#### RESEARCH ARTICLE

# The impact of continuity correction methods in Cochrane reviews with single-zero trials with rare events: A metaepidemiological study

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#### Abstract

Meta-analyses examining dichotomous outcomes often include single-zero studies, where no events occur in intervention or control groups. These pose challenges, and several methods have been proposed to address them. A fixed continuity correction method has been shown to bias estimates, but it is frequently used because sometimes software (e.g., RevMan software in Cochrane reviews) uses it as a default. We aimed to empirically compare results using the continuity correction with those using alternative models that do not require correction. To this aim, we reanalyzed the original data from 885 meta-analyses in Cochrane reviews using the following methods: (i) Mantel-Haenszel model with a fixed continuity correction, (ii) random effects inverse variance model with a fixed continuity correction, (iii) Peto method (the three models available in RevMan), (iv) random effects inverse variance model with the treatment arm continuity correction, (v) Mantel-Haenszel model without correction, (vi) logistic regression, and (vii) a Bayesian random effects model

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with binominal likelihood. For each meta-analysis we calculated ratios of odds ratios between all methods, to assess how the choice of method may impact results. Ratios of odds ratios <0.8 or <1.25 were seen in  $\sim$ 30% of the existing meta-analyses when comparing results between Mantel–Haenszel model with a fixed continuity correction and either Mantel–Haenszel model without correction or logistic regression. We concluded that injudicious use of the fixed continuity correction in existing Cochrane reviews may have substantially influenced effect estimates in some cases. Future updates of RevMan should incorporate less biased statistical methods.

#### K E Y W O R D S

continuity correction, meta-analysis, single-zero studies, zero event, zero-cell correction

#### Highlights

#### What is already known

- Meta-analyses of dichotomous outcomes often use "continuity correction" to avoid computational issues in studies with zero events in one arm (single-zero studies). However, this could potentially bias study estimates.
- Despite the availability of more advanced models for handling single-zero studies, RevMan, the official Cochrane software for meta-analyses, continues to use continuity corrections.
- While simulation studies have highlighted potential issues associated with the use of continuity corrections and despite the fact that more advanced methods have been proposed, the impact of using alternative methods on effect estimates within established Cochrane reviews remains uncertain.

#### What is new

- We contrasted the effect estimates obtained by several alternative methods against the Mantel-Haenszel model with a continuity correction (RevMan MH), the default model in RevMan software, using data from 885 established meta-analyses within Cochrane reviews.
- Meta-analyses including single-zero studies were commonly seen in Cochrane reviews, and 64% of them used RevMan MH to deal with single-zero studies.
- In scenarios with low event rates and small sample sizes, a difference in the point estimates of odds ratios of 25% or more was observed in approximately 30% of existing meta-analyses, when comparing results between RevMan MH and either MH or logistic regression.

### Potential impact for Research Synthesis Methods readers

• Our findings underscore that researchers, readers, peer-reviewers, and journal editors of meta-analyses should interpret results carefully when they appraise meta-analyses involving single-zero studies, as some commonly used methods may alter the estimates. Future meta-analyses should avoid using suboptimal methods.

# **1** | INTRODUCTION

Systematic reviews play an important role in decisionmaking.<sup>1</sup> A meta-analysis is the statistical combination of results from two or more separate studies. It yields an overall estimate of the effectiveness of an intervention compared with a control treatment. There are many methods that can be used for the meta-analysis of dichotomous outcomes, four of which are more widely used than others, and are also available as analysis options in RevMan web and RevMan 5, the current and prior official software used for Cochrane reviews.<sup>1–3</sup> These are three fixed-effect models, that is, Mantel–Haenszel (MH), Peto, and inverse variance (IV) methods, and one random-effects model, that is, the DerSimonian and Laird method.<sup>1</sup>

A meta-analysis of odds ratios or risk ratios sometimes includes studies in which one arm has zero events (single-zero studies). The inclusion of single-zero studies in meta-analyses can introduce computational errors; hence, several methods have been proposed to address these issues.<sup>4</sup> The fixed continuity correction, commonly implemented in software like RevMan, adds a specific value (usually 0.5) to all cells of the two-by-two tables in each study. Simulation studies, however, have raised concerns about its validity.<sup>4-6</sup> This method can artificially move the point estimate away from extremes, consequently leading to a bias toward the null effect, especially when the true effect is substantial. In contrast, alternative methods such as the MH without continuity correction. logistic regression models, and the Peto method may outperform methods utilizing the fixed continuity correction as they do not require zero-cell correction. However, Rev-Man automatically implements the fixed continuity correction when using the Mantel-Haenszel and IV methods and may result in biases toward no treatment effect.1

Although issues associated with the use of fixed continuity correction have been increasingly recognized and illustrated through simulation studies, the practice has not changed. This might be because, despite the theoretical arguments and simulations, review authors were uncertain about how various zero-cell correction methods would impact their results. No previous study has investigated whether the application of more sophisticated methods such as MH without corrections, logistic regression, or the Peto method would impact the effect estimates in existing meta-analyses within Cochrane reviews.<sup>7</sup> In the present study, we aim to empirically compare results after using the continuity correction with results from modes that do not require correction, in terms of the effect estimates and their interpretation in Cochrane reviews.

# 2 | METHODS

The protocol of the present study was posted on the OSF registry.  $^{\rm 8}$ 

# 2.1 | Eligibility criteria

We included all Cochrane reviews of interventions that included only randomized controlled trials (RCTs). We only included the most recent version of the reviews, when one or more updates are available. Reviews were eligible if a pair-wise meta-analysis using risk ratio or odds ratio was performed and included at least one single-zero study, that is, a study with zero events in one but not both treatment arms. Since this study primarily focused on methods to address single-zero studies, when reviews had included double-zero studies (studies with zero events in both treatment arms), we only included single-zero studies and excluded double-zero studies from our analyses. We selected meta-analyses with event rates of <5% and sample sizes of <1000, as a previous study showed that the method of dealing with single-zero studies only played a role in meta-analyses with small sample sizes and rare events.<sup>9</sup> We excluded a review if it was not possible to extract the  $2 \times 2$  table from any of the meta-analyses therein, or if we could not download the data by clicking "Download statistical data" in the Cochrane library.

# 2.2 | Searches and study selection

We searched the Cochrane Database of Systematic Reviews by using a filter aimed at returning reviews on interventions from inception to September 30, 2022. We scraped the relevant reviews and downloaded data from the Cochrane library's website for each review using Python selenium package version 3.141.0.<sup>14</sup> Thereafter, we loaded the data to R statistical software and checked the eligibility according to the criteria above.

# 2.3 | Data extraction

All data used in the present study was obtained from publicly available dataset of Cochrane reviews. For each meta-analysis that included a single-zero study we extracted the following data: number of participants and events included in each study in the metaanalysis, types of statistical models used for the metaanalysis.

# WILEY – Research Synthesis Methods 2.3.1 | Outcomes of interest of this study

The primary outcome was the difference in effect estimates between the results of each meta-analysis obtained after using Mantel–Haenszel model with a fixed continuity correction, that is, adding 0.5 to all cells of the  $2 \times 2$  table (the model implemented in the RevMan software— "RevMan MH") with results obtained after using various models listed in the next paragraph. Difference in estimates between two models was quantified as a ratio of odds ratios (ROR).

# 2.4 | Statistical analysis

We reported the proportion of reviews with a metaanalysis including single-zero studies, and the proportion of such reviews with event rates of <5% and sample sizes of <1000 among all Cochrane reviews. We tabulated the following characteristics of included meta-analyses; number of participants and events included in each study in the meta-analysis, types of statistical models used for the meta-analysis.

We repeated each meta-analysis in the included reviews using the following methods (i) RevMan MH, (ii) random effects inverse variance model with a fixed continuity correction (REIV), (iii) random effects inverse variance model with the treatment arm continuity correction (REIV TACC), (iv) Peto method, (v) Mantel-Haenszel model without correction, (vi) the random effects logistic regression model, and (vii) a Bayesian random effects logistic regression model using a binomial likelihood for the outcome. We used uninformative prior distributions for the log-odds of the reference treatment and the treatment effects ( $N_0$ ,  $\sigma^2 = 1000$ ). We also used a vague half normal prior for the heterogeneity parameter  $\tau^2$ . We ran 4 chains of 5000 iterations after 1000 burn in. The R script used for conducting the Bayesian analysis can be found in the Appendix S1.

Odds ratios were used for the effect estimates. For each meta-analysis, we calculated the ROR between these models. We presented the distribution of RORs using histograms and scatter plots. Further, we characterized their sizes using the following predefined categories:

- 1. Small, ROR in the range of 0.9–1.11.
- 2. Moderate, ROR in the range of 0.8–0.9 or 1.11–1.25.
- 3. Large, ROR in the range of  $\geq 1.25$  or  $\leq 0.8$ .

For meta-analyses with extremely large differences, we further explored their characteristics in terms of the

participants, intervention, comparator, outcomes, number of events in each study in the meta-analyses, and effect sizes from each statistical method. The criteria for selecting instances of exceptionally large differences were based on the highest and lowest values of the RORs observed in each comparison. All analyses were performed by meta package (ver.2.4-0) of R version 4.1.2, and RevMan 5.4.1.

# 3 | RESULTS

Our search identified 2300 Cochrane reviews of interventions, among which there were 1540 reviews that included 20,535 meta-analyses of dichotomous outcomes. Of those, 856 (56%) reviews included 4984 meta-analyses incorporating at least one single-zero study. Ultimately, we selected 383 (25%) reviews with 885 meta-analyses for our main analysis, each having a control event rate of less than 0.05 and a total participant count fewer than 1000 (Figure 1).

Table 1 shows characteristics of the included metaanalyses with a control event rate of <0.05 and a total participant count fewer than 1000. Median (interquartile range, IQR) number of studies included in the meta-analyses was 3 (2–4). RevMan MH model was the most frequently used model in the original Cochrane reviews.

Figure 2 visualizes the agreement between the results of meta-analyses using RevMan MH and other methods. Ten panels in the lower-left of the figure show histograms of logRORs, the denominator of which can be read in the diagonal element to the right, and the numerator to the diagonal element above. The upper-right panels present scatter plots of logORs, with the vertical axis representing the statistical methods indicated at diagonal element at the bottom and the horizontal axis representing the methods indicated at the left.

We found that the Peto method tended to be inconsistent with any other methods, indicated by the wide distribution of logROR histogram and by many outliners off the 45° diagonal in the scatterplot. RevMan MH was consistent with REIV or REIV TACC but not with MH, logistic regression, and the Bayesian model. MH was mostly consistent with the logistic regression model.

Table 2 shows the characteristics of the included meta-analyses categorized according to the RORs for each method versus RevMan MH. A total of 109 meta-analyses using MH and logistic regression did not converge due to various computational errors. In the remaining sample (n = 776), we observed a large



TABLE 1 Characteristics of included meta-analyses.

Characteristic	<i>n</i> = 885
Number of included studies	3 (2, 4)
Number of participants	430 (257, 690)
Number of events	10 (5, 20)
Statistical methods used in the Cochrane reviews	
Fixed IV method with a fixed correction	17 (2%)
RevMan MH model <sup>a</sup>	566 (64%)
REIV	302 (34%)

*Note*: Values in parentheses show percentages or interquartile range. Abbreviations: MH, Mantel–Haenszel; REIV, random effects inverse variance method with a fixed correction.

<sup>a</sup>The Mantel–Haenszel model with a fixed continuity correction, adding 0.5 to all cells of the  $2 \times 2$  table, implemented in the RevMan software.

difference between the results obtained from RevMan MH and MH, logistic regression, and Bayesian model in 27%, 32%, and 63% of cases, respectively. Meta-analyses with large RORs for methods other than the REIV or REIV TACC versus RevMan MH tended to have a small number of participants and events.

Table 3 shows details from meta-analyses that showed extremely large size of ROR. The extremely large sizes of ROR were observed when there were many events in either the intervention group or the control group, and few events in the opposite group.

# 4 | DISCUSSION

We found that many of existing Cochrane reviews included at least one meta-analysis including single-zero studies. Most were analyzed using RevMan MH or Random effects IV models, which involve using a fixed continuity correction. Our reanalysis showed RevMan MH gave many times substantially different results than MH without correction or the logistic regression model; both have been advocated as superior models for handling single-zero studies. MH without correction and logistic regression models showed agreement with each other, but the Peto method tended to be inconsistent with all other methods. Moreover, a substantial difference was evident in  $\sim$ 30% of the existing meta-analyses when comparing the results between RevMan MH and either MH or logistic regression. Such large differences were mainly seen in meta-analyses with a smaller number of participants and events. The extremely large difference in the ORs from RevMan MH and other methods was observed when there were many events in either the intervention group or the control group, and few events in the opposite group.

We found that a substantial proportion of the ORs from RevMan MH were either 25% smaller or larger than the ORs from MH or logistic regression models. Such large difference of treatment effects may alter conclusions drawn from meta-analyses. Our results strengthen previously expressed concerns that the use of continuity



**FIGURE 2** Agreement in effect estimates obtained by each statistical method to deal with single-zero studies. Panels at the lower-left present histograms of LogROR, for which the denominator of the ROR appears in the diagonal at the right and the numerator above. Upper right panels present scatter plots of Log odds ratios, with the vertical axis representing the statistical methods indicated in the diagonal at the bottom and the horizontal axis representing the methods indicated at the left. RevMan MH denotes the Mantel–Haenszel model with a fixed continuity correction, adding 0.5 to all cells of the  $2 \times 2$  table, which is the model implemented in the RevMan software. REIV denotes random effects inverse variance model with a fixed continuity correction, adding 0.5 to all cells of the treatment arm continuity correction. MH denotes the Mantel–Haenszel model without correction. Bayesian random effects model using a binomial likelihood for the outcome.

correction is common, even though it is not generally recommended.<sup>5–7</sup> This might be mainly due to the fact that RevMan, which is widely used in preparing systematic reviews and meta-analyses, has implemented the method as the default setting.<sup>15</sup> The Peto methods prone to break down when ORs are large. This observation is in agreement with prior studies which indicate that the approximation employed for calculating the log OR is reliable for modest effects of the intervention.<sup>1,16</sup>

Our results were consistent with a previous study that showed that the use of fixed continuity correction led to biased estimates, while MH without correction or logistic regression yielded the least biased estimates.<sup>6</sup> The agreement that we found between MH and logistic regression was also seen in a previous study.<sup>4</sup> Thus, our findings are not new; however, we were able to illustrate the issues related to using a fixed continuity correction utilizing real data from published meta-analyses.

Our descriptive analysis showed some situations where there is a high likelihood of large differences between comparing RevMan MH and other methods, namely (i) meta-analyses with small number of participants and events, or (ii) meta-analyses with many events in either the intervention group or the control group and few events in the opposite group (i.e., large effects). This information is crucial for informing researchers, readers, peer-reviewers, and journal editors of meta-analyses that when they encounter such situations, they need to interpret the results with caution, as the estimates might be considerably affected by zero-cell correction methods.

To our knowledge, this study is the largest to investigate the impact of different zero-cell correction methods **TABLE 2** Characteristics of the included meta-analyses categorized according to the ratio of odds ratios for each method versus RevMan Mantel-Haenszel model.<sup>a</sup>

	Sizes of RORs (vs. RevMan MH) <sup>b</sup>		
Characteristics	Small	Moderate	Large
Methods			
REIV <sup>c</sup>	658 (74%)	144 (16%)	83 (9%)
REIV TACC <sup>d</sup>	606 (68%)	179 (20%)	100 (11%)
Peto	492 (56%)	176 (20%)	217 (25%)
MH <sup>e</sup>	399 (51%)	167 (22%)	210 (27%)
Logistic regression	359 (46%)	167 (22%)	250 (32%)
Bayesian model <sup>f</sup>	136 (15%)	194 (22%)	555 (63%)
Median number of studies in meta-analysis			
REIV <sup>c</sup>	3 (2, 4)	3 (2, 5)	3 (2, 4)
REIV TACC <sup>d</sup>	3 (2, 4)	3 (2, 4)	2 (2, 4)
Peto	3 (2, 4)	3 (2, 4)	2 (2, 3)
MH <sup>e</sup>	3 (2, 4)	3 (2, 4)	2 (2, 3)
Logistic regression	3 (2, 4)	3 (2, 4)	3 (2, 4)
Bayesian model <sup>f</sup>	4 (3, 5)	3.5 (3, 4.75)	2 (2, 3)
Median number of participants			
REIV <sup>c</sup>	408 (242, 691)	507 (269, 675)	490 (262, 685)
REIV TACC <sup>d</sup>	430 (237, 702)	400 (270, 662)	443 (253, 683)
Peto	518 (298, 754)	359 (220, 627)	326 (191, 594)
MH <sup>e</sup>	552 (317, 777)	490 (273, 735)	330 (196, 551)
Logistic regression	528 (310, 761)	426 (242, 699)	398 (228, 654)
Bayesian model <sup>f</sup>	582 (319, 845)	558 (337, 746)	360 (206, 622)
Median number of events			
REIV <sup>c</sup>	9 (4, 18)	11 (7, 25)	21 (10, 36)
REIV TACC <sup>d</sup>	10 (5, 18)	10 (6, 21)	19 (8, 33)
Peto	13 (7, 22)	8 (4, 16)	5 (3, 19)
MH <sup>e</sup>	15 (8, 26)	11 (6, 24)	7 (4, 14)
Logistic regression	14 (7, 24)	10 (6, 23)	8 (5, 17)
Bayesian model <sup>f</sup>	15 (6, 25)	13 (8, 27)	8 (4, 17)

*Note*: Values in parentheses shows percentage or interquartile range. Percentage calculations were based on a denominator that excluded 109 missing values resulting from non-convergence for the MH and logistic regression models.

Abbreviations: MH, Mantel-Haenszel; REIV, random effects inverse variance; ROR, ratio of odds ratios; TACC, treatment arm continuity correction.

<sup>a</sup>The Mantel-Haenszel model with a fixed continuity correction, adding 0.5 to all cells of the  $2 \times 2$  table, which is the model implemented in the RevMan software.

<sup>b</sup>Small, ROR in the range of 0.9–1.11; Moderate, ROR in the range of 0.8–0.9 or 1.11–1.25; Large, ROR in the range of  $\geq$ 1.25 or  $\leq$ 0.8.

<sup>c</sup>Random effects inverse variance model with a fixed continuity correction, adding 0.5 to all cells of the  $2 \times 2$  table.

<sup>d</sup>Random effects inverse variance model with the treatment arm continuity correction.

<sup>e</sup>The Mantel-Haenszel model without correction.

<sup>f</sup>Bayesian random effects model using a binomial likelihood for the outcome.

on existing meta-analyses. We followed a pre-specified protocol and adhered to standard reporting guidelines.<sup>8,17</sup> Our study illuminates the real-world application of zero cell correction methods, aiding authors in understanding the importance of the choice between these methods.

However, our study has several limitations. First, we included meta-analyses having a control event rate of <0.05 and a total participant count of fewer than 1000. We found a significant number of Cochrane reviews included such meta-analyses, enabling to test our

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# **TABLE 3** narrative summary of the meta-analyses that had extremely large size of ROR.<sup>a</sup>

CDSR	Participants, intervention, control, and outcome	Events in the intervention arm for each study	Events in the control arm for each study	ORs from different r	nodels
CD006633 <sup>10</sup>	Participants: patients with schizophrenia	Study 1: 28/31	Study 1: 1/32	RevMan MH <sup>b</sup>	182.73
	Intervention: clozapine	Study 2: 23/36	Study 2: 0/36	REIV <sup>c</sup>	209.00
	Control: quetiapine			REIV TACC <sup>d</sup>	209.00
	Outcome: hypersalivation—short term			Peto	23.96
				MH <sup>e</sup>	530.83
				Logistic	372.02
				Bayesian model <sup>f</sup>	582.42
CD005067 <sup>11</sup>	Participants: patients with Old World cutaneous leishmaniasis	Study 1: 49/60	Study 1: 0/60	RevMan MH <sup>b</sup>	221.89
	Intervention: oral dapsone	Study 2: 18/20	Study 2: 2/20	REIV <sup>c</sup>	156.47
	Control: placebo			REIV TACC <sup>d</sup>	156.47
	Outcome: Participants complete cure			Peto	26.89
				MH <sup>e</sup>	326.00
				Logistic	276.91
				Bayesian model <sup>f</sup>	457.41
CD005590 <sup>12</sup>	Participants: non-HIV immunocompromised patients	Study 1: 0/30	Study 1: 1/30	RevMan MH <sup>b</sup>	0.12
	Intervention: TMP/SMX	Study 2: 0/80	Study 2: 18/80	REIV <sup>c</sup>	0.25
	Control: placebo, no treatment or non-PCP drug	Study 3: 1/22	Study 3: 0/20	REIV TACC <sup>d</sup>	0.25
	Outcome: documented PCP infections—hematological cancer	Study 4: 0/61	Study 4: 0/59	Peto	0.14
		Study 5: 0/74	Study 5: 0/63	MH <sup>e</sup>	0.05
	subgroup	Study 6: 0/27	Study 6: 0/61	Logistic	0.11
		Study 7: 0/52	Study 7: 0/50	Bayesian model <sup>f</sup>	0.04
		Study 8: 0/74	Study 8: 0/64		
CD008370 <sup>13</sup>	Participants: patients received pancreatic surgery	Study 1: 16/16	Study 1: 0/16	RevMan MH <sup>b</sup>	19.38
	Intervention: somatostatin analogues	Study 2: 2/38	Study 2: 1/37	REIV <sup>c</sup>	40.48
	Control: none	Study 3: 0/35	Study 3: 0/32	REIV TACC <sup>d</sup>	40.51
	Outcome: number with adverse effects due to treatment	Study 4: 0/107	Study 4: 0/104	Peto	21.81
				MH <sup>e</sup>	19.65
				Logistic	634.97
				Bayesian model <sup>f</sup>	92.25

#### TABLE 3 (Continued)

CDSR	Participants, intervention, control, and outcome	Events in the intervention arm for each study	Events in the control arm for each study	ORs from different mo	dels
CD010328 <sup>14</sup>	Participants: patients with symptomatic lumbar disc herniation	Study 1: 0/166	Study 1: 1/159	RevMan MH <sup>b</sup>	0.21
	Intervention: minimally invasive discectomy	Study 2: 0/55	Study 2: 3/57	REIV <sup>c</sup>	0.22
	Control: microdiscectomy/open discectomy	Study 3: 0/10	Study 3: 1/12	REIV TACC <sup>d</sup>	0.22
	Outcome: surgical site and other infections	Study 4: 0/100	Study 4: 4/100	Peto	0.21
		Study 5: 1/70	Study 5: 7/142	MH <sup>e</sup>	0.09
		Study 6: 0/30	Study 6: 0/30	Logistic	0.08
				Bayesian model <sup>f</sup>	0.04

Abbreviations: CDSR, Cochrane Database of Systematic Reviews; MH, Mantel-Haenszel; ORs, odds ratios; REIV, random effects inverse variance; ROR, ratio of odds ratios; TACC, treatment arm continuity correction.

<sup>a</sup>ROR in the range of  $\geq$ 1.25 or  $\leq$ 0.8.

<sup>b</sup>The Mantel-Haenszel model with a fixed continuity correction, adding 0.5 to all cells of the  $2 \times 2$  table, which is the model implemented in the RevMan software.

 $^{c}$ Random effects inverse variance model with a fixed continuity correction, adding 0.5 to all cells of the 2  $\times$  2 table.

<sup>d</sup>Random effects inverse variance model with the treatment arm continuity correction.

<sup>e</sup>The Mantel-Haenszel model without correction.

<sup>f</sup>Bayesian random effects model using a binomial likelihood for the outcome.

hypothesis. However, this also means that the generalizability of our findings beyond such scenarios might be limited. Furthermore, we did not examine bias in estimates per se, only differences in effect estimate across models. Second, although we used a generic Bayesian random effects model for all meta-analyses, we acknowledge that this is not an optimal way of performing Bayesian statistics. Ideally, such analyses should have been done in separation, with a more careful selection of prior distributions (e.g., after using informative priors for heterogeneity, as in Turner et al.<sup>18</sup>), by carefully checking convergence, and so on. We used the generic Bayesian model here, however, as a means of exploring general differences between models. Third, because we focused on Cochrane reviews of interventions, the proportion of reviews that used RevMan MH might be smaller in non-Cochrane reviews. Fourthly, we did not directly compare the effect estimates from RevMan MH obtained by the RevMan software, but instead, we compared those obtained using R software. Nevertheless, we expect potential differences to be minor, as they are based on the same mathematical models. Finally, although a 25% difference in odds ratios was deemed large, we were unable to explore whether the interpretation of the effect estimates would change when using different methods. In Cochrane reviews, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach is used to assess the certainty of evidence. When applying GRADE to the estimates, the small number of events in our sample could result in a downgrade of imprecision. If the certainty of evidence was already very low in the original reviews, GRADE guides us to interpret the evidence as being very uncertain about the effect of the intervention on an outcome. Therefore, the difference in effect estimates might not significantly impact the interpretation of the results in such cases.

In conclusion, the influence of zero-cell correction methods on effect estimates could be significant in existing Cochrane reviews. We strongly propose that RevMan web, the software for Cochrane reviews, should incorporate more advanced statistical methods such as MH with no continuity correction and logistic regression. Even more advanced models such as the beta-binomial model, which have been shown to perform well, should be also ideally utilized.<sup>19</sup> Additional research is required to determine if the use of these improved methods will change interpretation of results.

#### **AUTHOR CONTRIBUTIONS**

Yasushi Tsujimoto: Conceptualization; methodology; software; data curation; investigation; validation; formal

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analysis; funding acquisition; visualization; project administration; writing – original draft; writing – review and editing; resources. **Yusuke Tsutsumi:** Conceptualization; methodology; software; data curation; investigation; validation; formal analysis; writing – original draft; writing – review and editing. **Yuki Kataoka:** Conceptualization; methodology; software; data curation; investigation; writing – review and editing. **Akihiro Shiroshita:** Conceptualization; methodology; writing – review and editing; supervision. **Orestis Efthimiou:** Conceptualization; methodology; writing – review and editing; supervision; visualization. **Toshi A. Furukawa:** Conceptualization; project administration; writing – review and editing; supervision; visualization.

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#### CONFLICT OF INTEREST STATEMENT

Yasushi Tsujimoto: YT is a board member of Cochrane Japan, and received grants from Pfizer Health Research Foundation; Akihiro Shiroshita: AS received financial support for his doctoral study from Vanderbilt University Medical Center, Center for Asthma Research and the Fulbright Association. Toshi A. Furukawa: TAF reports personal fees from DT Axis, Kyoto University Original, MSD and SONY, and a grant from Shionogi, outside the submitted work; In addition, Toshi A. Furukawa has patents 2020-548587 and 2022-082495 pending, and intellectual properties for Kokoro-app licensed to Mitsubishi-Tanabe. The rest of the author did not have any conflict of interest.

# DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available at Cochrane Library (https://www. cochranelibrary.com/). Additional data that support the findings of this study are available upon reasonable request from the corresponding author.

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# SUPPORTING INFORMATION

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

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