$\hat{\theta}_i | \theta_i \sim N(\theta_i, s_i^2),$$

where θ_i is the true lnOR in each study. Following the convention in meta-analysis field, s_i is regarded as known and fixed. In the between-study level, it is assumed that

$$\theta_i \sim N(\theta, \tau^2),$$

where θ is the overall lnOR of interest, and τ^2 is the between-study variance. Marginally, $\hat{\theta}_i$ has the following normal distribution:

$$\hat{\theta}_i \sim N(\theta, s_i^2 + \tau^2). \quad (\text{A1})$$

In the NN model, the within-study likelihood is constructed based on the observations $\hat{\theta}_i$ which approximately follow normal distribution. Then, allowing for the existence of between-study heterogeneity, the unknown parameters (θ, τ) can be estimated based on the likelihood:

$$\prod_{i=1}^N \int_{-\infty}^{\infty} L_i(\theta_i) \frac{1}{\tau} \phi\left(\frac{\theta_i - \theta}{\tau}\right) d\theta_i \text{ with } L_i(\theta_i) = \frac{1}{\sqrt{2\pi}s_i} \exp\left(-\frac{(\hat{\theta}_i - \theta_i)^2}{2s_i^2}\right), \quad (\text{A2})$$

where $\phi(\cdot)$ denotes the density of standard normal distribution.

B REVIEW OF THE COPAS-HECKMAN-TYPE SELECTION MODEL FOR PB IN THE NN MODEL

As mentioned in Section 3 of the main text, we review the original Copas-Heckman-type selection model¹⁰ addressing PB in the NN model.

Based on the NN model (A1), Copas and Shi¹⁰ considered the variance components model for the outcome:

$$\hat{\theta}_i = \theta + (\sigma_i + \tau^2)^{1/2} \epsilon_i,$$

where $\epsilon_i \sim N(0, 1)$ and $\sigma_i^2 = \text{var}(\hat{\theta}_i | \theta_i)$ is the within-study sampling variance. (Given large numbers of subjects in each study, σ_i^2 can be replaced by s_i^2 .) They introduced a latent Gaussian variable Z_i with the selection equation:

$$Z_i = \gamma_0 + \gamma_1/s_i + \delta_i, \quad (\text{B3})$$

where γ_0 and γ_1 are constants and $\delta_i \sim N(0, 1)$; study i is published if and only if $Z_i > 0$. A correlation was presented to link publication with the outcome:

$$\rho = \text{corr}(\epsilon_i, \delta_i),$$

When $\rho = 0$, θ_i is independent of δ_i , indicating that study outcome does not influence its publication, and then there is no PB. A probit model was employed to model the probability of selectively publishing one study:

$$P(Z_i > 0 | s_i) = \Phi(\gamma_0 + \gamma_1/s_i), \quad (\text{B4})$$

where $\Phi(\cdot)$ is the standard normal cumulative distribution function. Probability (B4) indicates that studies with small SE (large studies) are more likely to be published.

Under selective publication of studies, the log-likelihood conditional on the published studies was derived based on the NN model, as shown in equation (4) in Copas and Shi:¹⁰

$$\begin{aligned} \sum_{i=1}^N \log p(\hat{\theta}_i | z_i > 0, s_i) &= \sum_{i=1}^N \left\{ \log p(\hat{\theta}_i) + \log p(z_i > 0 | \hat{\theta}_i, s_i) - \log p(z_i > 0 | s_i) \right\} \\ &= \sum_{i=1}^N \left\{ -\frac{1}{2} \log(\tau^2 + \sigma_i^2) - \frac{\hat{\theta}_i - \theta}{2(\tau^2 + \sigma_i^2)} - \log \Phi(\gamma_0 + \gamma_1/s_i) + \log \Phi(v_i) \right\} \end{aligned}$$

with

$$v_i = \frac{\gamma_0 + \gamma_1/s_i + \tilde{\rho}_i(\hat{\theta}_i - \theta)/\sqrt{\tau^2 + \sigma_i^2}}{\sqrt{1 - \rho_i^2}} \text{ and } \tilde{\rho}_i = \frac{\sigma_i}{\sqrt{\tau^2 + \sigma_i^2}} \rho.$$

The parameters (θ, τ, ρ) in the above likelihood can be estimated by the maximum likelihood method; meanwhile, the number of unpublished studies is estimated by $\sum_{i=1}^N \{1 - P(Z_i > 0 | s_i)\} / P(Z_i > 0 | s_i)$.

C THE ESTIMATION RESULTS IN APPLICATION

As mentioned in Section 3 of the main text, in Table C1, we presented the estimates of parameters taking PB into account by the proposed methods and the original Copas-Heckman-type selection model.

D NEW SENSITIVITY ANALYSIS FOR PB IN RARE-EVENT META-ANALYSIS OF PROPORTIONS

In Section 2-4 of the main text, we described the developed sensitivity analysis method for evaluating the impact of PB in rare-event meta-analysis of lnORs. As mentioned in Section 5, we introduce our sensitivity analysis method for PB in the rare-event meta-analysis of proportions.

TABLE C1 Application in the main text: Summary of the estimations of different sensitivity analysis methods

$(P_{\min}, P_{\max})$	Proposed method (HN-GLMM)				Proposed method (BN-GLMM)			Copas-Heckman-type selection model			
	M	θ (95% CI)	τ (SE)	ρ (SE)	θ (95% CI)	τ (SE)	ρ (SE)	M	θ (95% CI)	τ (SE)	ρ (SE)
	0	-1.35 (-2.04, -0.67)	0.83 (0.38)		-1.30 (-1.97, -0.64)	0.78 (0.38)		0	-0.95 (-1.41, -0.49)	0.00 (0.81)	
(0.9, 0.99)	1	-1.34 (-2.11, -0.56)	0.84 (0.39)	-0.20 (2.24)	-1.29 (-2.04, -0.54)	0.78 (0.39)	-0.20 (2.29)	1	-0.90 (-1.38, -0.42)	0.00 (0.66)	-0.54 (0.61)
(0.8, 0.99)	2	-1.32 (-2.13, -0.51)	0.84 (0.39)	-0.22 (1.66)	-1.28 (-2.06, -0.49)	0.78 (0.39)	-0.22 (1.71)	2	-0.85 (-1.34, -0.37)	0.00 (0.58)	-0.60 (0.46)
(0.7, 0.99)	3	-1.31 (-2.15, -0.47)	0.84 (0.39)	-0.23 (1.39)	-1.26 (-2.08, -0.45)	0.78 (0.39)	-0.23 (1.44)	4	-0.81 (-1.31, -0.31)	0.00 (0.53)	-0.63 (0.40)
(0.6, 0.99)	4	-1.30 (-2.17, -0.42)	0.84 (0.39)	-0.24 (1.21)	-1.25 (-2.09, -0.41)	0.78 (0.39)	-0.23 (1.26)	5	-0.76 (-1.29, -0.24)	0.00 (0.49)	-0.63 (0.38)
(0.5, 0.99)	6	-1.29 (-2.19, -0.38)	0.84 (0.39)	-0.24 (1.08)	-1.24 (-2.11, -0.37)	0.78 (0.39)	-0.24 (1.12)	8	-0.73 (-1.28, -0.17)	0.00 (0.47)	-0.61 (0.36)
(0.4, 0.99)	8	-1.27 (-2.21, -0.34)	0.84 (0.39)	-0.24 (0.97)	-1.23 (-2.13, -0.32)	0.78 (0.39)	-0.24 (1.01)	11	-0.70 (-1.29, -0.12)	0.00 (0.46)	-0.56 (0.35)
(0.3, 0.99)	11	-1.26 (-2.23, -0.29)	0.84 (0.39)	-0.23 (0.87)	-1.21 (-2.15, -0.28)	0.78 (0.39)	-0.23 (0.91)	16	-0.69 (-1.29, -0.08)	0.00 (0.45)	-0.50 (0.32)
(0.2, 0.99)	17	-1.24 (-2.25, -0.23)	0.84 (0.39)	-0.23 (0.78)	-1.20 (-2.17, -0.23)	0.78 (0.39)	-0.23 (0.81)	24	-0.68 (-1.29, -0.06)	0.00 (0.44)	-0.43 (0.29)
(0.1, 0.99)	32	-1.22 (-2.28, -0.16)	0.84 (0.39)	-0.22 (0.67)	-1.18 (-2.20, -0.16)	0.78 (0.39)	-0.22 (0.70)	47	-0.67 (-1.29, -0.05)	0.00 (0.44)	-0.35 (0.24)

M indicates the number of potentially unpublished studies; CI indicates the confidence interval; SE indicates the standard error.

D.1 Likelihood conditional on the published studies

Suppose we are conducting the meta-analysis of proportions of event, and the parameter of interest is the proportion π . Each study i ($i = 1, \dots, N$) reports the number of events y_i and the total number of subjects n_i . In the absence of PB, the generalized linear mixed model (GLMM) works with the log odds $\theta_i = \text{logit}(\pi_i) = \log \frac{\pi_i}{1 - \pi_i}$ as the measurement of effect, where π_i denotes the proportion of event in each study. The GLMM uses the binomial distribution $y_i \sim \text{Binomial}(n_i, \pi_i)$ as the within-study model.⁴ The likelihood is written as

$$\prod_{i=1}^N \int_{-\infty}^{\infty} L_i(\theta_i) \frac{1}{\tau} \phi\left(\frac{\theta_i - \theta}{\tau}\right) d\theta_i \text{ with } L_i(\theta_i) = \binom{n_i}{y_i} \frac{\exp(\theta_i)^{y_i}}{\{1 + \exp(\theta_i)\}^{n_i}}. \quad (\text{D5})$$

To evaluate the impact of PB, we follow the approach in Section 3 of the main text to construct the likelihood conditional on the published studies. The likelihood (5) in the main text can be applied by replacing the within-study likelihood $L_i(\theta_i)$ with the one in likelihood (D5).

D.2 Application

As illustration of the proposed method in rare-event meta-analysis of proportions, we adopted the same data in Box 2 of the main text but only analyze data in the AIT catheter group; the parameter of interest is the logit-transformed proportion of CRBSI. Without considering PB, the logit-proportion of events was estimated to be -4.812 (95% CI: -5.508 to -4.116) by the likelihood (D5) of GLMM and -4.238 (-4.793 to -3.682) by the likelihood (A2) NN model.³ The same scenarios of sensitivity parameters in Section 4 of the main text were considered to evaluate PB on the estimates of logit-transformed proportion.

We presented the comparison of the proposed method and the Copas-Heckman-type selection model in Figure D1. In the presence of potentially unpublished studies, the estimated proportion still remained significantly different from zero in both methods. The detailed estimated results of the proposed sensitivity analysis method and the Copas-Heckman-type selection model are in Table D2. For the proposed method, there was little change of the logit-transformed proportion over $P_{\min}$ (x -axis in Figure D1). On the other hand, for the NN model, certain change was observed possibly due to the influence of sparsity of data.

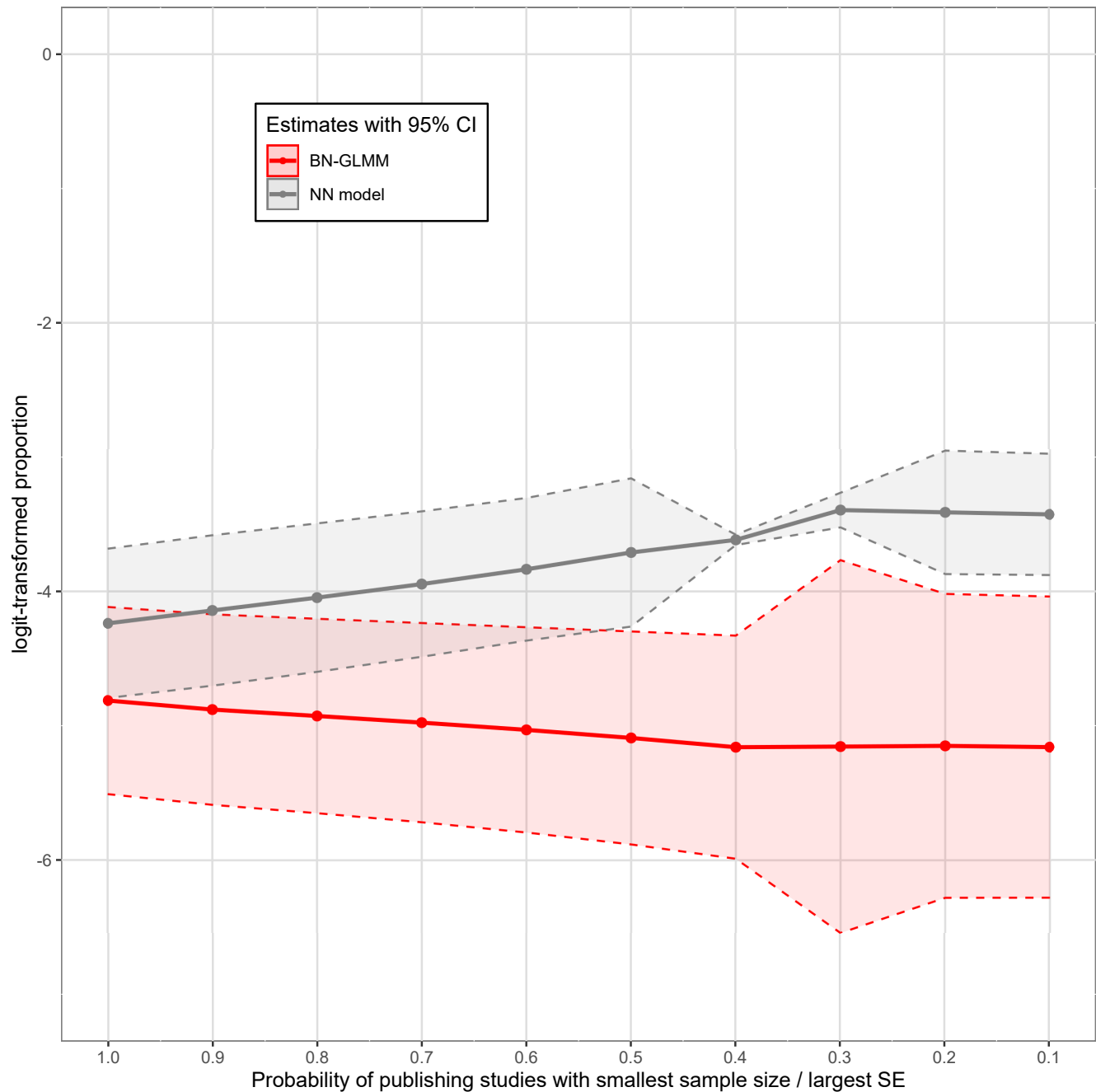


FIGURE D1 Comparison of the sensitivity analysis methods for PB in meta-analysis of proportions.

TABLE D2 Summary of the estimations of different sensitivity analysis methods

$(P_{\min}, P_{\max})$	Proposed method (BN-GLMM)				Copas-Heckman-type selection model			
	M	θ (95% CI)	τ (SE)	ρ (SE)	M	θ (95% CI)	τ (SE)	ρ (SE)
	0	-4.81 (-5.51, -4.12)	0.91 (0.33)		0	-4.24 (-4.79, -3.68)	0.58 (0.26)	
(0.9, 0.99)	1	-4.88 (-5.59, -4.17)	0.94 (0.34)	1.00 (NaN)	1	-4.14 (-4.70, -3.58)	0.53 (0.26)	-0.71 (0.46)
(0.8, 0.99)	2	-4.93 (-5.65, -4.20)	0.96 (0.35)	1.00 (NaN)	3	-4.05 (-4.60, -3.49)	0.48 (0.27)	-0.82 (0.29)
(0.7, 0.99)	3	-4.98 (-5.72, -4.24)	0.98 (0.36)	1.00 (NaN)	5	-3.95 (-4.49, -3.40)	0.41 (0.28)	-0.88 (0.20)
(0.6, 0.99)	4	-5.03 (-5.79, -4.27)	1.00 (0.36)	1.00 (NaN)	7	-3.84 (-4.37, -3.31)	0.34 (0.29)	-0.93 (8192.00)
(0.5, 0.99)	6	-5.09 (-5.88, -4.30)	1.02 (0.37)	1.00 (NaN)	10	-3.71 (-4.26, -3.16)	0.25 (0.35)	-0.97 (8192.00)
(0.4, 0.99)	8	-5.16 (-5.99, -4.33)	1.03 (0.38)	1.00 (NaN)	15	-3.62 (-3.66, -3.58)	0.00 (0.04)	-1.00 (8192.00)
(0.3, 0.99)	11	-5.15 (-6.54, -3.77)	0.99 (0.45)	0.83 (1.21)	22	-3.39 (-3.52, -3.27)	0.00 (0.07)	-1.00 (8192.00)
(0.2, 0.99)	17	-5.15 (-6.28, -4.02)	0.96 (0.37)	0.69 (0.73)	36	-3.41 (-3.87, -2.95)	0.00 (0.29)	-0.84 (0.11)
(0.1, 0.99)	32	-5.16 (-6.28, -4.04)	0.93 (0.34)	0.57 (0.60)	76	-3.43 (-3.88, -2.98)	0.00 (0.30)	-0.71 (0.11)

M indicates the number of potentially unpublished studies; CI indicates the confidence interval; SE indicates the standard error; NaN indicates “not a value”, an undefined value.