IDENTIFICATION OF OPTIMAL STUDY WEIGHTS IN META-ANALYSES WITH A BINARY OUTCOME

IDENTIFICATION OF OPTIMAL STUDY WEIGHTS IN META-ANALYSES WITH A BINARY OUTCOME

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Abstract

Meta-analysis is a method that combines the results of multiple studies, so that the overall treatment effect can be estimated. However, the traditional method of study weight estimation by taking the reciprocals of the estimated variances is biased. For binary outcome data from a clinical trial, the accuracy of estimation of single study weight, summary effect, and variance of summary effect from the developed bias correction factors for log relative risk (*RD*), log relative risk (ln*RR*) or log odds ratio (ln*OR*) were assessed. When sample sizes are small, zero cell frequencies often occur in contingency tables and make parameter estimation more difficult. Methods of dealing with zero-cells were elaborated, which including adding 0.5 to the zero cell, adding 0.5 to all cells in the table if a zero frequency occurs, adding 0.5 to all cells all the time, and adding the reciprocal of the size of the contrasting study arm to each cell when a zero frequency occurs. In addition, for risk difference, adding 0.5 to the zero cells when two zero cells occur, and adding 0.5 to all the cells when two zero cells occur are also considered since the continuity of the weight of risk difference is only affected by double zero frequencies. Impact of bias correction on real meta-analyses from Cochrane Database was demonstrated.

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1. Introduction

1.1. Meta-analysis

Meta-analysis is a method that integrates the results of multiple individual studies to get an overall estimate of a treatment effect. The first published paper involving a meta-analytic approach applied in clinical studies appeared in 1904 by Pearson [1]. In 1976, Glass coined the term “meta-analysis” [2]. In meta-analyses, the overall estimate of a treatment effect is calculated as a weighted average of the estimated effect sizes in individual studies. In practice, the standard approach to obtain the weights is to use the reciprocal of the variance of the treatment effect in each study [3-9]. If other factors (such as the outcome event rate) are comparable between the studies, the treatment effect of a given study has smaller variance when its sample size is large, hence a larger weight is assigned. However, the weights estimated by the inverse variance approach are biased even when the estimated variances are unbiased, since reciprocation is not a linear transformation [10]. A bias correction method for fixed effect model with a continuous outcome has been published [10]. In this thesis, we focus on studies and meta-analyses with fixed effect model with binary outcomes, where the underlying distributions of treatment effects in all the studies are assumed to be the same.

1.2. Measures of Association

Measures of association (also referred to as effect sizes or treatment effects in the context of meta-analyses and medical studies) are statistics that quantify the association between exposure and outcome variables.

Assume that each study is a randomized trial with a parallel group design, having an experimental and control group, with sample sizes n_1 and n_2 respectively. Let a and b be integers denoting the number of events and non-events respectively, in the treatment group; c and d be integers denoting the number of events and non-events respectively, in the control group. Table 1.2.1 illustrates a 2×2 contingency table without continuity correction. The expected outcome rates for these groups will be denoted as π_1 and π_2, respectively, and their corresponding observed outcome rates as $p_1 = a/n_1$ and $p_2 = c/n_2$. For studies or meta-analyses with a binary outcome, there are three commonly used measures.

Table 1.2.1: a 2×2 contingency table without continuity correction

Group	Event	Non-event	Total
Treatment	a	b	$n_1 = a + b$
Control	c	d	$n_2 = c + d$

The risk difference (*RD*) is the difference between the two outcome rates (i.e., *RD* = $\pi_1 - \pi_2$).

The relative risk (*RR*), also known as risk ratio, is the ratio of the outcome rate in one group to that in the other group (i.e., *RR* = π_1/π_2). Relative risk is usually analyzed on a logarithmic scale, typically the natural log transformation is used, i.e., $\ln RR = \ln(\pi_1/\pi_2)$.

The odds ratio (*OR*) is the ratio of odds of one group to that of the other group (i.e., *OR* = $\frac{\pi_1}{1-\pi_1}/\frac{\pi_2}{1-\pi_2}$), where the odds is the ratio of the probability that event occurs to the probability that the event does not occur (e.g., odds of groups 1 is $\frac{\pi_1}{1-\pi_1}$). Like the relative risk, the natural logarithm of odds ratio $\ln OR = \ln\left(\frac{\pi_1}{1-\pi_1}/\frac{\pi_2}{1-\pi_2}\right)$ is usually used, rather than the odds ratio itself.

1.3. Zero Cell Frequencies

For binary data, one challenge is how to deal with observed zero frequencies. Zero frequencies can lead to undefined *lnRR* and *lnOR* as well as undefined variances and corresponding weights when the zeros appear in the denominators. Although the estimate of *RD* is not affected by zero frequencies, its variance degenerates to 0 when there are zero cells in both the treatment and control group, and hence cause inadmissible weight. Many authors have suggested modification methods to deal with zero frequencies, such as the +1/2 correction suggested by Haldane [11] and Anscombe [12], -1/2 correction suggested by Cox [13], and adding the reciprocal of the sample size of the opposite arm to the cells in tables with zeros prior to computing the estimators and their variances suggested by Sweeting et al. [14].

The typically recommended method is to add 1/2 to each cell in the contingency table [5]. In practice, some people apply the continuity correction only when there are zero cells [15], while some others prefer to add 1/2 regardless of having zero cells or not [16, 17]. The Cochrane Collaboration recommends adding 1/2 to all cells of a 2×2 table where the problems occur [3]. Extensive numerical evaluation [18 - 20] suggests that adding 1/2 to all cells in the table, regardless of whether a zero exists is preferable in most cases.

1.4. Cochrane Database of Systematic Reviews

The Cochrane Database of Systematic Reviews (CDSR) documents systematic reviews in the field of health research, which consists of Cochrane Reviews (systematic reviews), protocols, editorials, and supplements.

From the data that scraped from the CDSR by Schwab et al. [21], there are in total 758447 studies, where 475819 have a binary outcome and 215443 have a continuous outcome. Among the studies with a binary outcome, 113584 studies have at least one zero cell, which is approximately 24% of the studies with a binary outcome.

Table 1.4.1 shows the five-number summary, i.e., minimum (Min), 1st quartile (Q1), median (Q2), 3rd quartile (Q3), maximum (Max), and the mean of group sizes for studies with a binary or a continuous outcome. Table 1.4.2 shows the five-number summary and mean of group sizes for studies with a binary outcome. Table 1.4.3 shows the five-number summary and mean of group sizes for studies with a continuous outcome. The majority of the group sizes are in the range of small to moderate. Table 1.4.4 shows the five-number summary and the mean for the number of events for either group in studies with a binary outcome. Although the events might be defined differently (e.g., some studies count the number of deaths, while some other studies count the number of survivals), the outcomes reported in clinical trials are often "failures", such as disease-related mortality [22]. Among the recorded studies, the median number of events is only 6, which could be even smaller if one only considers failures as the outcomes. Small sample studies and small event rates happen frequently. Since small sample sizes and frequencies are not unusual, bias correction and continuity correction for the study weights will be important especially for small sample analyses.

Table 1.4.1: summary of group sizes for studies with a binary or continuous outcome

Min	Q1	Q2	Q3	Max	Mean
0	23	47	110	2164006	286.4

Table 1.4.2: summary of group sizes for studies with a binary outcome

Min	Q1	Q2	Q3	Max	Mean
0	26	54	134	2164006	377.7

Table 1.4.3: summary of group sizes for studies with a continuous outcome

Min	Q1	Q2	Q3	Max	Mean
0	18	32	68	193681	84.61

Table 1.4.4: summary of number of events for studies with a binary outcome

Min	Q1	Q2	Q3	Max	Mean
0	1	6	21	126466	32.54

Tables 1.4.5 – 1.4.7 summarize the ratio of group sizes for studies having two groups with nonzero sample sizes (the ratio is defined as the larger group size divided by the smaller group size) for studies with a binary or continuous outcome, studies with only a binary outcome, and studies with only a continuous outcome. In addition to the five number summaries and means, the 90th percentiles are also shown in the tables. About a half of the studies have close to balanced sample sizes for the two groups. Only approximately 10% of studies have ratio greater than 2:1. Thus in the later sections, we will mainly focus on sample sizes with ratio 1:1 and 2:1.

Table 1.4.5: summary of group size ratios for studies with a binary or continuous outcome

Min	Q1	Q2	Q3	90th per.	Max	Mean
1.000	1.004	1.049	1.177	2.000	2149.252	1.407

Table 1.4.6: summary of group size ratios for studies with a binary outcome

Min	Q1	Q2	Q3	90^{th} per.	Max	Mean
1.000	1.005	1.044	1.167	2.000	2149.252	1.473

Table 1.4.7: summary of group size ratios for studies with a continuous outcome

Min	Q1	Q2	Q3	90th per.	Max	Mean
1.000	1.000	1.061	1.194	1.917	1107.000	1.262

The majority of studies and meta-analyses with a binary outcome in CDSR use relative risk as the effect measure, as shown in Table 1.4.8 and 1.4.9, since relative risk has the advantage of being easier to interpret and is collapsible, where a measure of association is said to be collapsible if the marginal measure of association is equal to a weighted average of covariate specific measures of association with a nonconfounding covariate [23]. However, odds ratio has a symmetrical structure that is not affected by the choice of the outcome event, which is a better property for data analysis [24]. Although odds ratio is noncollapsible even without confounding, the noncollapsibility is still a useful characteristic that could be beneficial for medical research [25]. Peto's method is an alternative approach that can only be used to combine odds ratios, where OR is calculated using an approximate method [26]. We will not involve further details about this method in the later sections.

Table 1.4.8: number of times that each effect measure being used in studies with a binary outcome

OR	Peto *OR*	*RD*	*RR*
72732	30736	11393	360958

Table 1.4.9: number of times that each effect measure being used in meta-analyses with a binary outcome

OR	Peto *OR*	*RD*	*RR*
30531	10418	3855	150632

2. Methods

Let θ_i denote the treatment effect of the i^{th} study, and $\hat{\theta}_i$ denote the estimated θ_i. Under the fixed effect model, the study weight w_i is defined as the inverse of the variance of the estimated treatment effect, $w_i = \frac{1}{\mathrm{Var}(\hat{\theta}_i)}$, which is usually estimated as $\hat{w}_i = \frac{1}{\widehat{\mathrm{Var}(\hat{\theta}_i)}}$. The summary effect θ is estimated as $\hat{\theta} = \frac{\sum w_i \hat{\theta}_i}{\sum w_i}$, and the variance of the summary effect is $\mathrm{Var}(\hat{\theta}) = \frac{1}{\sum w_i}$ or in general $\mathrm{Var}(\hat{\theta}) = \frac{\sum w_i^2 \mathrm{Var}(\hat{\theta}_i)}{(\sum w_i)^2}$.

The sample variance of the treatment effect $\widehat{\mathrm{Var}(\hat{\theta}_i)}$ might be an unbiased estimator for $\mathrm{Var}(\hat{\theta}_i)$, i.e., $\mathrm{E}\left[\mathrm{Var}(\hat{\theta}_i)\right] = \mathrm{Var}(\hat{\theta}_i)$. However, since reciprocating is not a linear transformation, $\mathrm{E}\left[\frac{1}{\widehat{\mathrm{Var}(\hat{\theta}_i)}}\right] \neq \frac{1}{\mathrm{Var}(\hat{\theta}_i)}$, the weight estimated by the inverse variance is always biased. To eliminate this bias, we derive approximations of the expected value of the sample variances of the treatment effects $\mathrm{E}\left[\frac{1}{\widehat{\mathrm{Var}(\hat{\theta}_i)}}\right]$, and a bias correction is made based on its approximate expectation.

2.1. Risk Difference

Assuming independence of p_1 and p_2, the exact variance of risk difference is $\mathrm{Var}(\widehat{RD}) = \frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}$, so the ideal weight of risk difference is $w(\pi_1, \pi_2) = \left[\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}\right]^{-1}$. In the commonly used inverse variance method, the weight is estimated as $w(p_1, p_2) = \left[\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}\right]^{-1}$.

The second order Taylor expansion of $w(p_1, p_2)$ is

$$w(p_1, p_2) \approx w(\pi_1, \pi_2) + \left[(p_1 - \pi_1)\frac{\partial w(p_1, p_2)}{\partial p_1}\right]_{(\pi_1, \pi_2)} + \left[(p_2 - \pi_2)\frac{\partial w(p_1, p_2)}{\partial p_2}\right]_{(\pi_1, \pi_2)}$$
$$+ \left[\frac{1}{2}(p_1 - \pi_1)^2 \frac{\partial^2 w(p_1, p_2)}{\partial p_1^2}\right]_{(\pi_1, \pi_2)} + \left[\frac{1}{2}(p_2 - \pi_2)^2 \frac{\partial^2 w(p_1, p_2)}{\partial p_2^2}\right]_{(\pi_1, \pi_2)}$$

$$+ \left[(p_1 - \pi_1)(p_2 - \pi_2)\frac{\partial^2 w(p_1,p_2)}{\partial p_1 \partial p_2}\right]_{(\pi_1,\pi_2)}$$

Then we take expectation of $w(p_1,p_2)$. $\mathrm{E}(p_1 - \pi_1) = \mathrm{E}(p_2 - \pi_2) = 0$, so the two terms with $(p_1 - \pi_1)$ and $(p_2 - \pi_2)$ can be omitted. Since p_1 and p_2 are independent, $\mathrm{E}[(p_1 - \pi_1)(p_2 - \pi_2)] = 0$, the term with $(p_1 - \pi_1)(p_2 - \pi_2)$ can also be omitted. The first and second partial derivatives of $\mathrm{w}(p_1,p_2)$ are

$$\frac{\partial w(p_1,p_2)}{\partial p_1} = \frac{-\frac{1-2p_1}{n_1}}{\left[\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}\right]^2},$$

and

$$\frac{\partial^2 w(p_1,p_2)}{\partial p_1^2} = \frac{2}{n_1}\frac{1}{\left[\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}\right]^2} + 2\left(\frac{1-2p_1}{n_1}\right)^2 \frac{1}{\left[\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}\right]^3}.$$

Therefore, the second order approximation of the expectation of $w(p_1,p_2)$ is

$$\mathrm{E}[w(p_1,p_2)] \approx \frac{1}{\left[\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}\right]} + \frac{\frac{\pi_1(1-\pi_1)}{n_1^2} + \frac{\pi_2(1-\pi_2)}{n_2^2}}{\left[\frac{\pi_1(1-\pi_1)}{n_1} + \frac{\pi_2(1-\pi_2)}{n_2}\right]^2},$$

which is not an unbiased estimator of $w(\pi_1,\pi_2)$. A bias corrected sample weight based on this approximation is therefore

$$w^*(p_1,p_2) = w(p_1,p_2) - w^2(p_1,p_2)\left[\frac{p_1(1-p_1)}{n_1^2} + \frac{p_2(1-p_2)}{n_2^2}\right].$$

2.2. Log Relative Risk

The exact variance of log relative risk is unknown. From the Taylor expansion of $\ln p_1$,

$$\ln p_1 \approx \ln \pi_1 + \frac{1}{\pi_1}(p_1 - \pi_1) - \frac{1}{\pi_1^2}\frac{(p_1-\pi_1)^2}{2} + \frac{1}{\pi_1^3}\frac{(p_1-\pi_1)^3}{3} - \frac{1}{\pi_1^4}\frac{(p_1-\pi_1)^4}{4},$$

the first order (i.e., neglecting terms of $O(n^{-2})$ and lower) approximated variance can be derived from the moments of binomial distribution as $\mathrm{Var}_1(\ln p_1) \approx \frac{1-\pi_1}{n_1\pi_1}$, and the second order (i.e., neglecting terms of $O(n^{-3})$ and lower) approximation is $\mathrm{Var}_2(\ln p_1) \approx \frac{1-\pi_1}{n_1\pi_1} + \frac{(1-\pi_1)(3-\pi_1)}{2n_1^2\pi_1^2}$.

Since p_1 and p_2 are independent, the first order approximation of $\ln \widehat{RR}$ is

$$\mathrm{Var}_1\left(\ln \widehat{RR}\right) \approx \frac{1-\pi_1}{n_1\pi_1} + \frac{1-\pi_2}{n_2\pi_2},$$

which is commonly used in practice with corresponding inverse variance weight

$$w(p_1, p_2) = \left[\frac{1-p_1}{n_1p_1} + \frac{1-p_2}{n_2p_2}\right]^{-1}.$$

However, since the bias correction for weight of $\ln \widehat{RR}$ based on the first order approximated variance may lead to negative weights, where in this case the expectation of the first order inverse variance weight is

$$\mathrm{E}[w(p_1, p_2)] \approx w(\pi_1, \pi_2) + \left(\frac{\pi_1(1-\pi_1)}{n_1^2\pi_1^3} + \frac{\pi_2(1-\pi_2)}{n_2^2\pi_2^3}\right) w^2(\pi_1, \pi_2).$$

The corresponding first order corrected weight is

$$w^*(p_1, p_2) = w(p_1, p_2) - w^2(p_1, p_2)\left(\frac{p_1(1-p_1)}{n_1^2p_1^3} + \frac{p_2(1-p_2)}{n_2^2p_2^3}\right),$$

where the second term is not always less than the first term.

Hence, to avoid negative weights, a bias correction for the weight of is derived based on the second order approximated variance

$$\mathrm{Var}_2\left(\ln \widehat{RR}\right) \approx \frac{1-\pi_1}{n_1\pi_1} + \frac{(1-\pi_1)(3-\pi_1)}{2n_1^2\pi_1^2} + \frac{1-\pi_2}{n_2\pi_2} + \frac{(1-\pi_2)(3-\pi_2)}{2n_2^2\pi_2^2},$$

with corresponding ideal weight as

$$w_2(\pi_1, \pi_2) = \left[\frac{1-\pi_1}{n_1\pi_1} + \frac{(1-\pi_1)(3-\pi_1)}{2n_1^2\pi_1^2} + \frac{1-\pi_2}{n_2\pi_2} + \frac{(1-\pi_2)(3-\pi_2)}{2n_2^2\pi_2^2}\right]^{-1}.$$

The expectation of $w_2(\pi_1, \pi_2)$ can be derived from the Taylor expansion

$$\begin{aligned} w_2(p_1, p_2) \approx\ & w_2(\pi_1, \pi_2) - \left[w_2^2(\pi_1, \pi_2)\frac{\partial f_1(p_1)}{\partial p_1}\right]_{\pi_1}(p_1 - \pi_1) \\ & - \left[w_2^2(\pi_1, \pi_2)\frac{\partial f_2(p_2)}{\partial p_2}\right]_{\pi_2}(p_2 - \pi_2) \\ & + \left\{\left[2w_2^3(\pi_1, \pi_2)\left(\frac{\partial f_1(p_1)}{\partial p_1}\right)^2\right]_{\pi_1} - \left[w_2^2(\pi_1, \pi_2)\frac{\partial^2 f_1(p_1)}{\partial p_1^2}\right]_{\pi_1}\right\}\frac{(p_1-\pi_1)^2}{2} \\ & + \left\{\left[2w_2^3(\pi_1, \pi_2)\left(\frac{\partial f_2(p_2)}{\partial p_2}\right)^2\right]_{\pi_2} - \left[w_2^2(\pi_1, \pi_2)\frac{\partial^2 f_2(p_2)}{\partial p_2^2}\right]_{\pi_2}\right\}\frac{(p_2-\pi_2)^2}{2}, \end{aligned}$$

where

$$f_1(p_1) = \frac{1-p_1}{n_1 p_1} + \frac{(1-p_1)(3-p_1)}{2n_1^2 p_1^2},$$

and

$$f_2(p_2) = \frac{1-p_2}{n_2 p_2} + \frac{(1-p_2)(3-p_2)}{2n_2^2 p_2^2}.$$

By simplifying the terms, the expected second order weight is

$$\mathrm{E}[w_2(p_1, p_2)] \approx w_2(\pi_1, \pi_2) - w_2^2(\pi_1, \pi_2)\left(\frac{1-\pi_1}{n_1^2 \pi_1^2} + \frac{1-\pi_2}{n_2^2 \pi_2^2}\right),$$

with a bias corrected sample weight is obtained as

$$w^*(p_1, p_2) = w_2(p_1, p_2) + w_2^2(p_1, p_2)\left(\frac{1-p_1}{n_1^2 p_1^2} + \frac{1-p_2}{n_2^2 p_2^2}\right).$$

2.3. Log Odds Ratio

The exact variance of log odds ratio is also unknown. As for the variance of $\ln \widehat{RR}$, the variance is usually approximated using a Taylor expansion

$$\ln\left(\frac{p_1}{1-p_1}\right) \approx \ln\left(\frac{\pi_1}{1-\pi_1}\right) + (p_1 - \pi_1)\left[\frac{1}{\pi_1} + \frac{1}{1-\pi_1}\right] - \frac{(p_1-\pi_1)^2}{2}\left[\frac{1}{\pi_1^2} - \frac{1}{(1-\pi_1)^2}\right]$$
$$+ \frac{(p_1-\pi_1)^3}{3}\left[\frac{1}{\pi_1^3} + \frac{1}{(1-\pi_1)^3}\right] - \frac{(p_1-\pi_1)^4}{4}\left[\frac{1}{\pi_1^4} - \frac{1}{(1-\pi_1)^4}\right].$$

From the moments of $\ln\left(\frac{p_1}{1-p_1}\right)$, the first order variance approximation of $\ln \widehat{OR}$ is

$$\mathrm{Var}_1\left(\ln \widehat{OR}\right) \approx \frac{1}{n_1 \pi_1 (1-\pi_1)} + \frac{1}{n_2 \pi_2 (1-\pi_2)},$$

such that the inverse variance estimated weight is

$$w(p_1, p_2) = \left[\frac{1}{n_1 p_1 (1-p_1)} + \frac{1}{n_2 p_2 (1-p_2)}\right]^{-1}.$$

The bias correction for weight of $\ln \widehat{OR}$ based on the first order approximated variance may lead to negative weights. The expectation of the first order inverse variance weight is

$$E[w(p_1, p_2)] \approx w(\pi_1, \pi_2)$$
$$+ w^2(\pi_1, \pi_2)\left\{\frac{1}{n_1^2}\left[\frac{1}{(1-\pi_1)^2} - \frac{1}{\pi_1(1-\pi_1)} + \frac{1}{\pi_1^2}\right] + \frac{1}{n_2^2}\left[\frac{1}{(1-\pi_2)^2} - \frac{1}{\pi_2(1-\pi_2)} + \frac{1}{\pi_2^2}\right]\right\}.$$

The corresponding first order corrected weight is

$$w^*(p_1, p_2) = w(p_1, p_2) - w^2(p_1, p_2)$$
$$\left\{\frac{1}{n_1^2}\left[\frac{1}{(1-p_1)^2} - \frac{1}{p_1(1-p_1)} + \frac{1}{p_1^2}\right] + \frac{1}{n_2^2}\left[\frac{1}{(1-p_2)^2} - \frac{1}{p_2(1-p_2)} + \frac{1}{p_2^2}\right]\right\},$$

where the second term is not always less than the first term.

Therefore, a bias correction for the weight of is derived based on the second order approximated variance

$$\mathrm{Var}_2\left(\ln \widehat{OR}\right) \approx \frac{1}{n_1\pi_1(1-\pi_1)} + \frac{1}{2n_1^2\pi_1^2(1-\pi_1)^2}(3 - 8\pi_1 + 8\pi_1^2).$$
$$+ \frac{1}{n_2\pi_2(1-\pi_2)} + \frac{1}{2n_2^2\pi_2^2(1-\pi_2)^2}(3 - 8\pi_2 + 8\pi_2^2)\ .$$

So that the second order ideal weight is

$$w_2(\pi_1, \pi_2) = \left[\frac{1}{n_1\pi_1(1-\pi_1)} + \frac{1}{2n_1^2\pi_1^2(1-\pi_1)^2}(3 - 8\pi_1 + 8\pi_1^2)\right.$$
$$\left. + \frac{1}{n_2\pi_2(1-\pi_2)} + \frac{1}{2n_2^2\pi_2^2(1-\pi_2)^2}(3 - 8\pi_2 + 8\pi_2^2)\right]^{-1}$$

As in the process for $\ln \widehat{RR}$ in the previous subsection, taking the expectation of $w_2(p_1, p_2)$

$$\mathrm{E}[w_2(p_1, p_2)] \approx w_2(\pi_1, \pi_2) - \frac{w_2^2(\pi_1,\pi_2)}{n_1^2\pi_1^2(1-\pi_1)^2}(1 - 3\pi_1 + 3\pi_1^2) - \frac{w_2^2(\pi_1,\pi_2)}{n_2^2\pi_2^2(1-\pi_2)^2}(1 - 3\pi_2 + 3\pi_2^2).$$

Thus, a bias corrected weight of $\ln \widehat{OR}$ is

$$w^*(p_1, p_2) = w_2(p_1, p_2)$$
$$+ w_2^2(p_1, p_2)\left\{\frac{1}{n_1^2p_1^2(1-p_1)^2}(1 - 3p_1 + 3p_1^2) + \frac{1}{n_2^2p_2^2(1-p_2)^2}(1 - 3p_2 + 3p_2^2)\right\}.$$

2.4. Zero Cell Modification Methods

There are various continuity correction methods to deal with inadmissible risk measures and weights caused by zero cell frequencies when zeros happen in the denominators. We consider the following commonly used methods to deal with empty cells:

- Method 1: disregarding studies with at least one zero cell.
- Method 2: adding $\frac{1}{2}$ to the empty cells (e.g., Table 2.4.1).

- Method 3: adding $\frac{1}{2}$ to all cells in the table when there is at least one zero (i.e., Table 2.4.2 when any one or two of a, b, c, d are zero, and $k_T = k_C = \frac{1}{2}$) [11, 12].
- Method 4: adding $\frac{1}{2}$ to all cells in all tables no matter if there is a zero cell or not (i.e., Table 2.4.2 when $k_T = k_C = \frac{1}{2}$, regardless of the values of a, b, c, d) [11, 12].
- Method 5: adding the reciprocal of the size of the contrasting study arm to each cell when there is at least one zero (i.e., Table 2.4.2 when any one or two of a, b, c, d are zero, $k_T = \frac{1}{n_2}$ and $k_C = \frac{1}{n_1}$) [14].

Our goal is to examine which of these methods result in the least biased study weights when using the bias corrected sample weights described above.

Table 2.4.1: a 2×2 contingency table after continuity correction method 2

Group	Event	Non-event	Total
Treatment	$0 + 1/2$	n_1	$n_1 + 1/2$
Control	c	d	n_2

Table 2.4.2: a 2×2 contingency table after continuity correction method 3, 4, or 5

Group	Event	Non-event	Total
Treatment	$a + k_T$	$b + k_T$	$n_1 + 2k_T$
Control	$c + k_C$	$d + k_C$	$n_2 + 2k_C$

Since the bias corrected weight of risk difference is only affected by double zero cells, we also adapt Method 2 and 3 for studies with double zeros for risk difference only:

- Method 6.1: adding $\frac{1}{2}$ to the empty cells when there are two zero cells.
- Method 6.2: adding $\frac{1}{2}$ to all cell in the table when there are two zero cells.

Note that the distributions of the observed event rates after applying the zero cell corrections p_1^* and p_2^* become different from the original p_1 and p_2. Alternative estimators for the variances of effect measure were proposed [27 - 29]. For simplicity, we treat the zero corrections as constants and use the usual variance estimators for the measure.

3. Simulation Studies for a Single Study Weight

To examine the accuracy of estimated weights, simulation studies were conducted. The simulation procedure is as the following:

1. Set sample sizes n_1 and n_2, and event rates π_1 and π_2.
2. Calculate the true weight for risk difference and the approximated true weight for log relative risk and log odds ratio based on the parameter values.
3. Generate number of events in treatment and control group from Binomial distributions, $X_1 \sim Bin(n_1, \pi_1)$ and $X_2 \sim Bin(n_2, \pi_2)$ respectively.
4. Apply the zero modification methods.
5. Calculate the sample weights using inverse variance method and bias corrected method for each measure.
6. Repeat steps 3-5 for $R = 10000$ times, as this is a relatively large number of replication while does not cost much computational efficiency.
7. Calculate the relative bias (RB) in percentage of each estimated weight,

$$RB(\widehat{w}, w) = \frac{1}{R}\sum_{i=1}^{R} \frac{\widehat{w}_i - w}{w} \times 100\%$$

and the relative root mean squared error (RRMSE) in percentage,

$$RRMSE(\widehat{w}) = \frac{\sqrt{Var(\widehat{w}) + Bias^2(\widehat{w}, w)}}{w} \times 100\%$$

where $\widehat{w}$ denotes an estimator, $\widehat{w}_i$ is an estimate from the i^{th} replication, and w is the true value being estimated. Note that only the true weight of risk difference is known. For log relative risk and log odds ratio, since the truths are unknown, the relative bias and relative root mean squared error are calculated relative to the second order weights with the true event rates π_1 and π_2.

Since in practice, it is more common to have studies with a balanced design, and less common to have the ratio of group sizes exceeding 2:1, we fix the combined group size $n = n_1 + n_2 \in \{10, 20, 30, \cdots, 190, 200\}$, then consider studies with balanced group sizes $n_1 = n_2$ and studies with imbalanced group sizes $2n_1 \approx n_2$ (rounding $\frac{n}{3}$ and $\frac{2n}{3}$ to the closest integer to get n_1 and n_2).

The event rates are set equally with $\pi_1 = \pi_2 \in \{0.1, 0.3, 0.5\}$ and unequally with $(\pi_1, \pi_2) \in \{(0.1, 0.2), (0.2, 0.4), (0.25, 0.5), (0.2, 0.1), (0.4, 0.2), (0.5, 0.25)\}$, so that the typical cases with low, moderate, and high event rates are covered. Moreover, the settings cover the cases where there is no treatment effect and cases with a constant relative risk. The symmetrical cases of unequal event rates are only necessary for unequal imbalanced sizes.

In the following subsections, we focus on demonstrating the cases with large and small event rates where $(\pi_1, \pi_2) \in \{(0.5, 0.5), (0.1, 0.1), (0.25, 0.5), (0.25, 0.5), (0.1, 0.2), (0.2, 0.1)\}$. Since the cases with moderate event rates share similar properties with cases having large event rates, the figures for moderate event rates are put in Appendix A. The plots of root mean squared errors are also in Appendix A. Bias corrected weights tend to have larger variance despite their smaller bias, and the root mean squared error is close to the root mean squared error of the inverse variance weight.

In the following figures, relative bias of bias corrected weights and inverse variance weights are plotted using different continuity correction methods. The *x*-axis shows the total sample size of treatment and control group. The *y*-axis shows relative bias in percentage. The thresholds of an acceptable relative bias are set arbitrarily as 20% and 10%. The coloured intervals are the $\pm 10\%$ and $\pm 20\%$ relative bias thresholds.

3.1. Risk Difference

3.1.1. Balanced studies with equal event rates

Figures 3.1.1 and 3.1.2 show the relative percentage bias comparing the bias corrected weights and inverse variance weights under different zero modification methods for risk difference with equal sample sizes and equal event rates. For all zero modification methods, the bias corrected weight converges to the truth faster than the inverse variance weight as sample size gets larger.

For $\pi_1 = \pi_2 = 0.5$, bias corrected weights using zero modification methods 2, 3, 5, 6.1, and 6.2 are within 10% relative bias for the entire range of sample sizes. All the methods give bias corrected weights less than 20% relative bias. Method 2 is deemed the best in this setting as the bias corrected weight is the least biased among all the methods when the sample size is small. In the case of $\pi_1 = \pi_2 = 0.1$, method 4 is the best, where both standard and bias corrected weight have smaller bias than the other methods. Methods 5, 6.1, and 6.2 show higher bias when sample size is small.

3.1.2. Balanced studies with unequal event rates

Figures 3.1.3 and 3.1.4 are the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for risk difference with equal sample sizes and unequal event rates. The trend is similar to that of the equal event rates cases. With relatively large event rate, all methods perform well, especially method 2. For small event rates, methods 2, 3, and 4 work better than the other methods, with method 4 being the best.

3.1.3. Imbalanced studies with equal event rates

Figures 3.1.5 and 3.1.6 are the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for risk difference with unequal sample sizes and equal event rates.

For $\pi_1 = \pi_2 = 0.5$, the bias corrected weights from method 2 and 3 are within the 10% bias interval for all n. The other methods have bias greater than 20% for small n. For $\pi_1 = \pi_2 = 0.1$, method 4 is the least biased.

3.1.4. Imbalanced studies with unequal event rates

Figures 3.1.7 to 3.1.10 are the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for risk difference with unequal sample sizes and unequal event rates.

The performance of the various methods is similar to the previous cases, where bias corrected weights from method 2, 3, and 4 are more favourable. Method 4 performs particularly well for small samples.

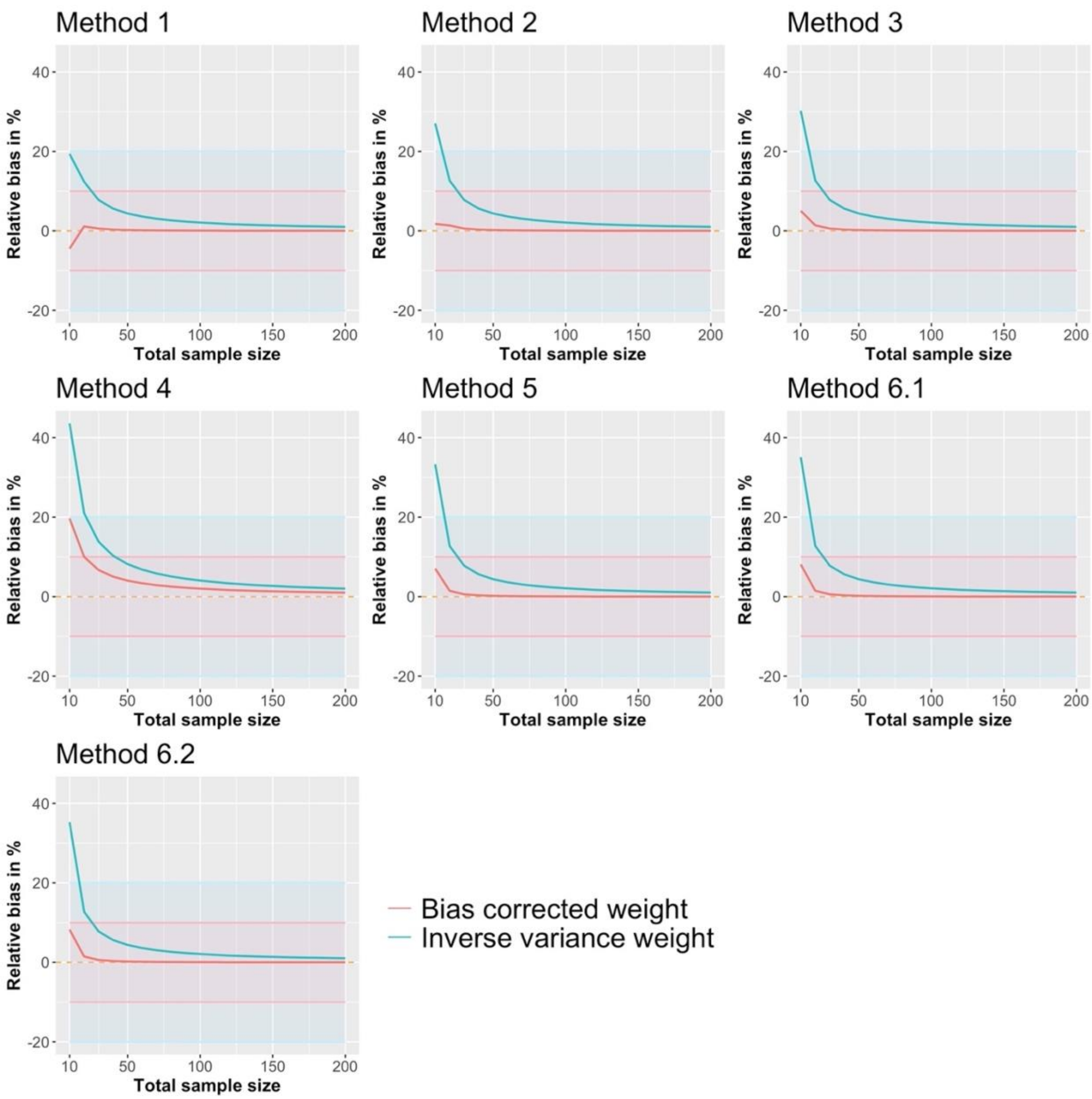

Figure 3.1.1: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.5$

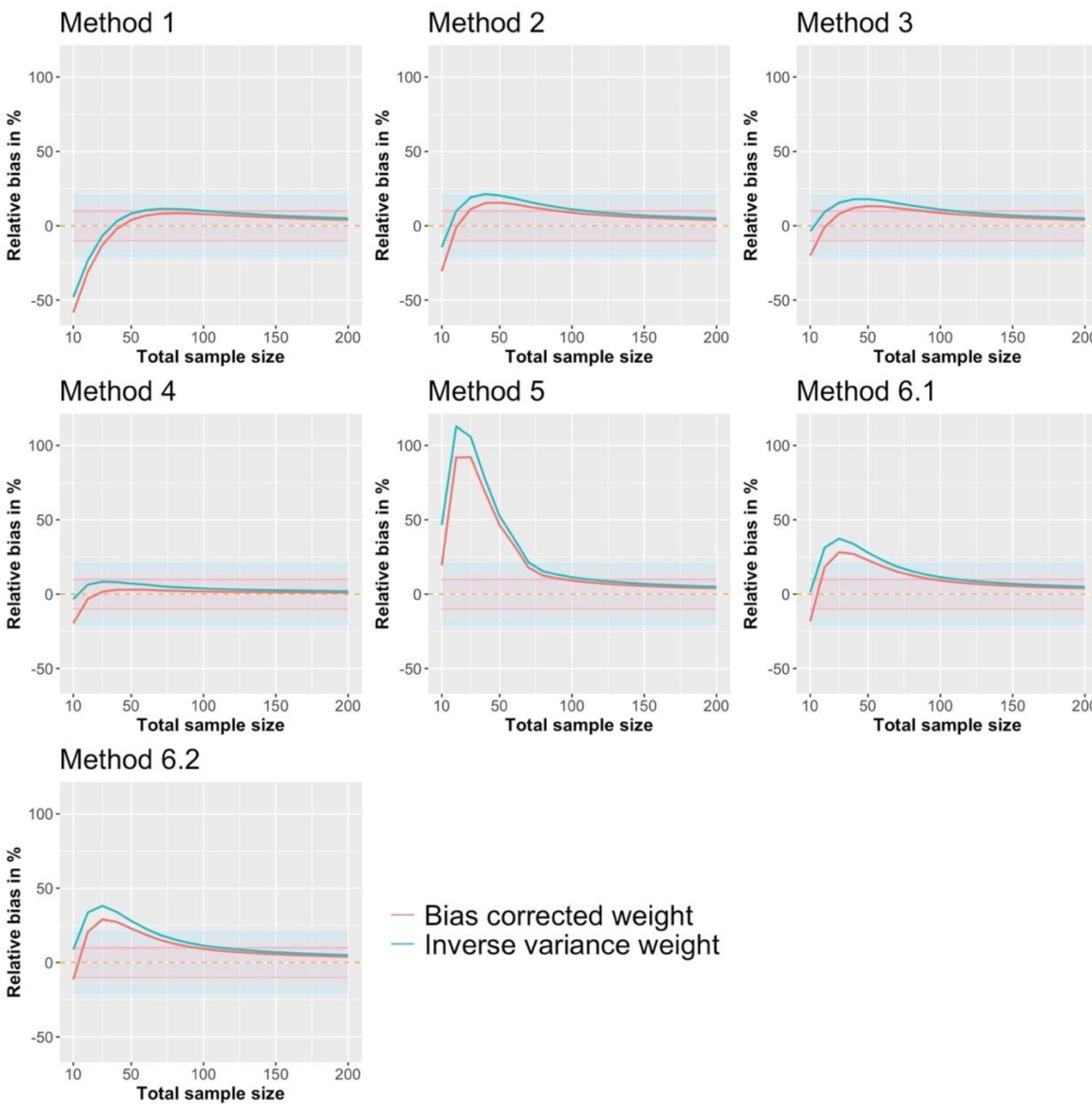

Figure 3.1.2: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.1$

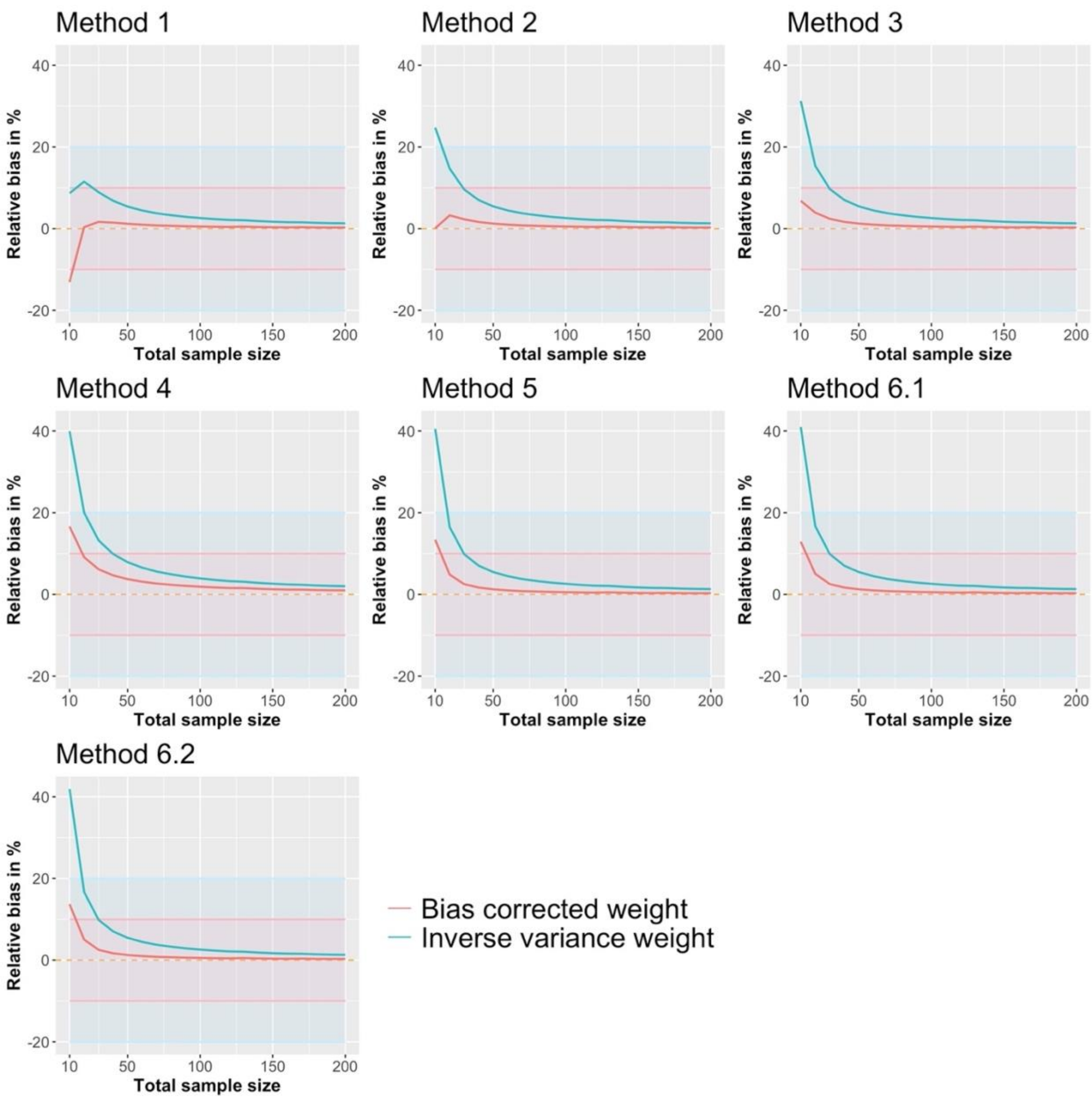

Figure 3.1.3: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $n_1 = n_2$, with unequal event rates $\pi_1 = 0.5, \pi_2 = 0.25$

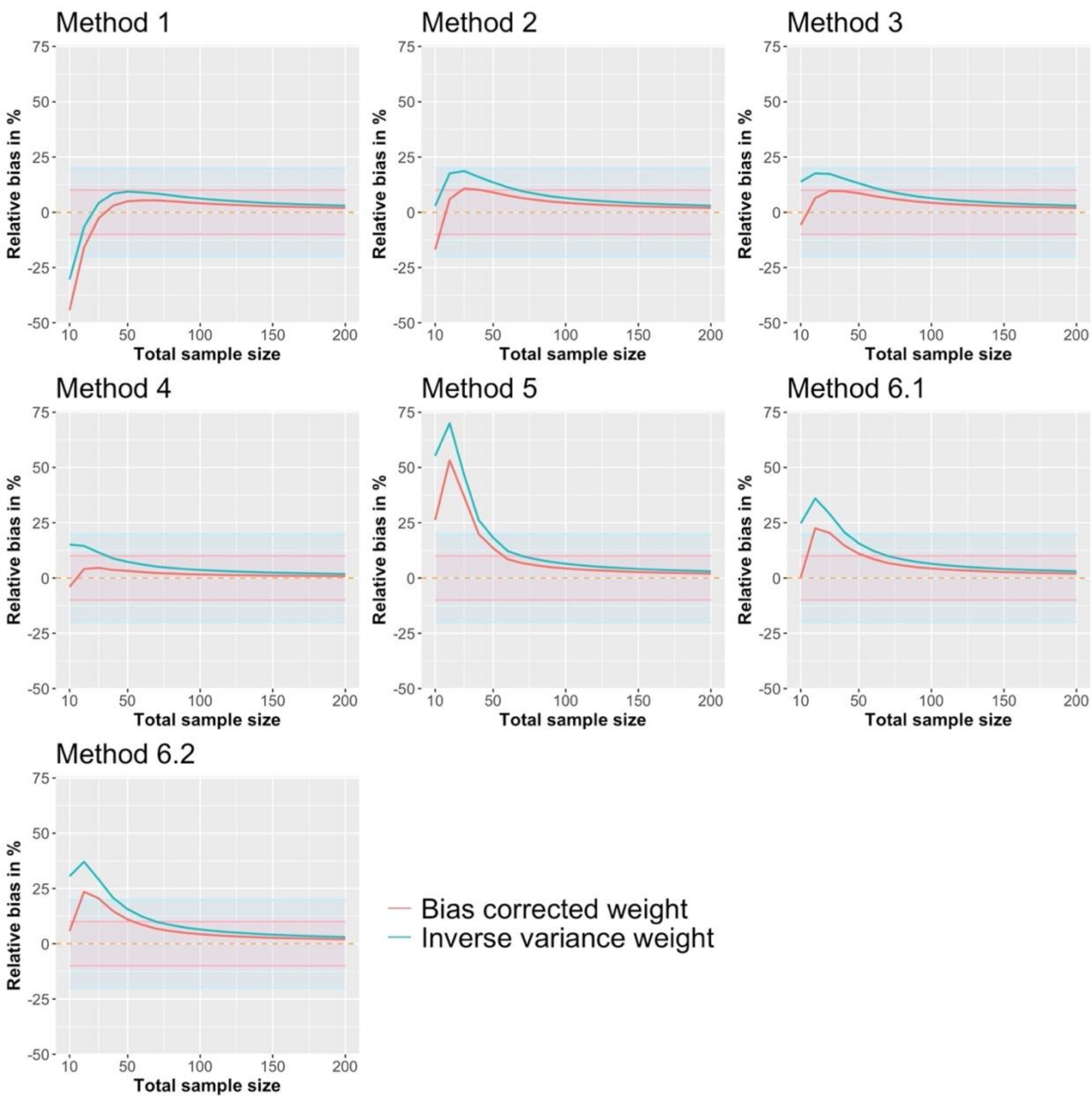

Figure 3.1.4: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $n_1 = n_2$, with unequal event rates $\pi_1 = 0.2, \pi_2 = 0.1$

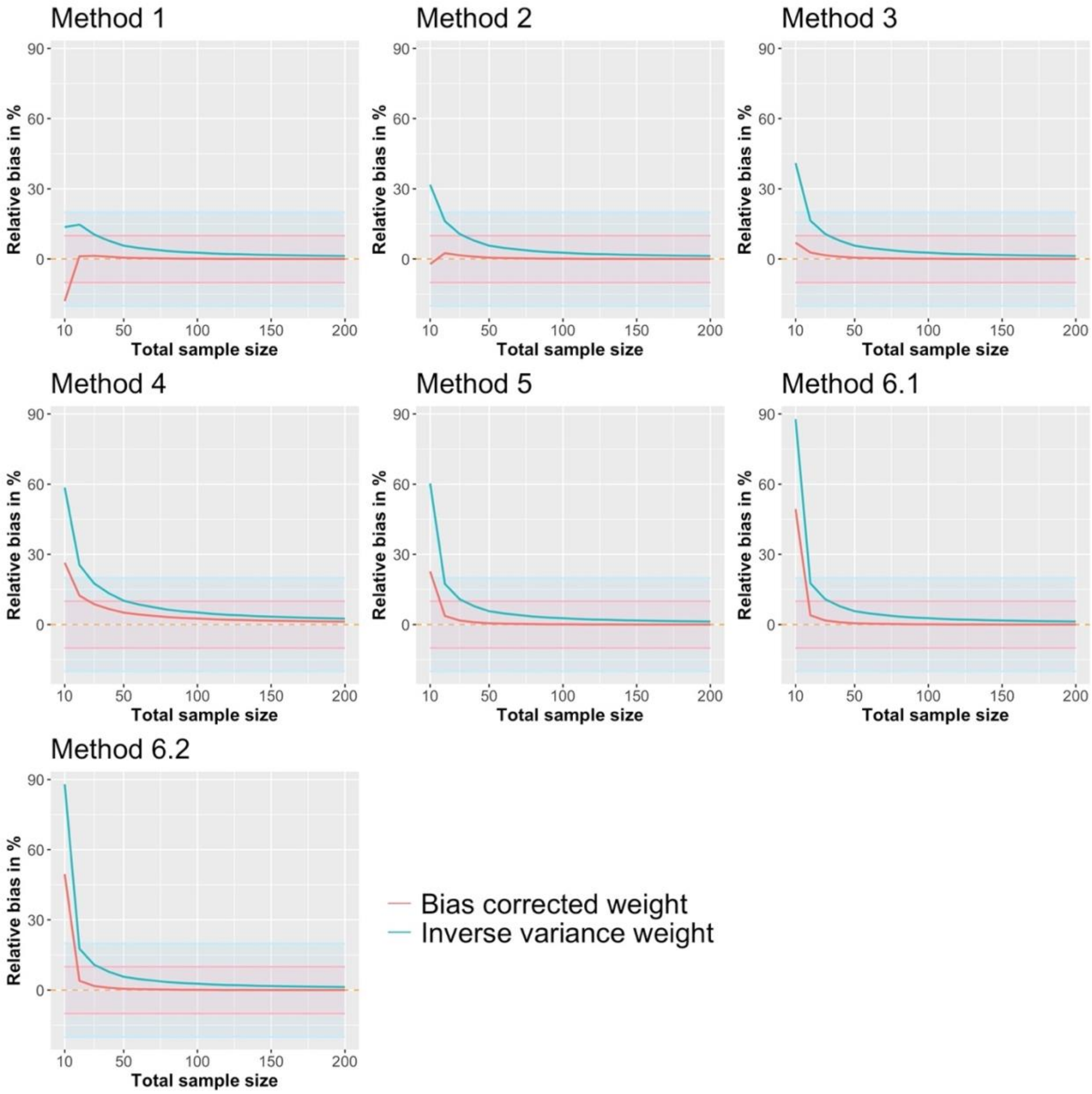

Figure 3.1.5: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $2n_1 \approx n_2$, with equal event rates $\pi_1 = \pi_2 = 0.5$

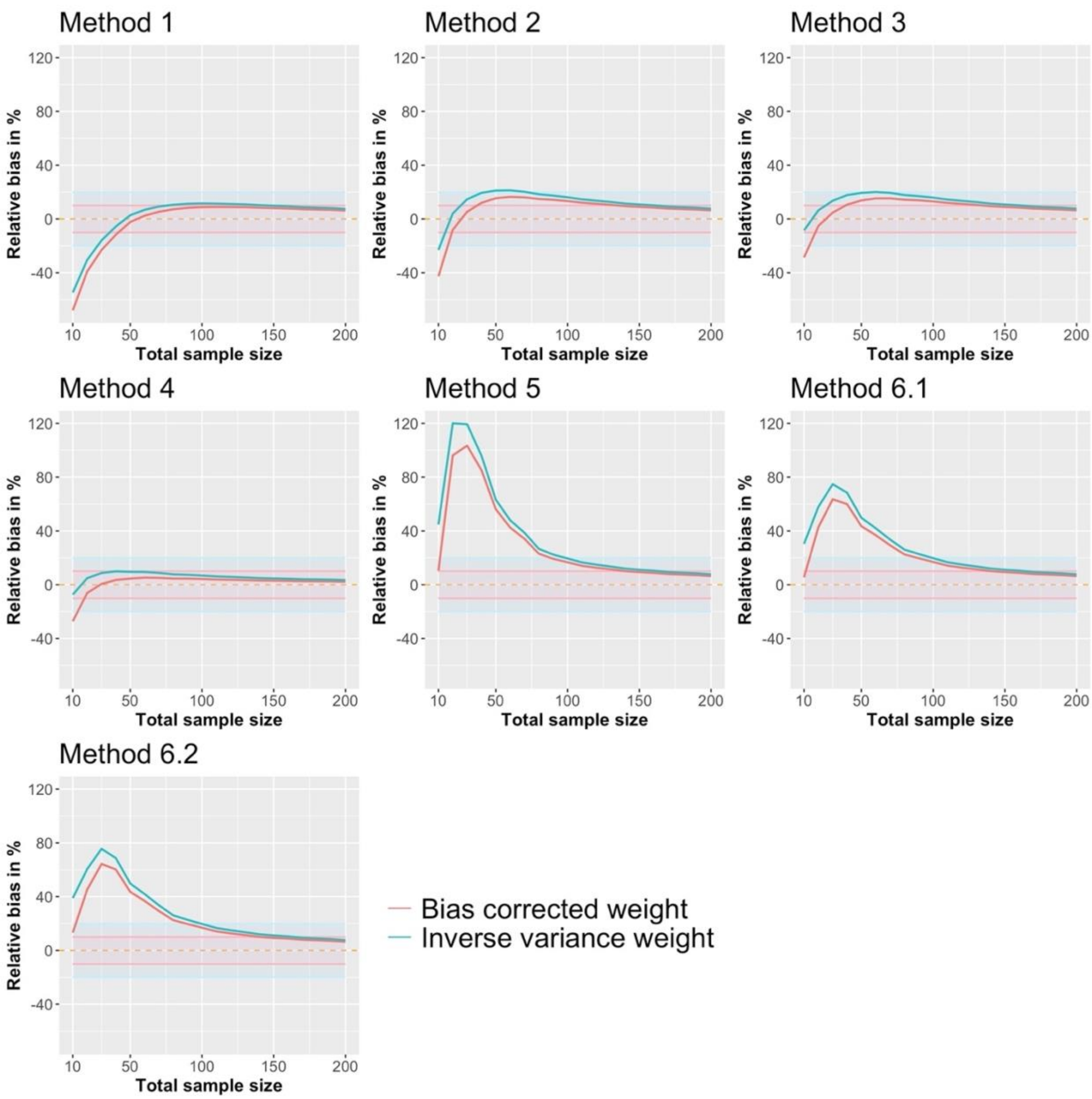

Figure 3.1.6: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $2n_1 \approx n_2$, with equal event rates $\pi_1 = \pi_2 = 0.1$

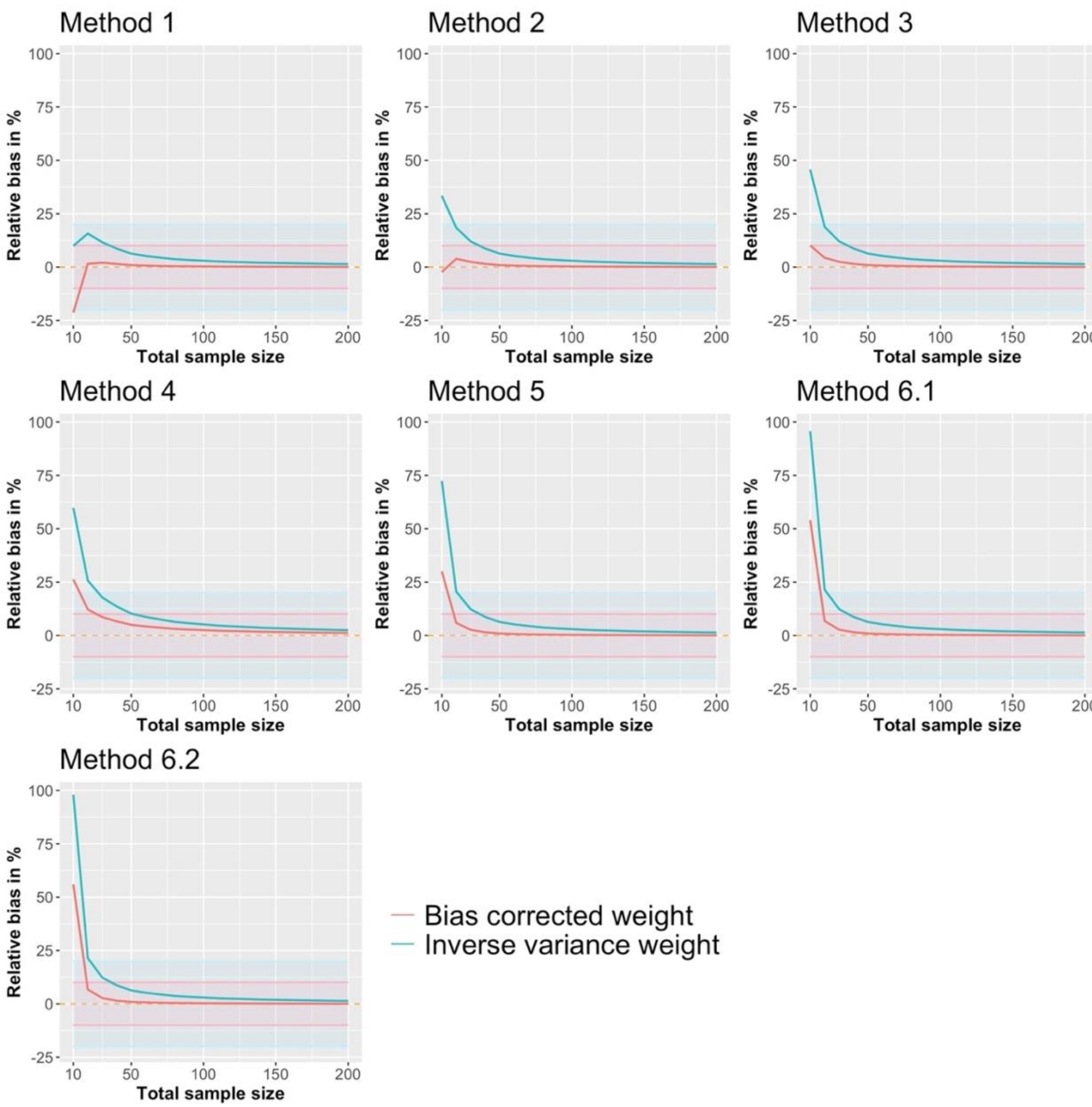

Figure 3.1.7: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.5, \pi_2 = 0.25$

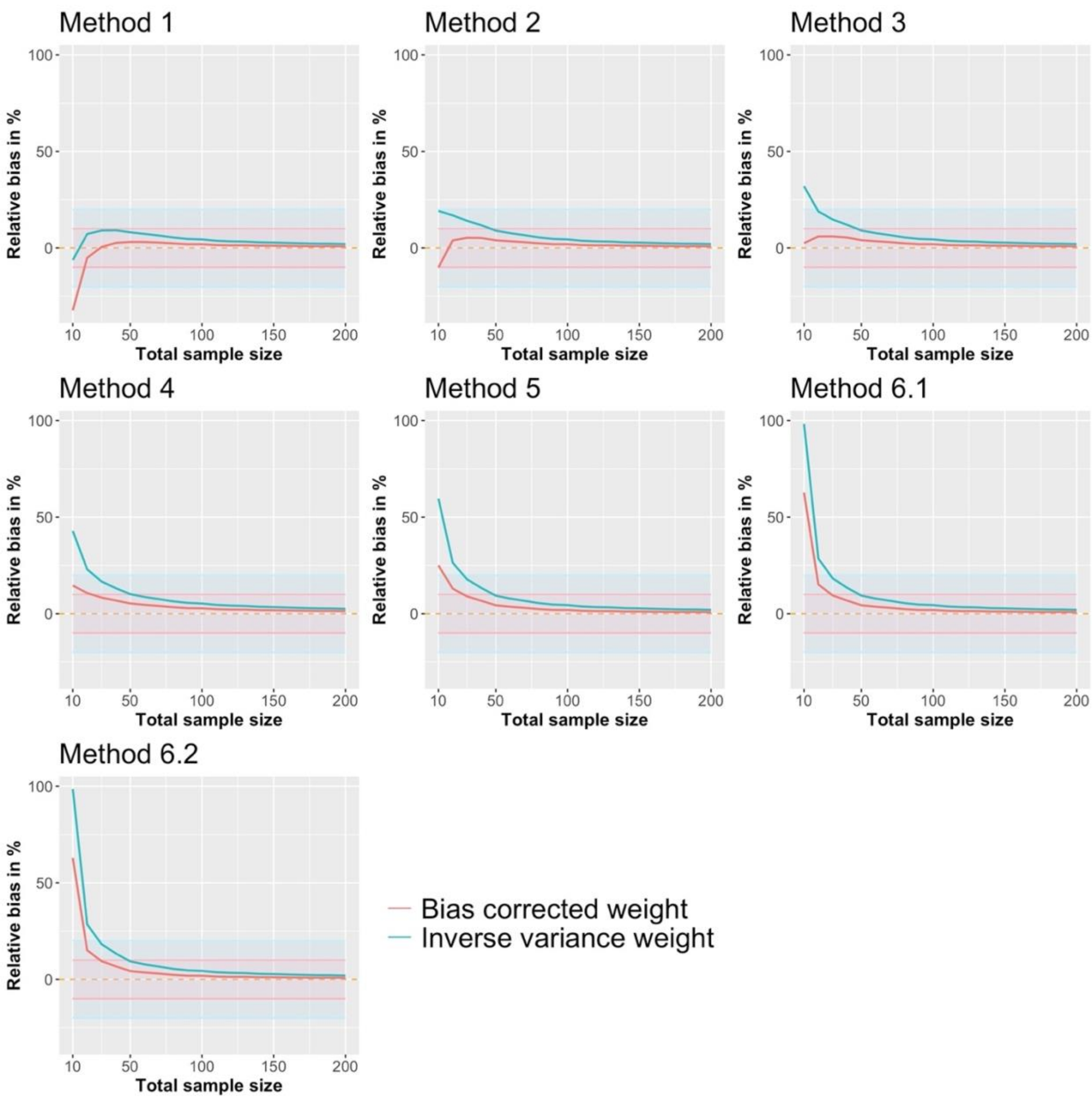

Figure 3.1.8: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.25, \pi_2 = 0.5$

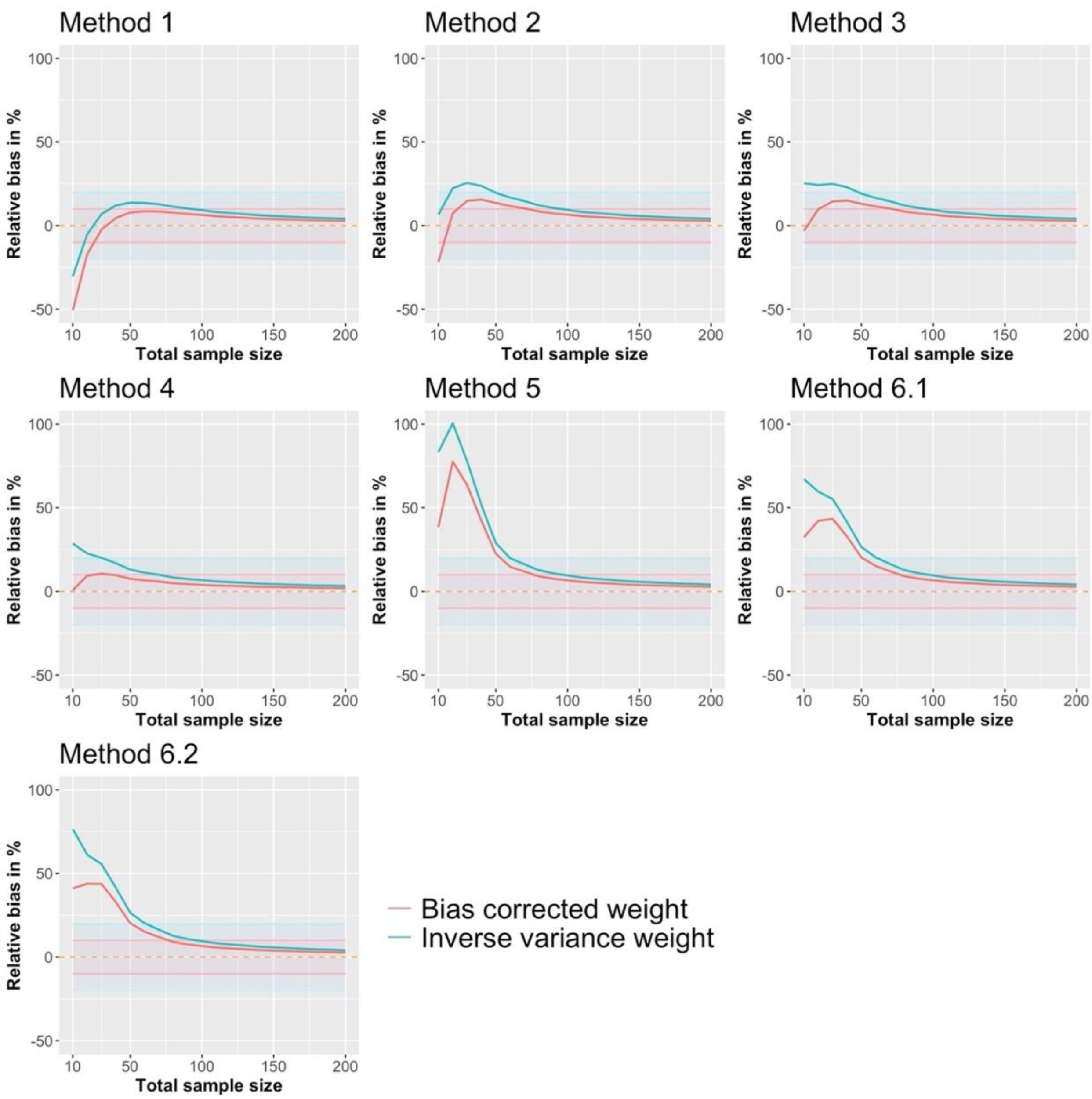

Figure 3.1.9: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $2n_1 \approx n_2$, *with unequal event rates* $\pi_1 = 0.2, \pi_2 = 0.1$

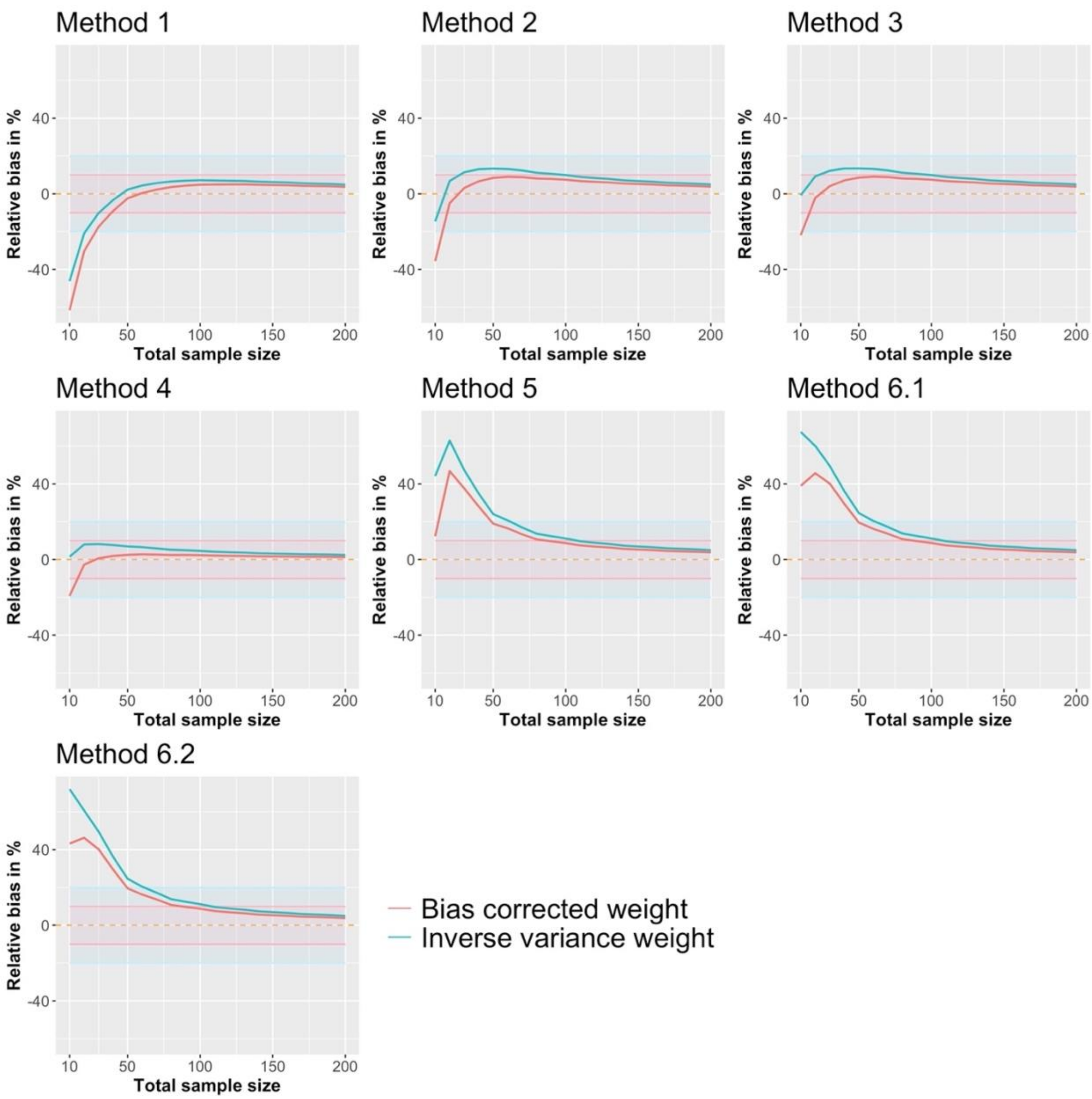

Figure 3.1.10: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.1, \pi_2 = 0.2$

3.2. Log Relative Risk

3.2.1. Balanced studies with equal event rates

Figures 3.2.1 and 3.2.2 show the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for log relative risk with equal sample sizes and equal event rates.

The bias of the inverse variance weight is much larger than the bias corrected weight for small n. For $\pi_1 = \pi_2 = 0.5$, method 2 seem to have the lowest bias when the sample size is very small, although for small samples such as $n_1 = n_2 = 5$, the bias is slightly greater than 30%. For $\pi_1 = \pi_2 = 0.1$, method 5 is notably the least biased, with bias around 50% for very small sample sizes. All other methods have greater 200% bias even for the bias corrected weights when sample sizes are very small.

3.2.2. Balanced studies with unequal event rates

Figures 3.2.3 and 3.2.4 show the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for log relative risk with equal sample sizes and unequal event rates.

For moderate to large event rates, method 2, 3, and 5 are better than the rest of the methods. For small event rates, method 5 is much less biased than the other methods.

3.2.3. Imbalanced studies with equal event rates

Figures 3.2.5 and 3.2.6 show the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for log relative risk with unequal sample sizes and equal event rates.

Method 2 gives smaller biased weight when $\pi_1 = \pi_2 = 0.5$. For $\pi_1 = \pi_2 = 0.1$, all the methods have extremely large bias when n is small. Method 5 have relatively smaller bias compared to the other methods.

3.2.4. Imbalanced studies with unequal event rates

Figures 3.2.7 to 3.2.10 show the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for log relative risk with unequal sample sizes and unequal event rates.

As in previous cases, all methods behave poorly for small n. Methods 2, 3, and 5 are better choices for moderate to large event rates. Method 5 is a better choice for small event rates.

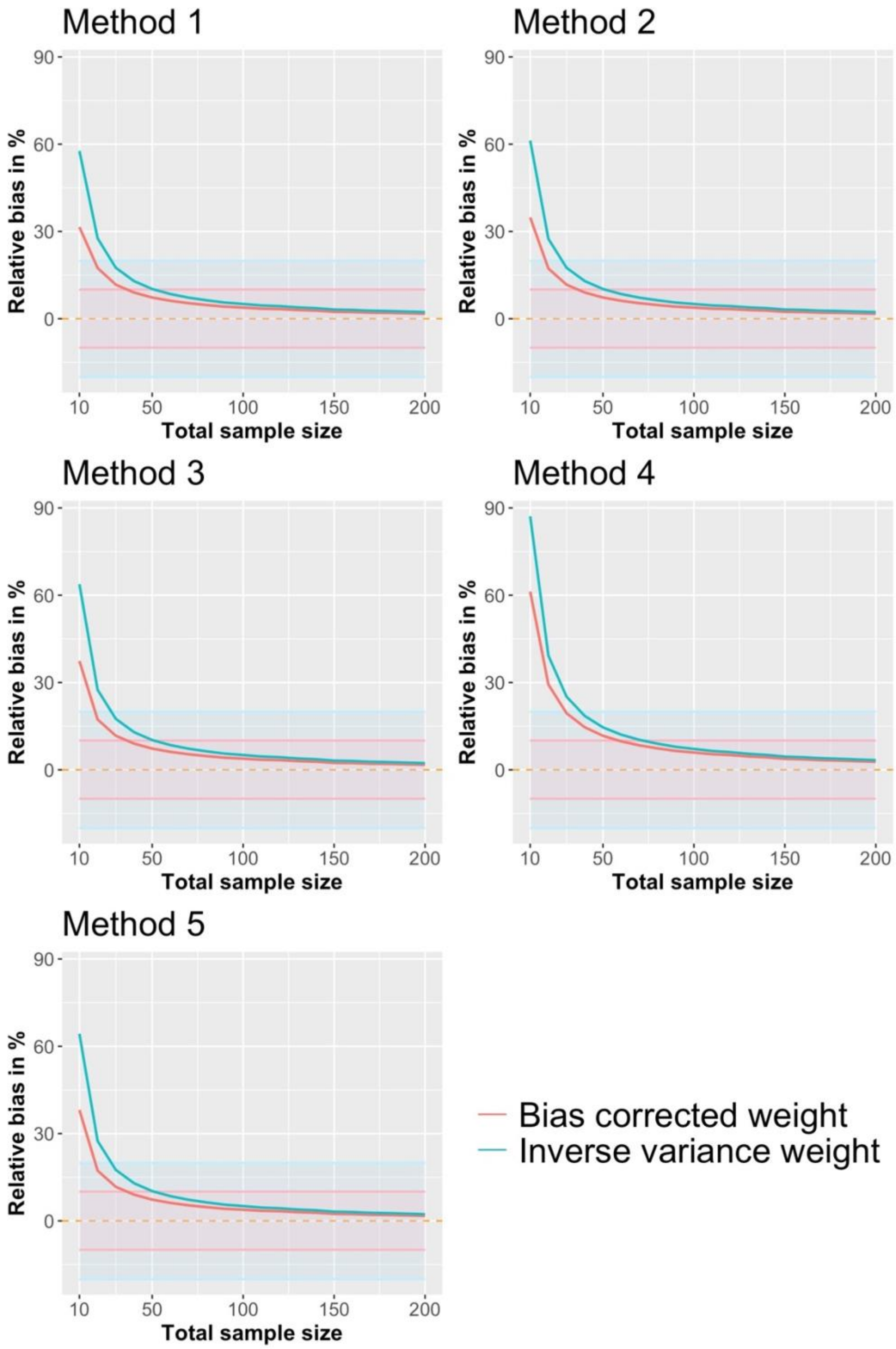

Figure 3.2.1: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.5$

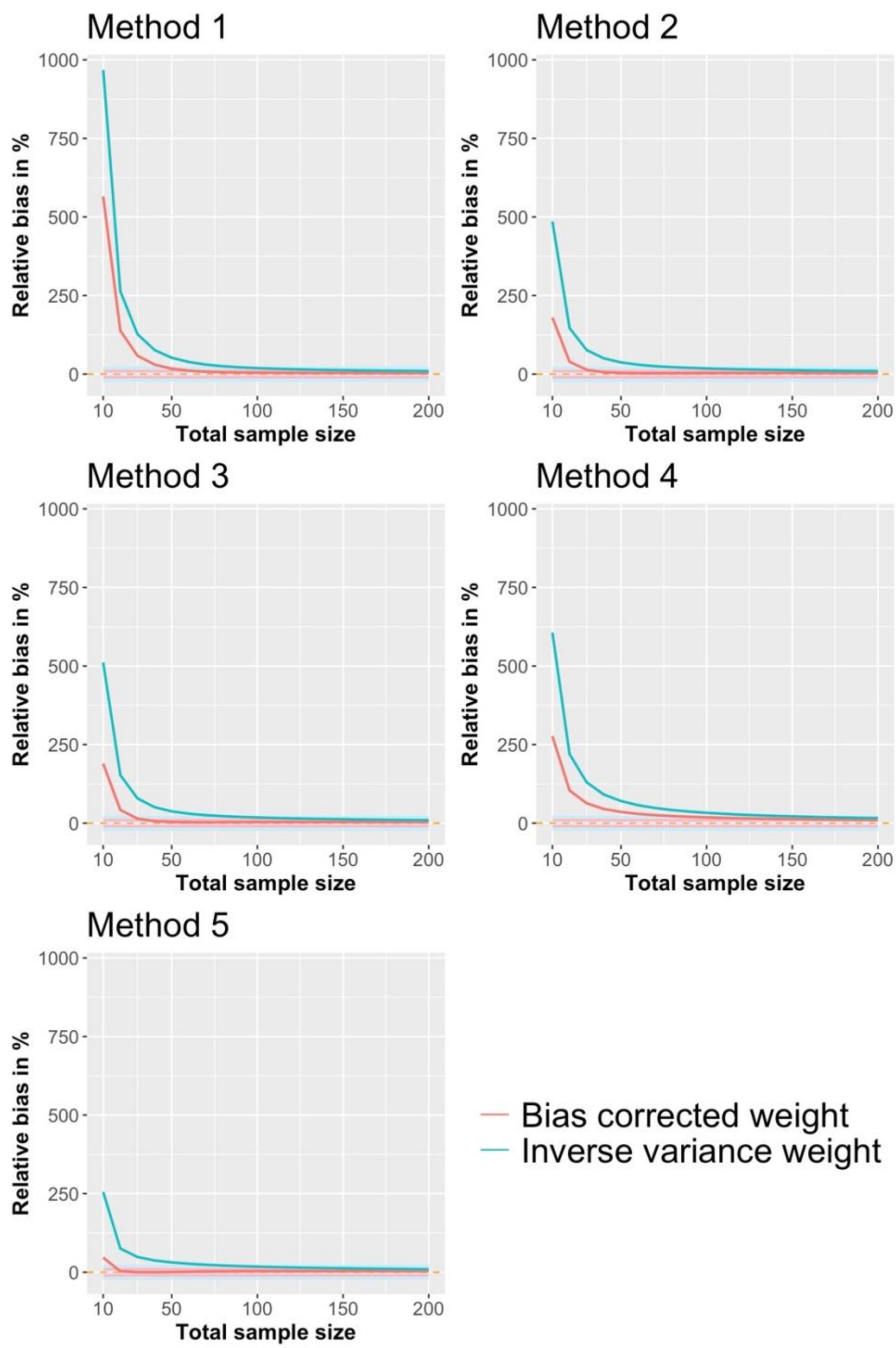

Figure 3.2.2: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.1$

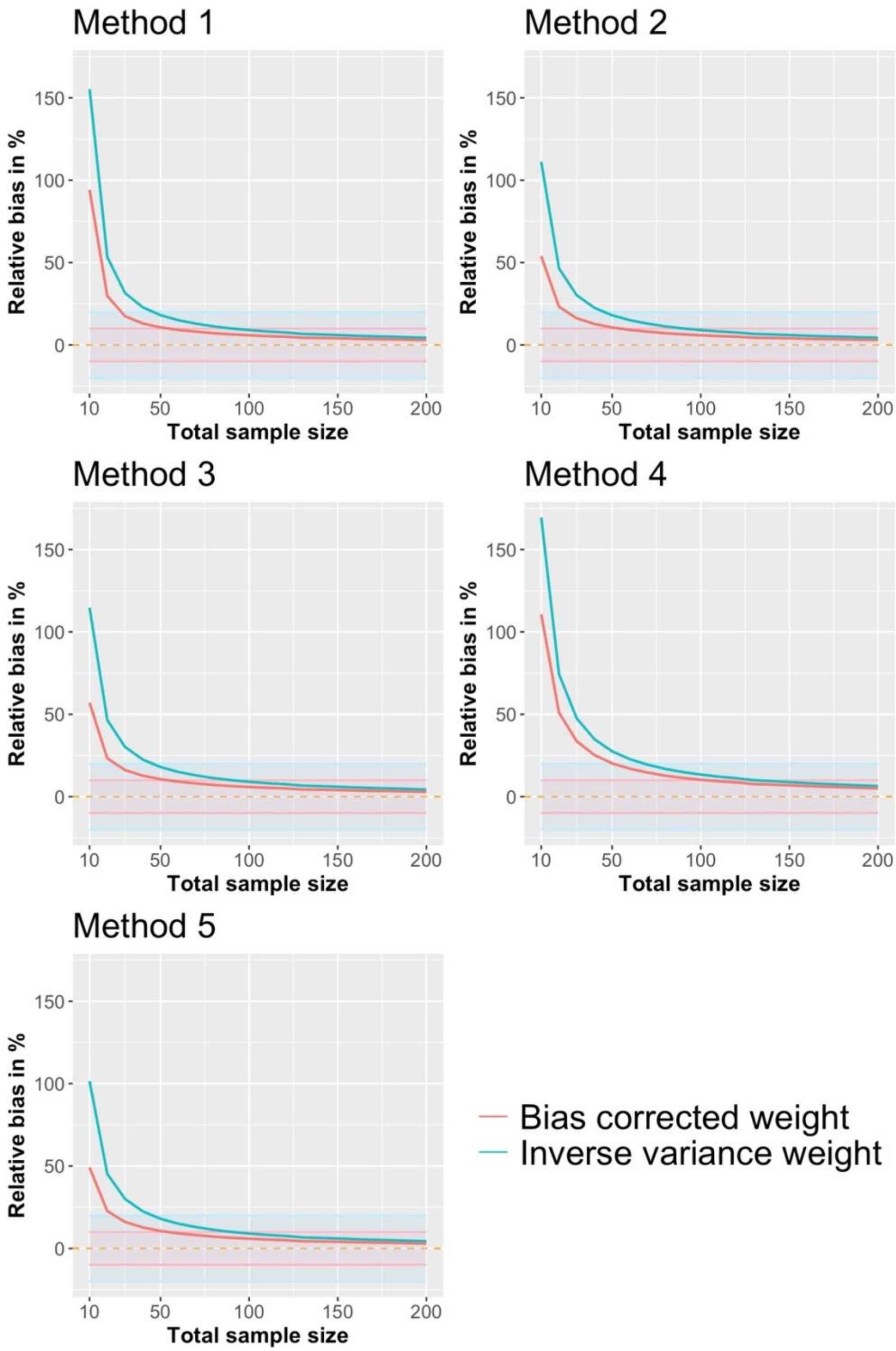

Figure 3.2.3: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $n_1 = n_2$, with unequal event rates $\pi_1 = 0.5, \pi_2 = 0.25$

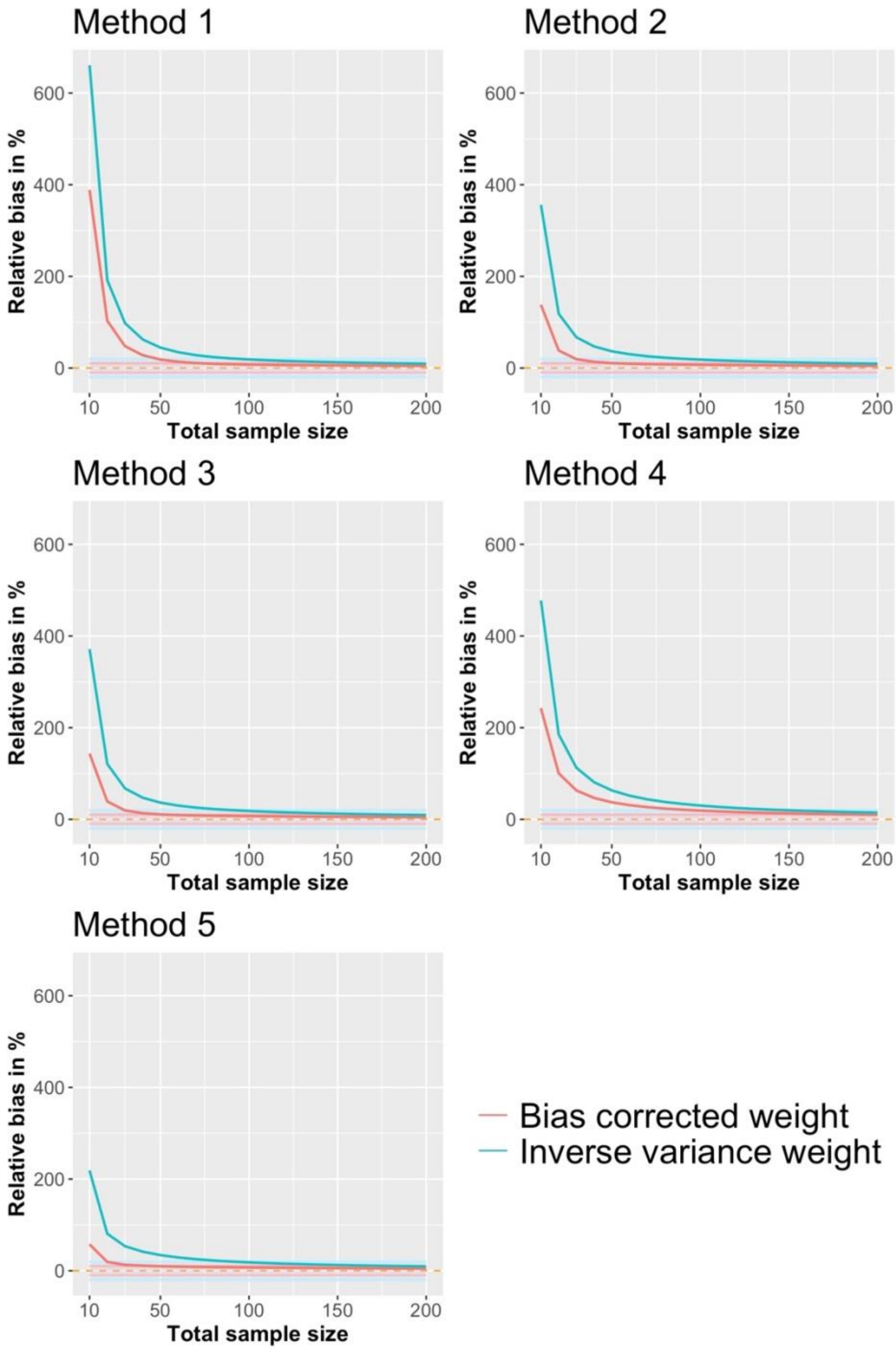

Figure 3.2.4: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $n_1 = n_2$, with unequal event rates $\pi_1 = 0.2, \pi_2 = 0.1$

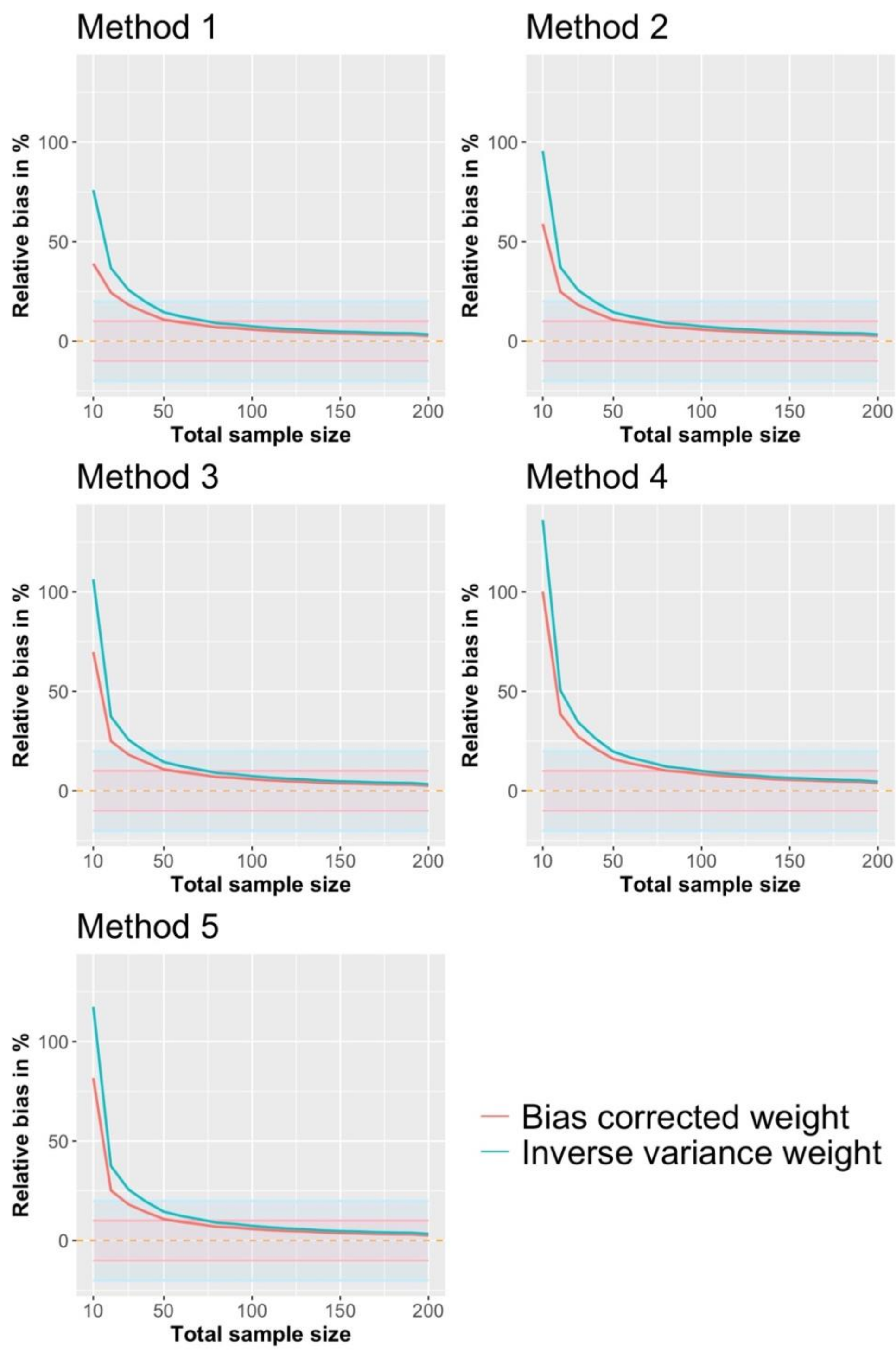

Figure 3.2.5: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $2n_1 \approx n_2$, with equal event rates $\pi_1 = \pi_2 = 0.5$

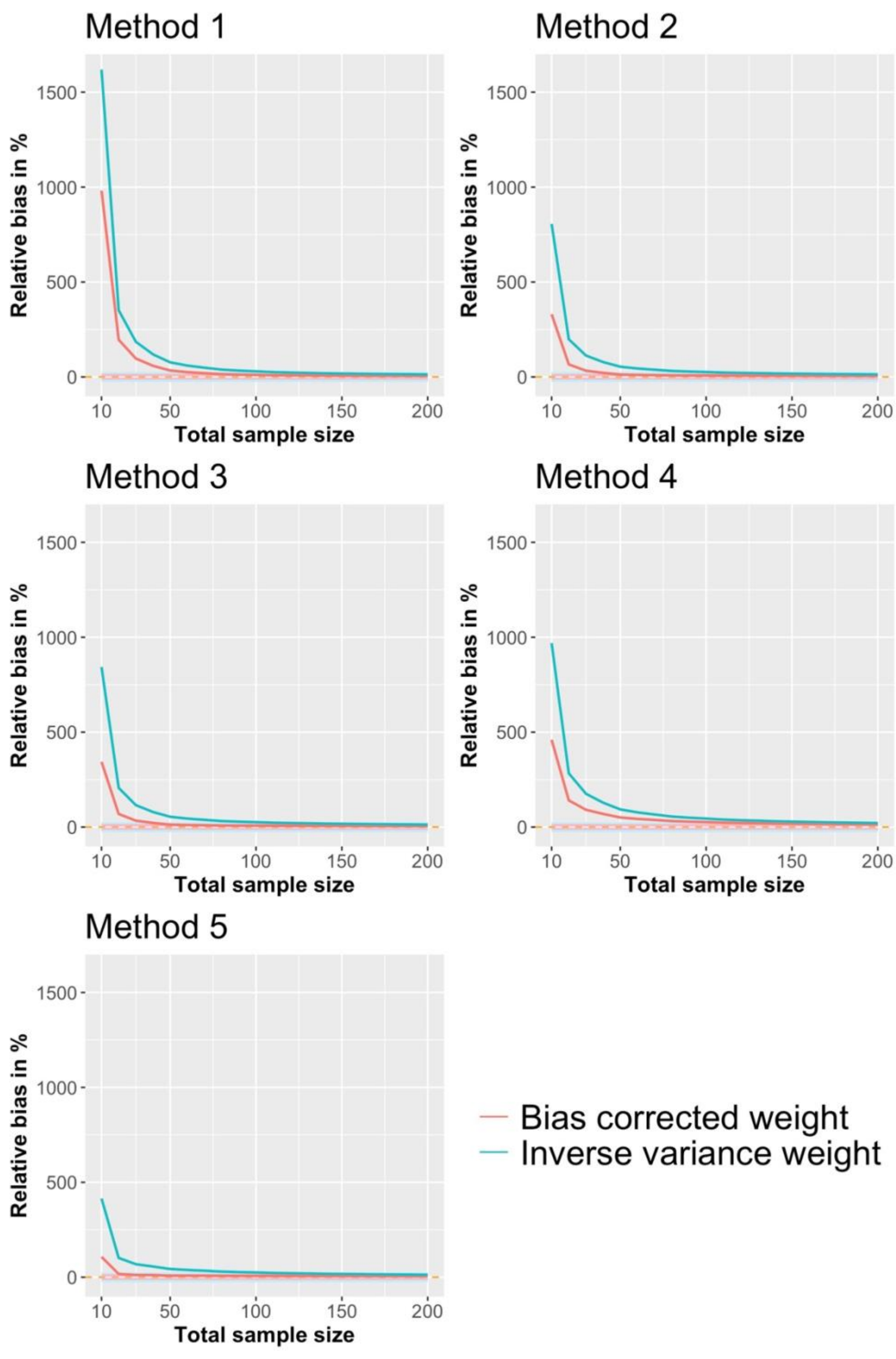

Figure 3.2.6: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $2n_1 \approx n_2$, with equal event rates $\pi_1 = \pi_2 = 0.1$

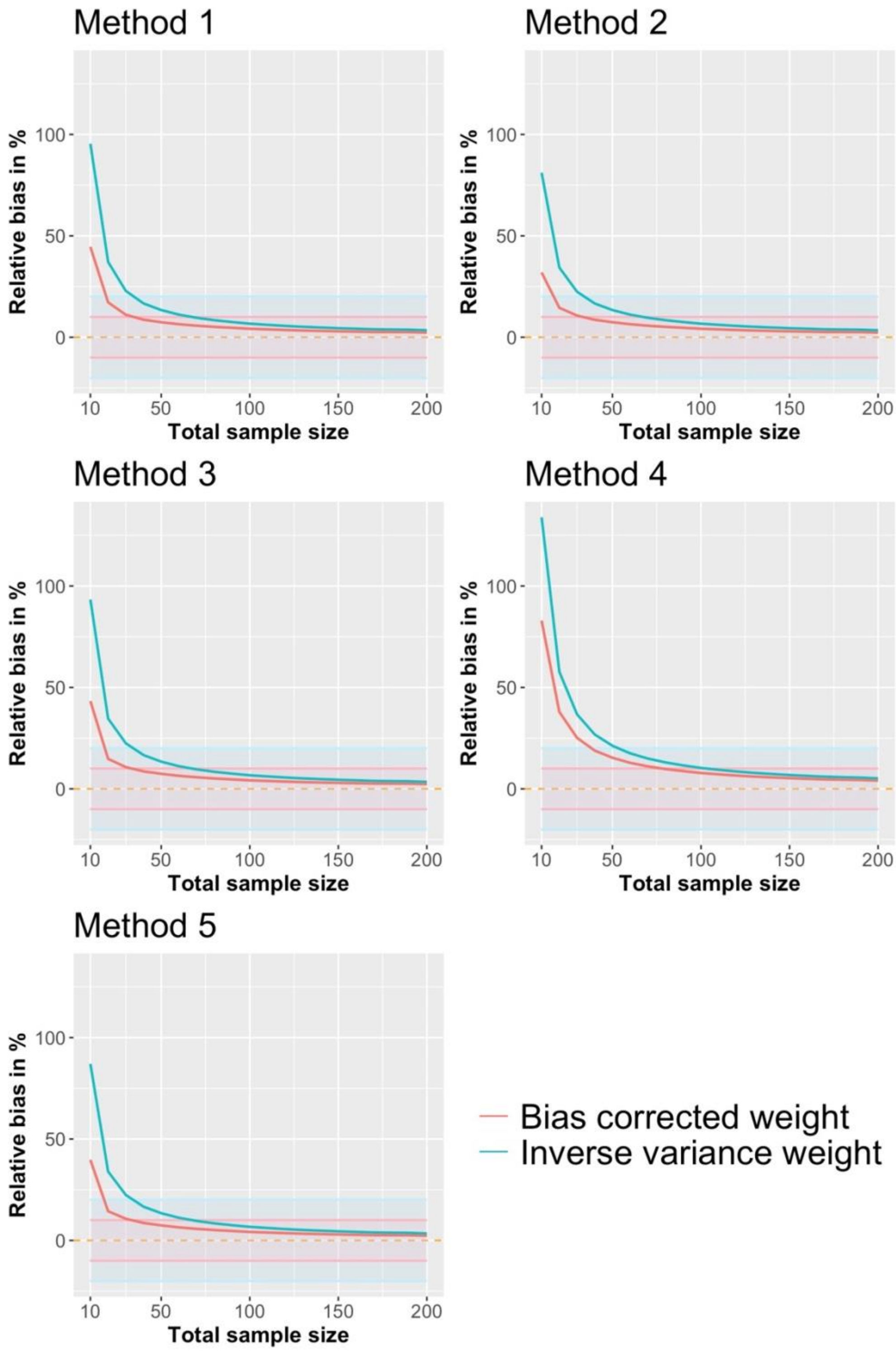

Figure 3.2.7: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.5, \pi_2 = 0.25$

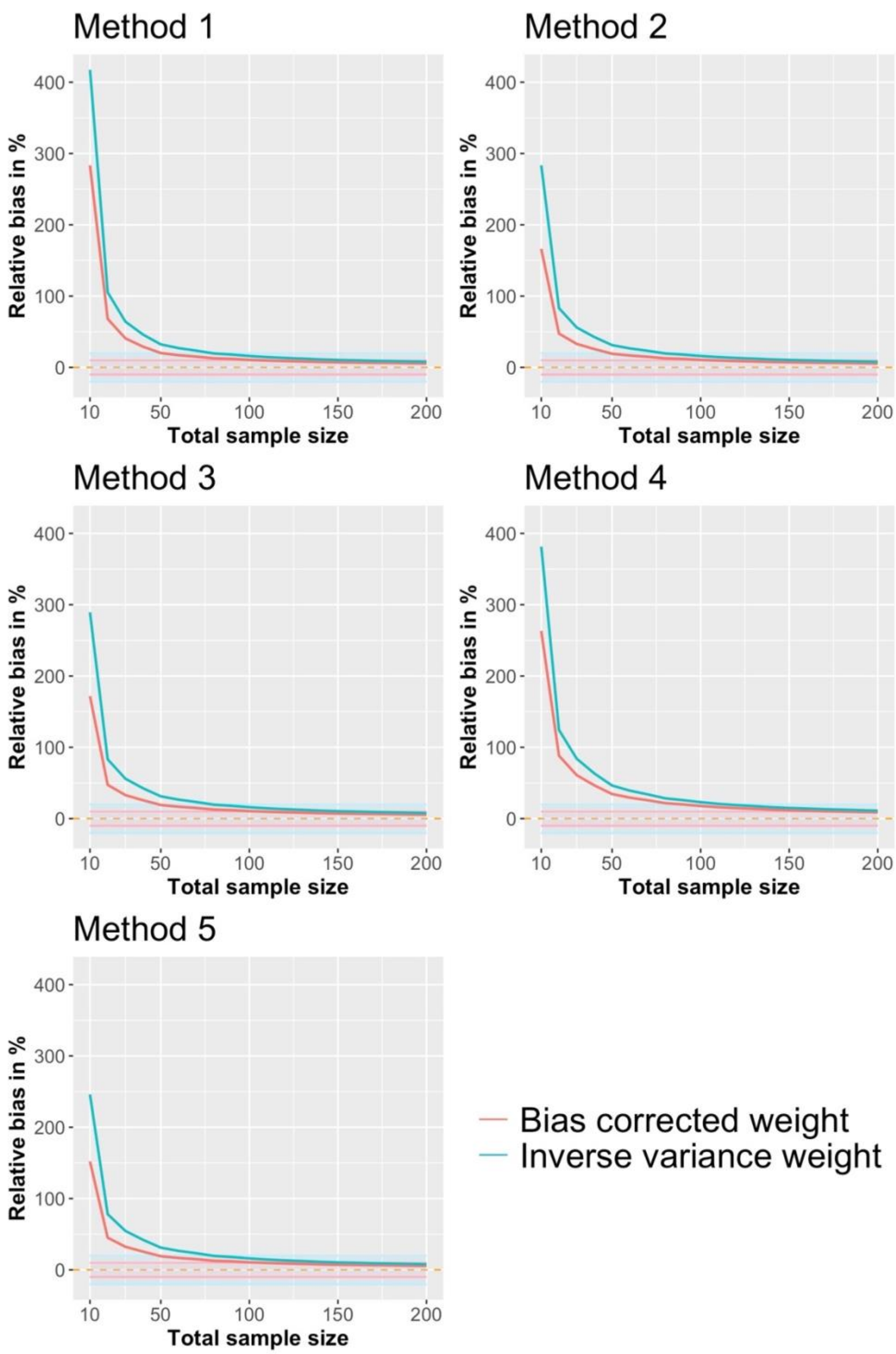

Figure 3.2.8: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.25, \pi_2 = 0.5$

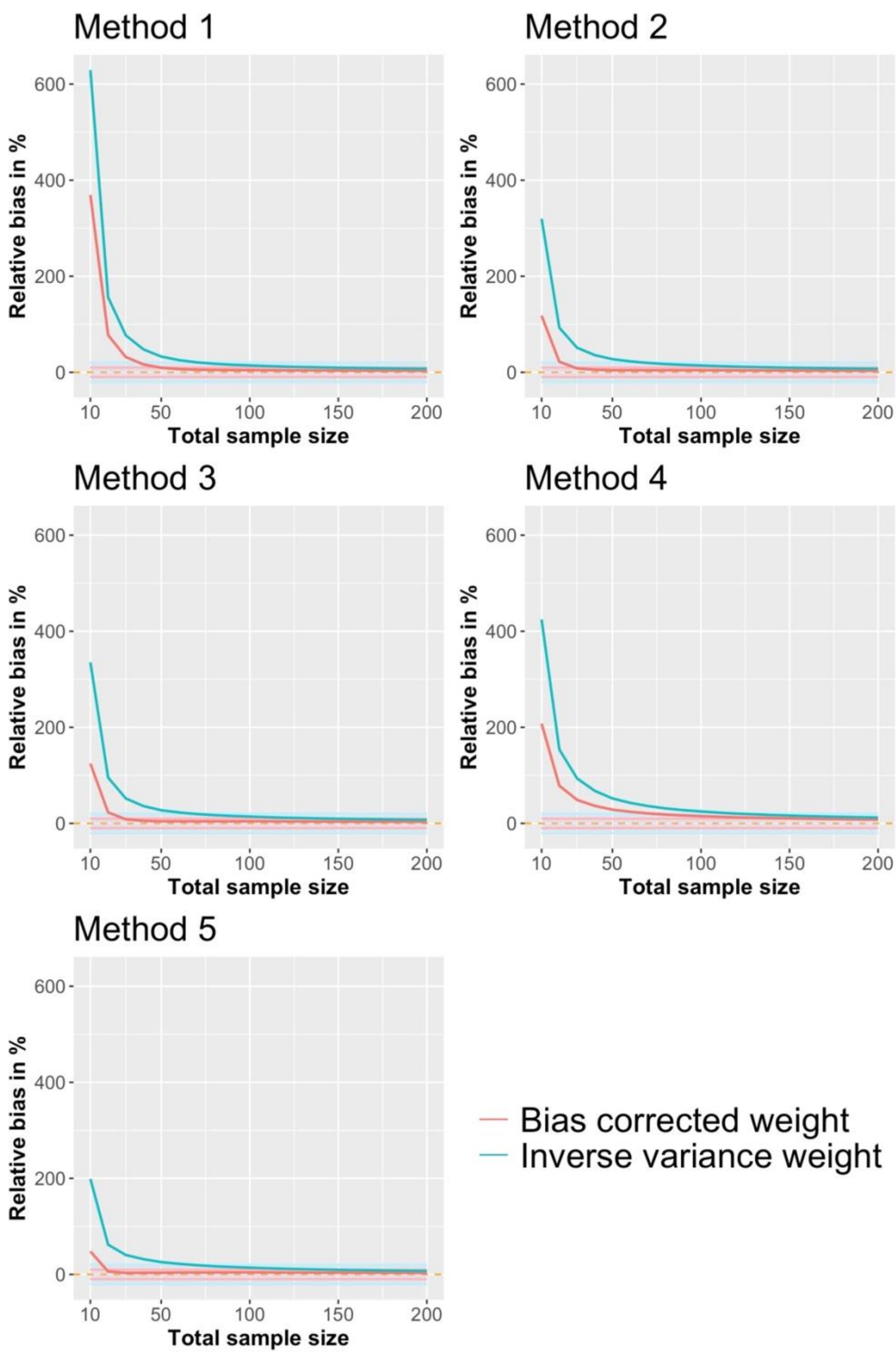

Figure 3.2.9: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.2, \pi_2 = 0.1$

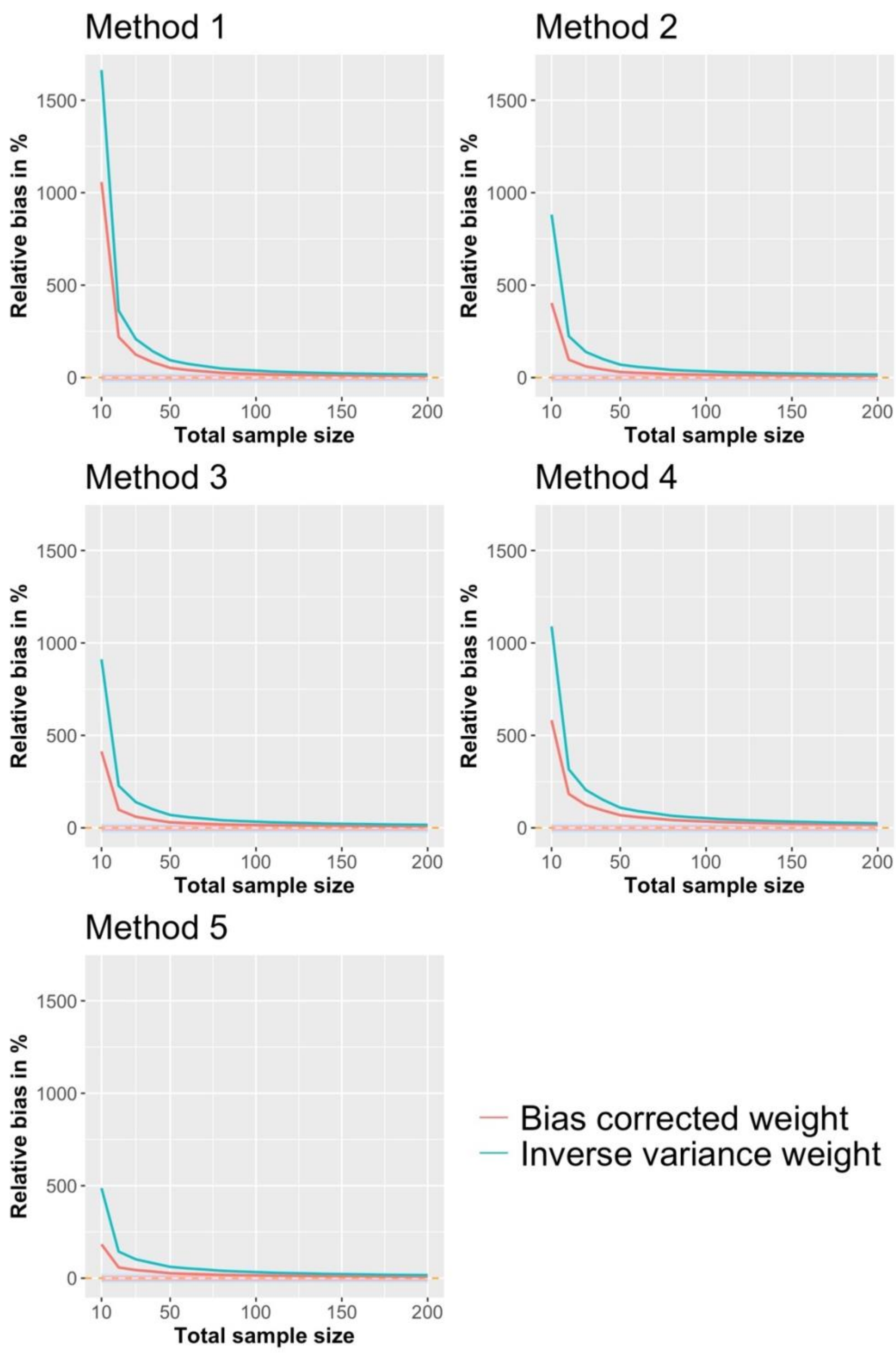

Figure 3.2.10: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.1, \pi_2 = 0.2$

3.3. Log Odds Ratio

3.3.1. Balanced studies with equal event rates

Figures 3.3.1 and 3.3.2 show the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for log odds ratio with equal sample sizes and equal event rates.

For $\pi_1 = \pi_2 = 0.5$, bias corrected weight of methods 2, 3, and 5 has negative bias when the sample sizes are small, which underestimate the weights, while the inverse variance weights are positively biased. In the current stage it is uncertain about the influence of under- or over- estimation of a single study weight to the final summary effects and variance of summary effects, since the corresponding proportional weight in a meta-analysis might not change too much. But in this case the biases are all approximately within the $\pm$20% bias threshold. Only method 4 has bias corrected weight less biased than the standard weight, and is within the interval of 10% bias. For $\pi_1 = \pi_2 = 0.1$, bias corrected weight in method 5 is the least biased and the only one within the $\pm$20% bias interval, while the other methods give greater than 100% bias.

3.3.2. Balanced studies with unequal event rates

Figures 3.3.3 and 3.3.4 show the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for log odds ratio with equal sample sizes and unequal event rates.

For $\pi_1 = 0.5, \pi_2 = 0.25$, bias corrected weights from method 2 and 3 are always less than $\pm$10% of bias. For $\pi_1 = 0.2, \pi_2 = 0.1$, bias corrected weight from method 5 is less than $\pm$20% of bias whereas the other methods all have very large bias when n is small.

3.3.3. Imbalanced studies with equal event rates

Figures 3.3.5 and 3.3.6 show the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for log odds ratio with unequal sample sizes and equal event rates.

For $\pi_1 = 0.5, \pi_2 = 0.25$, bias corrected weights from method 2, 3, and 4 are always less than 10% of bias. For $\pi_1 = 0.2, \pi_2 = 0.1$, bias corrected weight from method 5 is less than 20% of bias whereas the other methods all have very large bias when n is small.

3.3.4. Imbalanced studies with unequal event rates

Figures 3.3.7 to 3.3.10 show the relative bias in percentage comparing the bias corrected weights and inverse variance weights under different zero modification methods for log odds ratio with unequal sample sizes and unequal event rates.

Methods 2, 3, and 5 give less biased than method 4 for small sample sizes when event rates are moderate to large. The bias corrected weight using method 5 is again the least biased for small event rates.

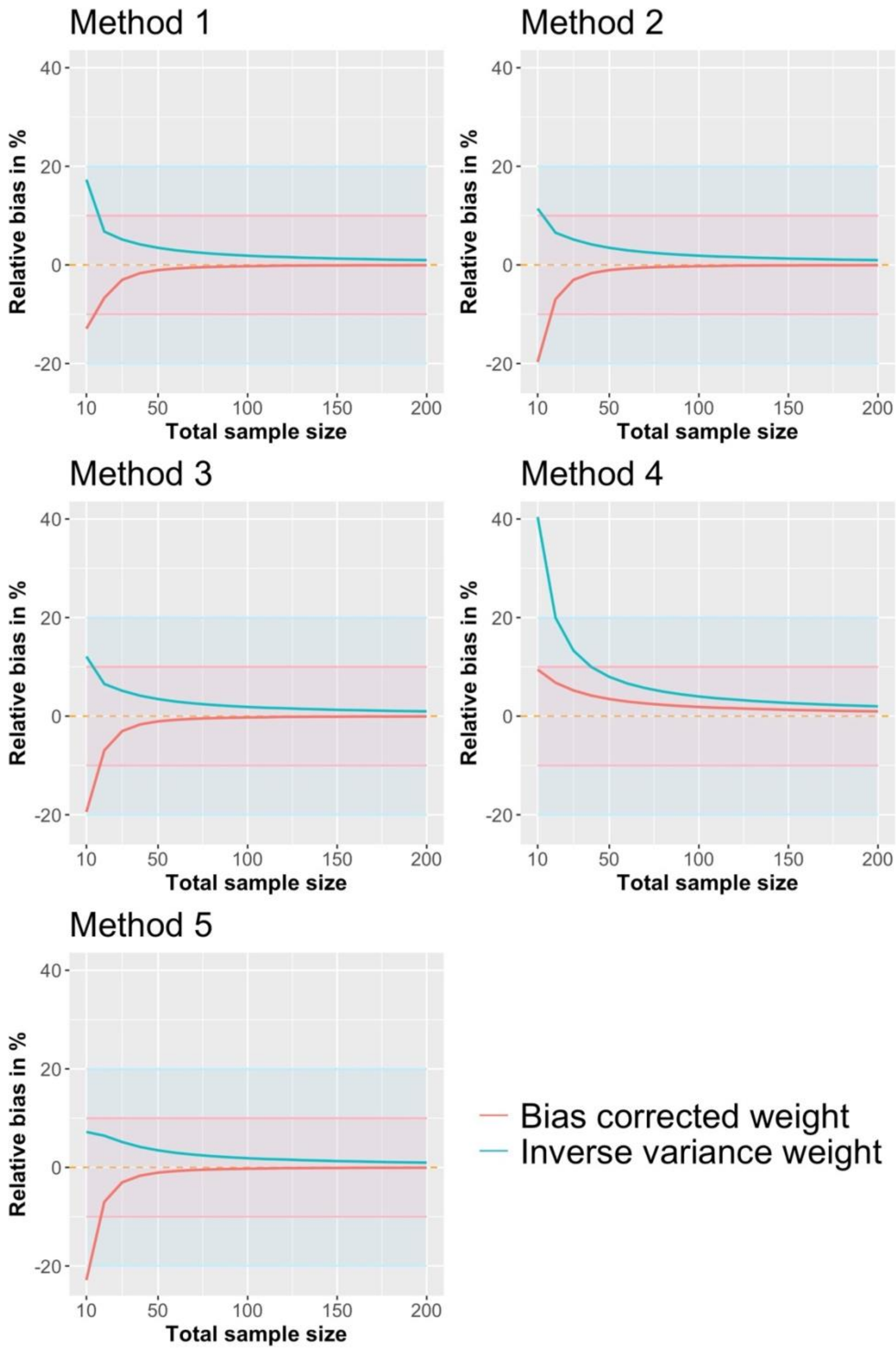

Figure 3.3.1: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.5$

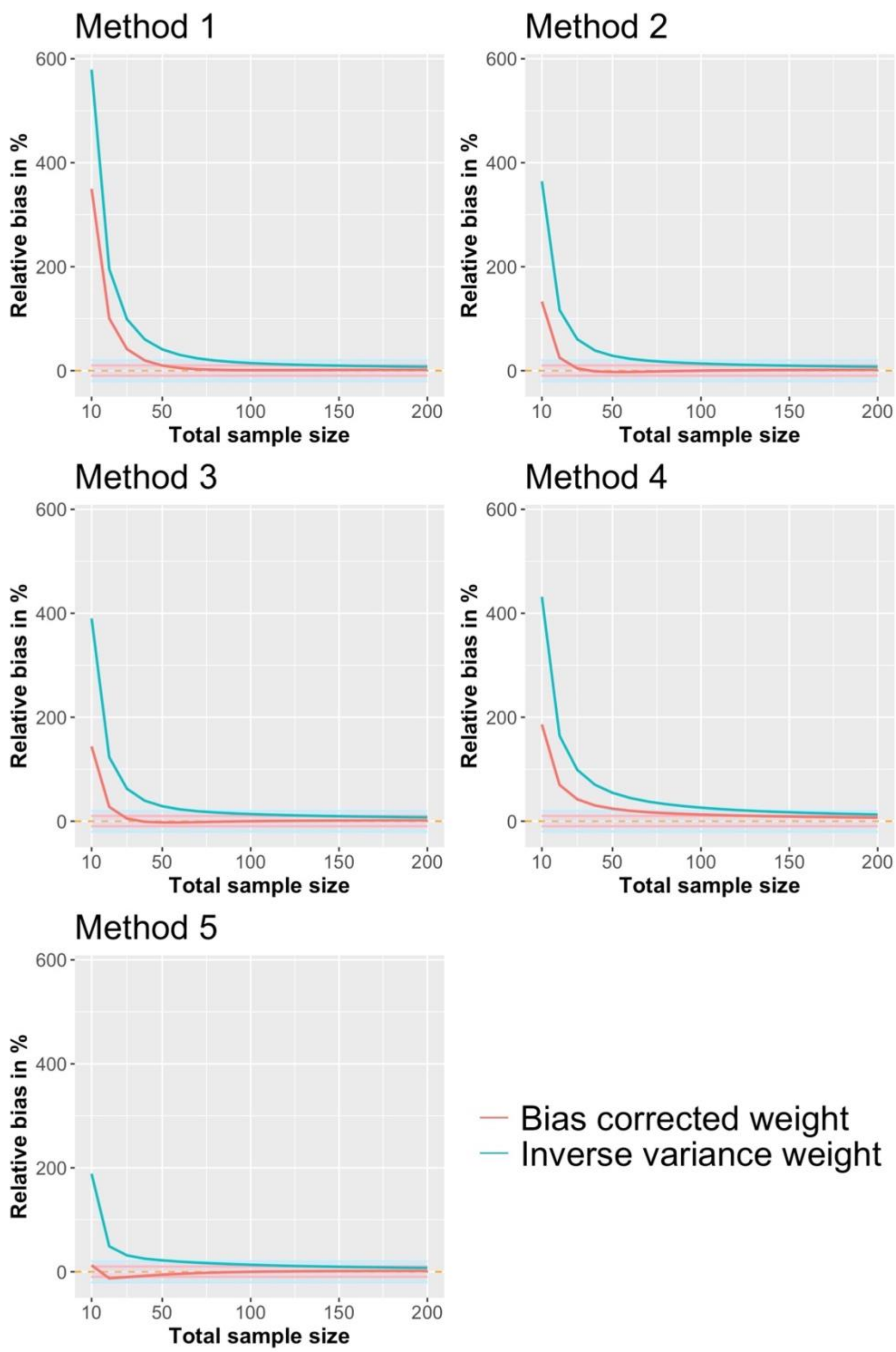

Figure 3.3.2: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.1$

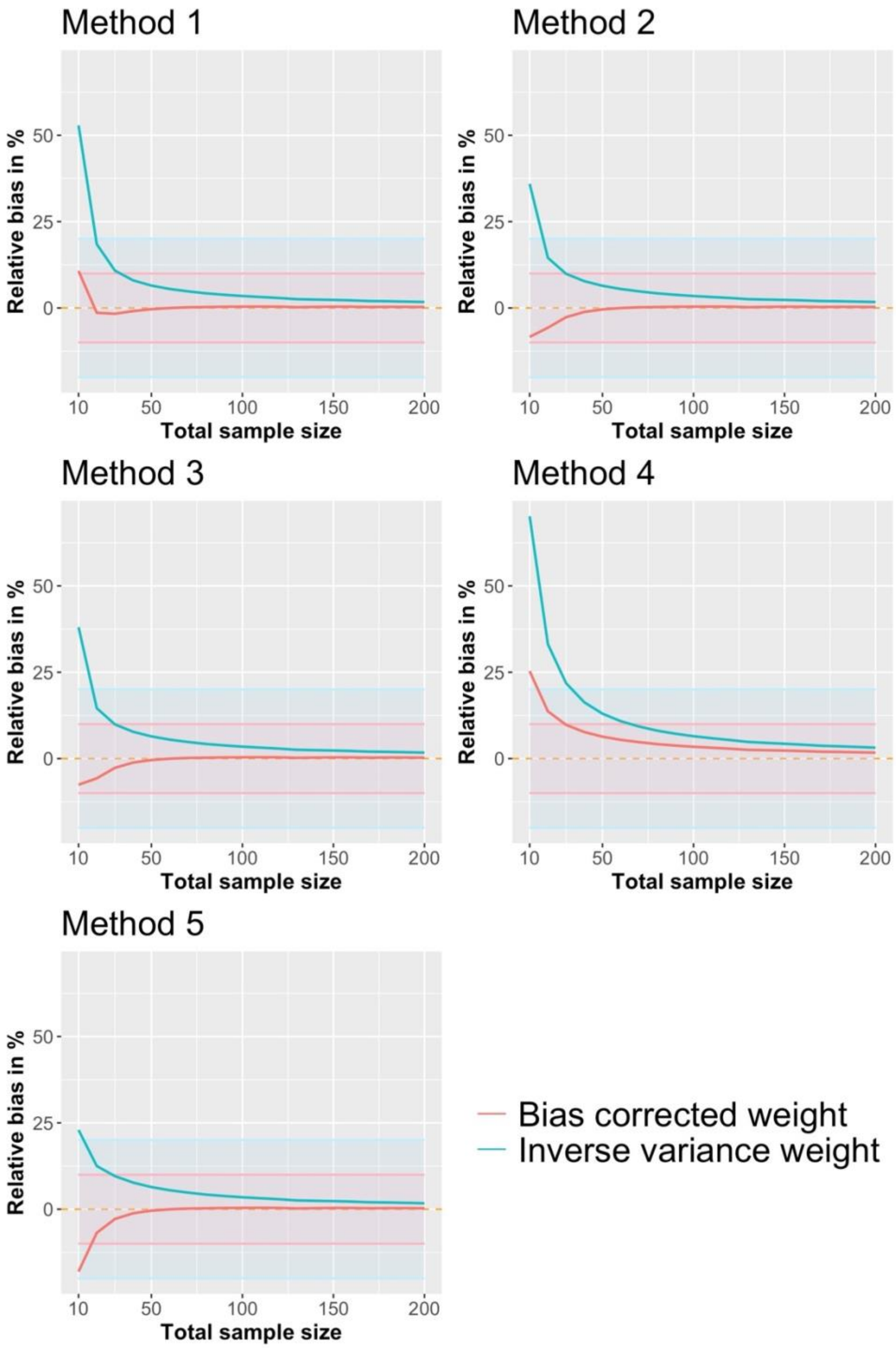

Figure 3.3.3: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $n_1 = n_2$, with unequal event rates $\pi_1 = 0.5, \pi_2 = 0.25$

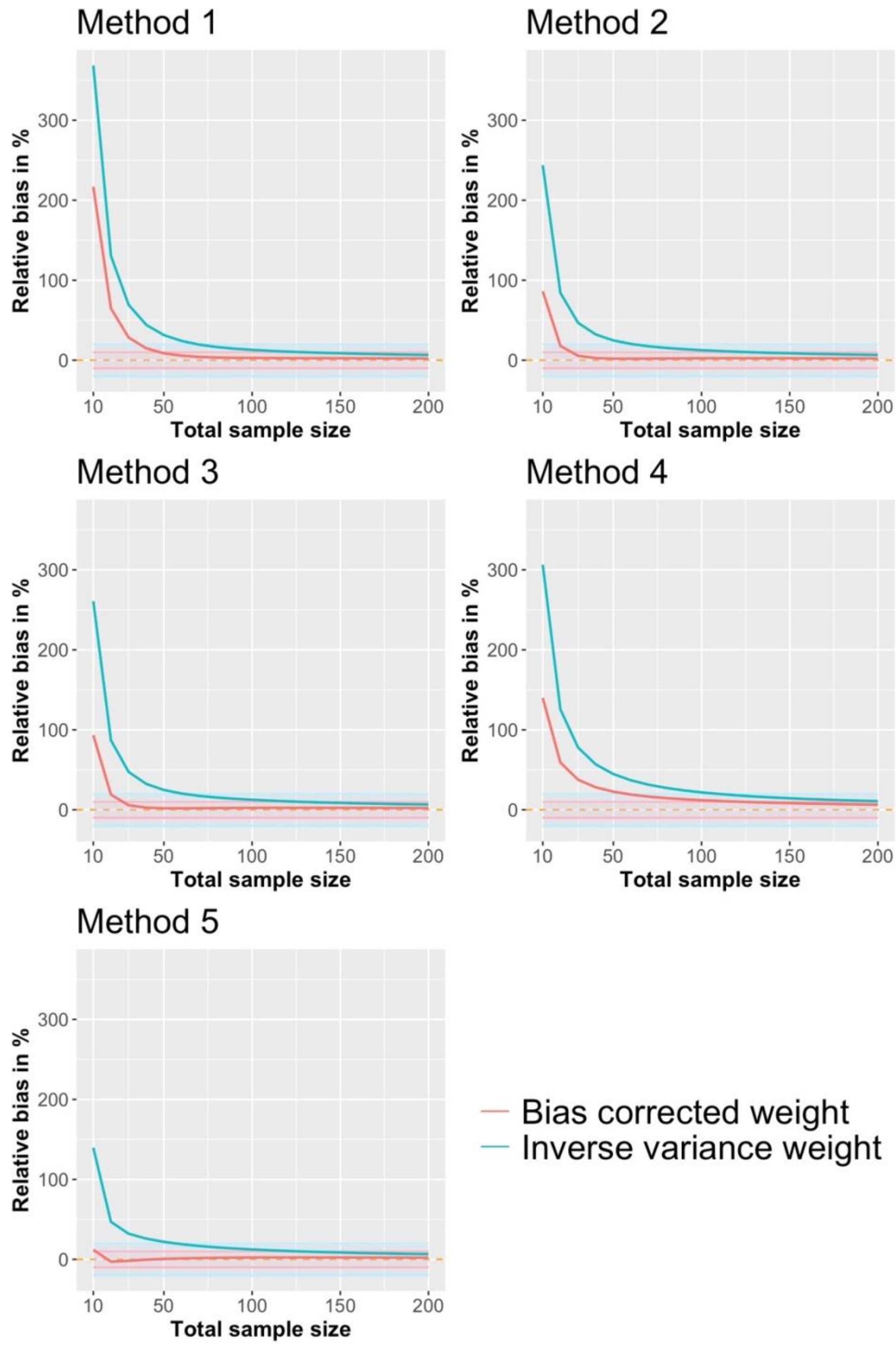

Figure 3.3.4: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $n_1 = n_2$, with unequal event rates $\pi_1 = 0.2, \pi_2 = 0.1$

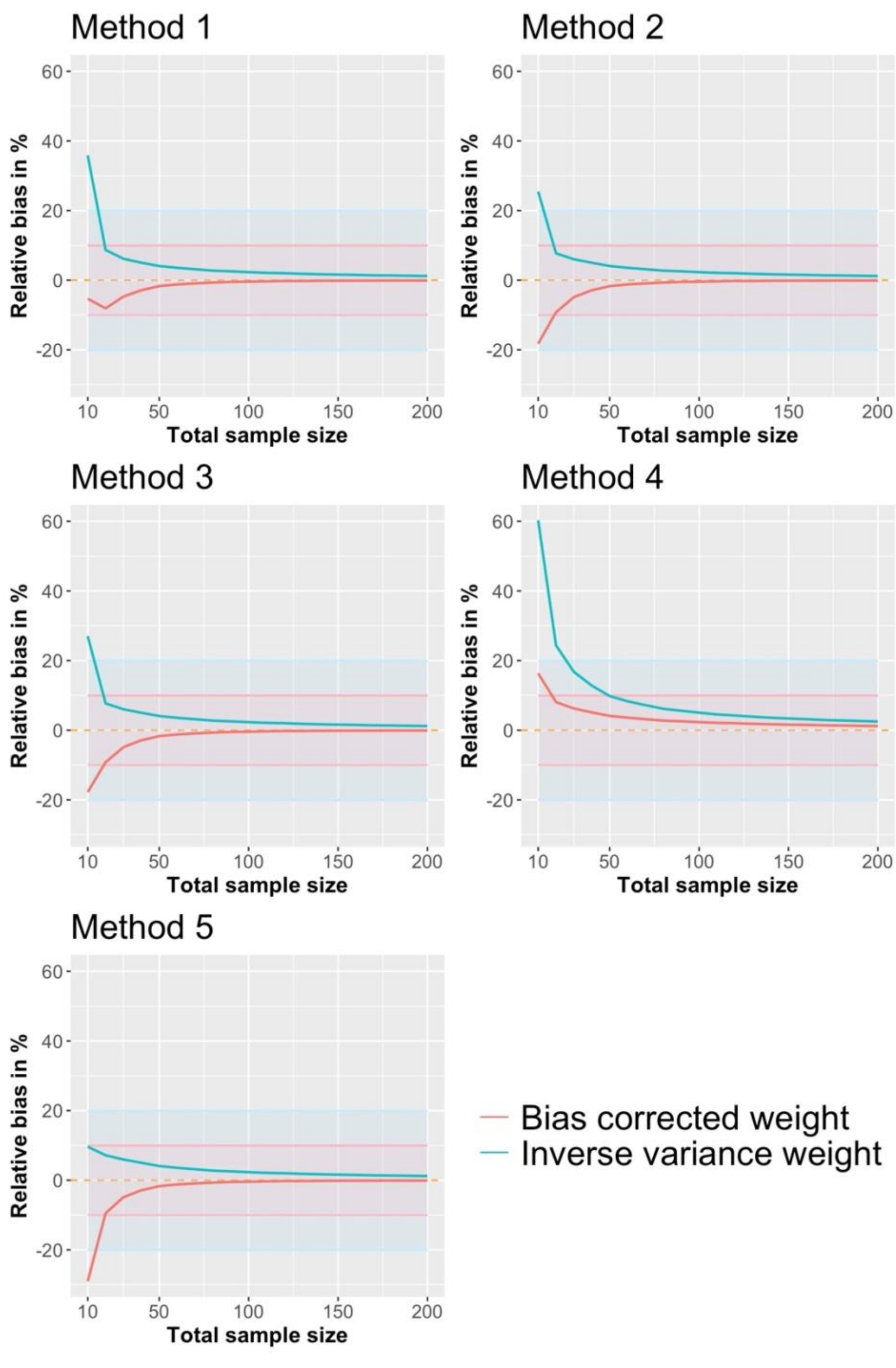

Figure 3.3.5: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $2n_1 \approx n_2$, with equal event rates $\pi_1 = \pi_2 = 0.5$

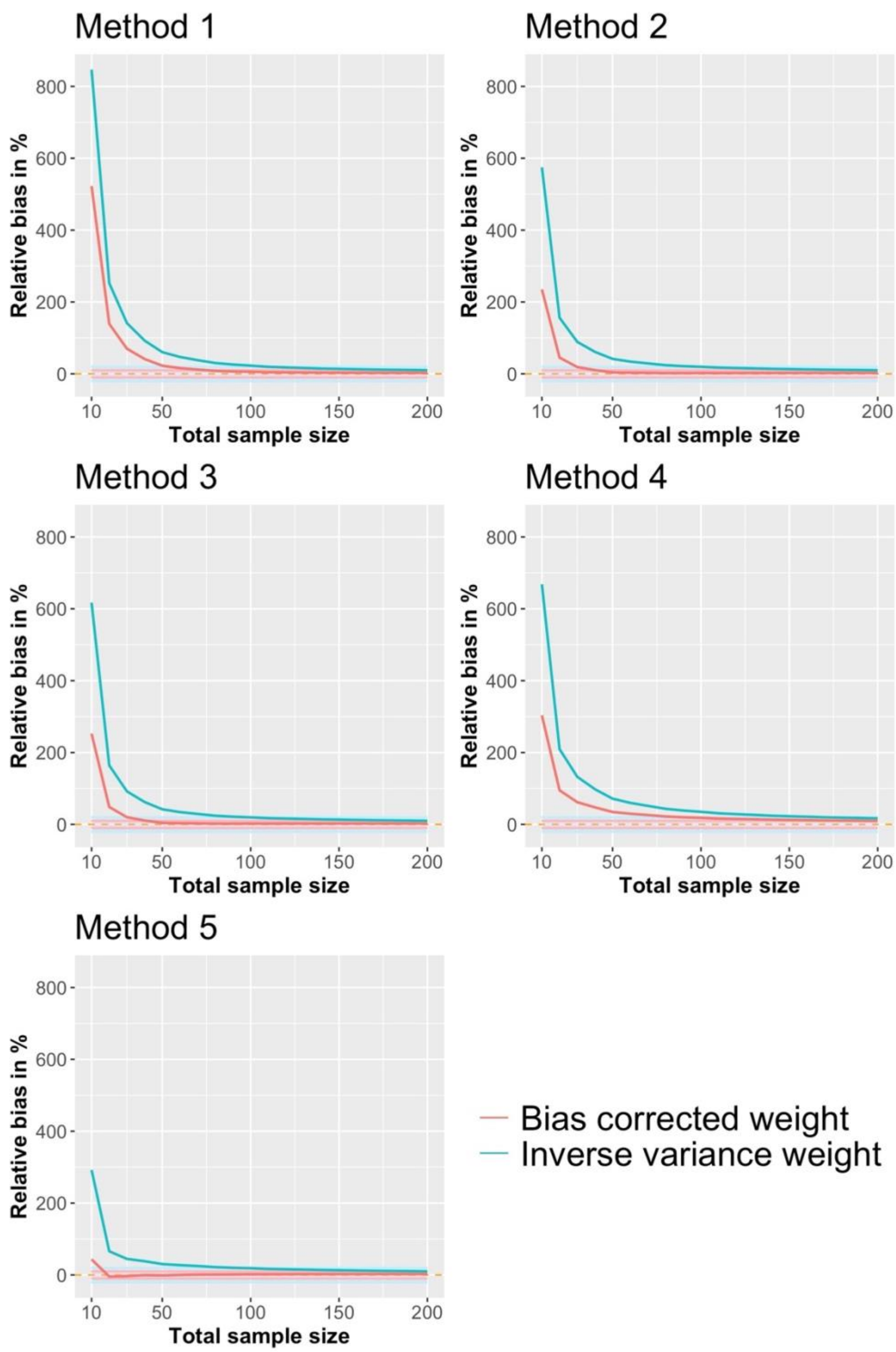

Figure 3.3.6: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $2n_1 \approx n_2$, with equal event rates $\pi_1 = \pi_2 = 0.1$

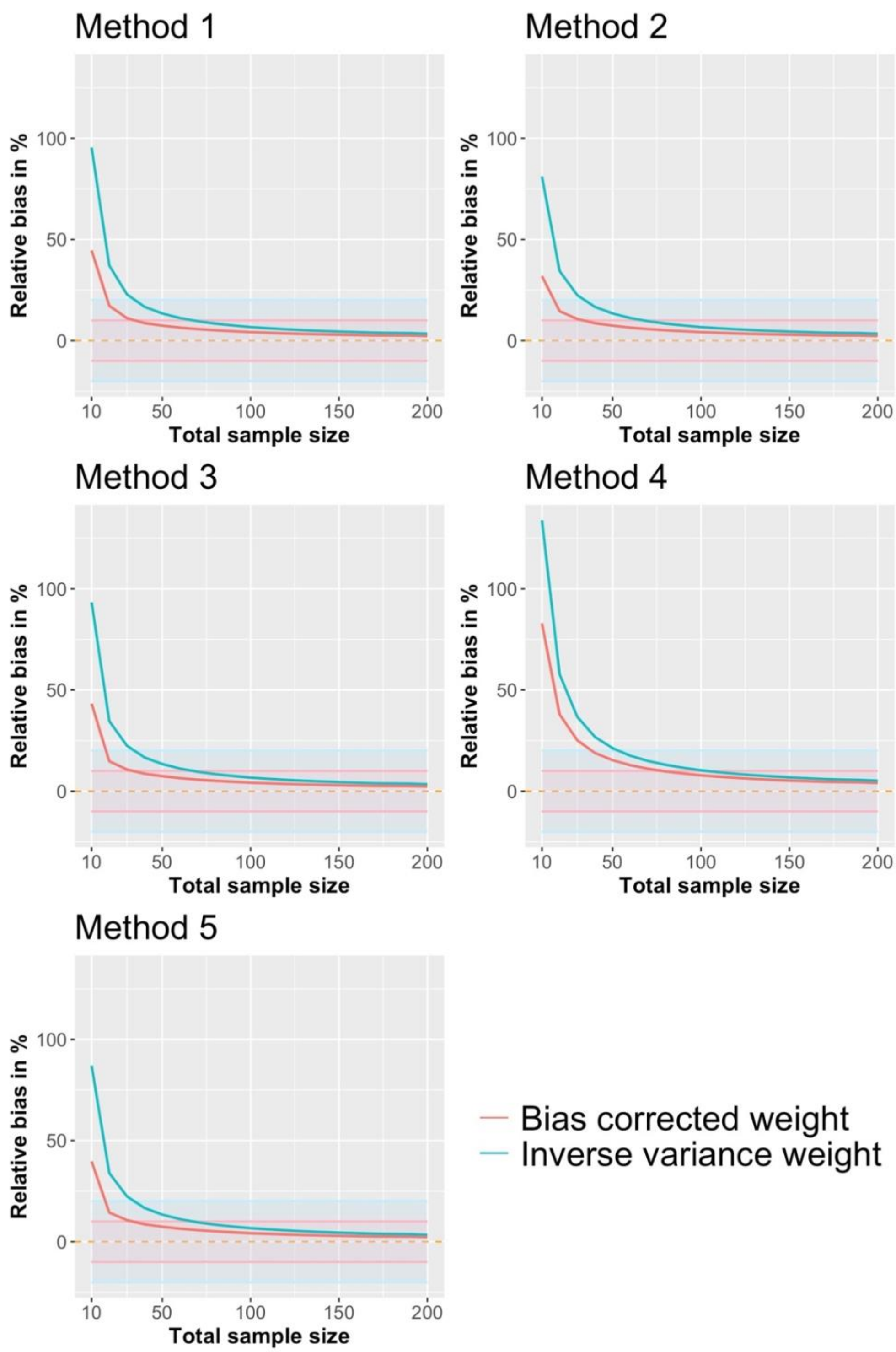

Figure 3.3.7: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.5, \pi_2 = 0.25$

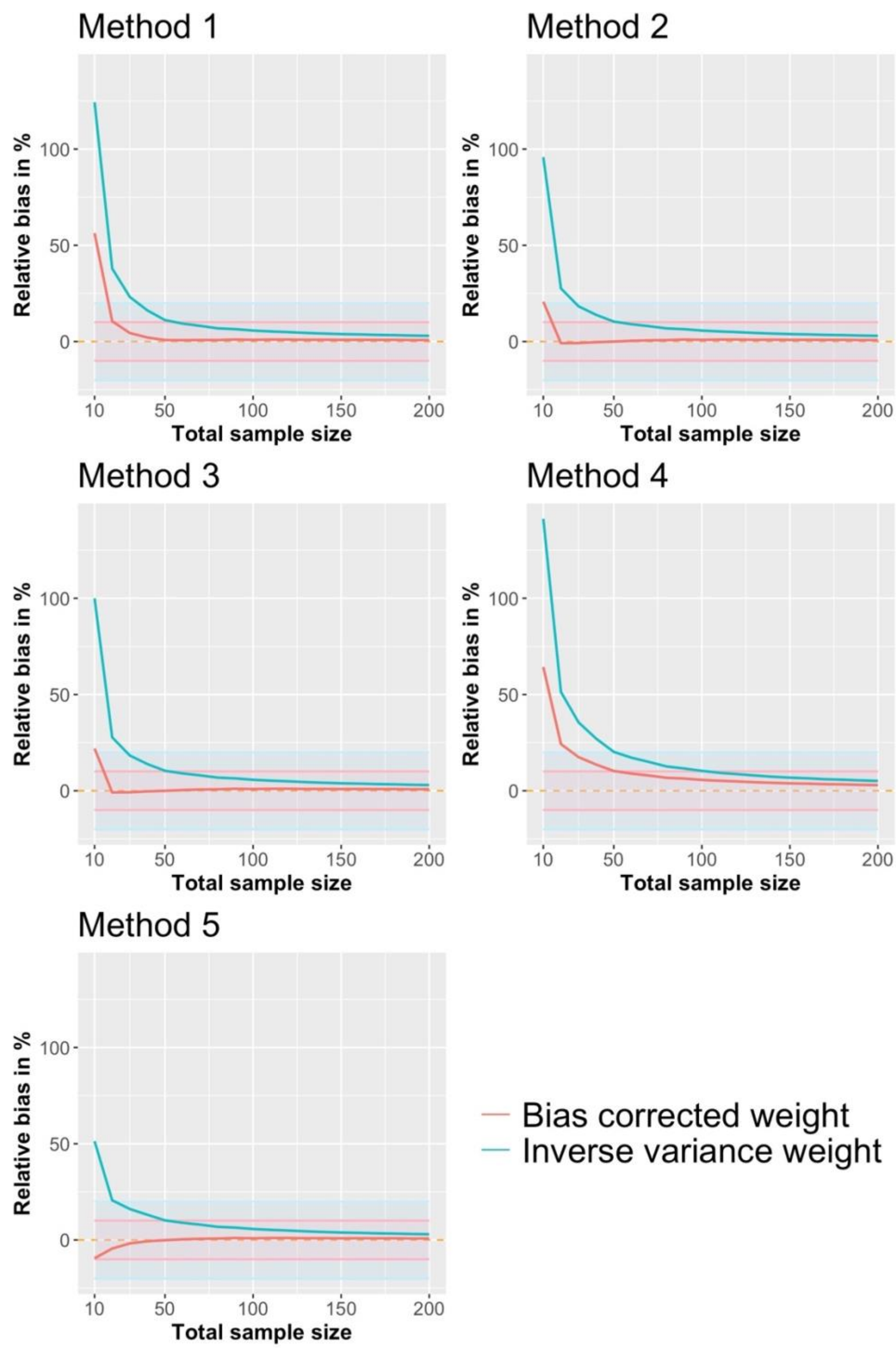

Figure 3.3.8: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.25, \pi_2 = 0.5$

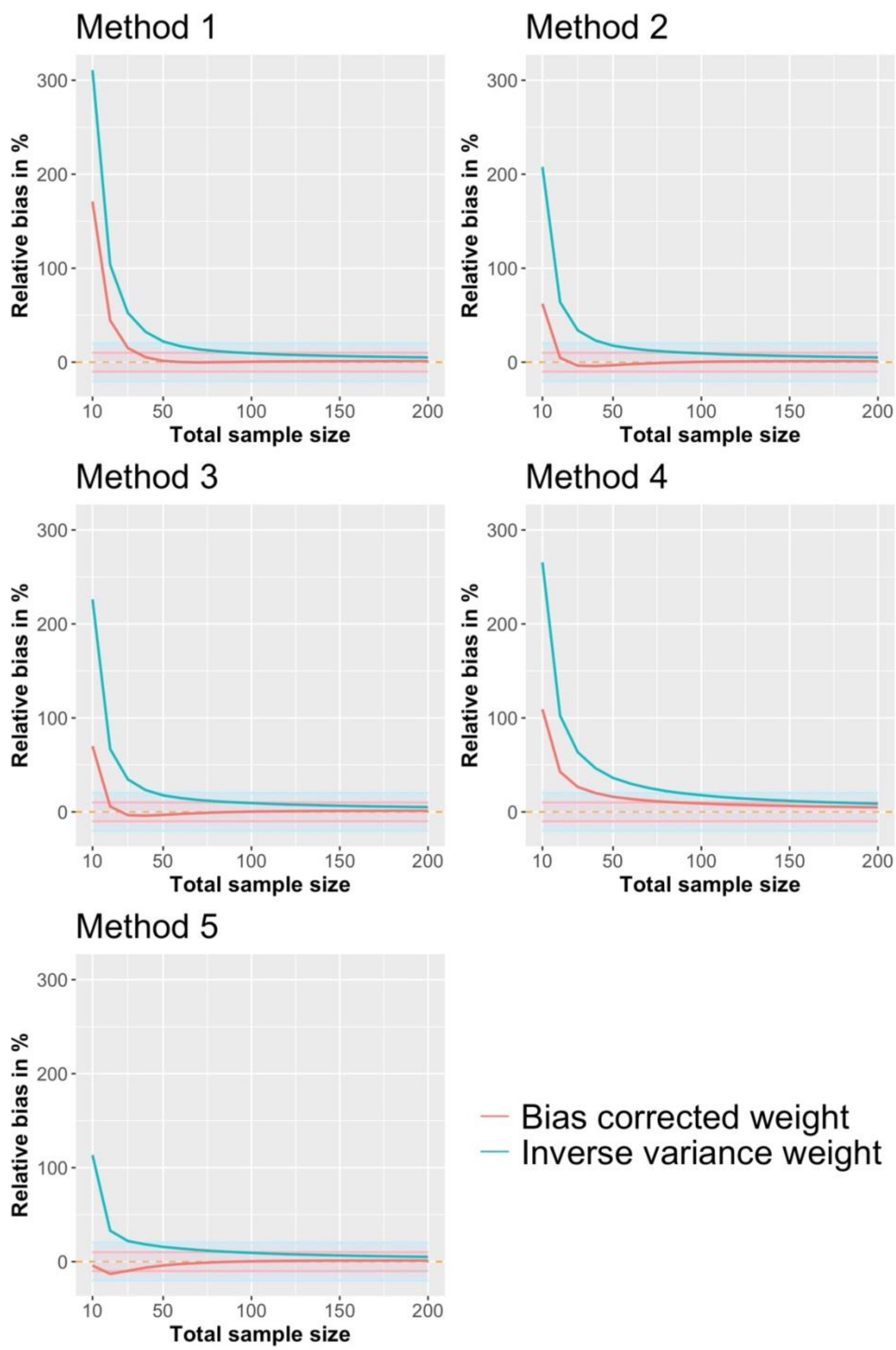

Figure 3.3.9: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.2, \pi_2 = 0.1$

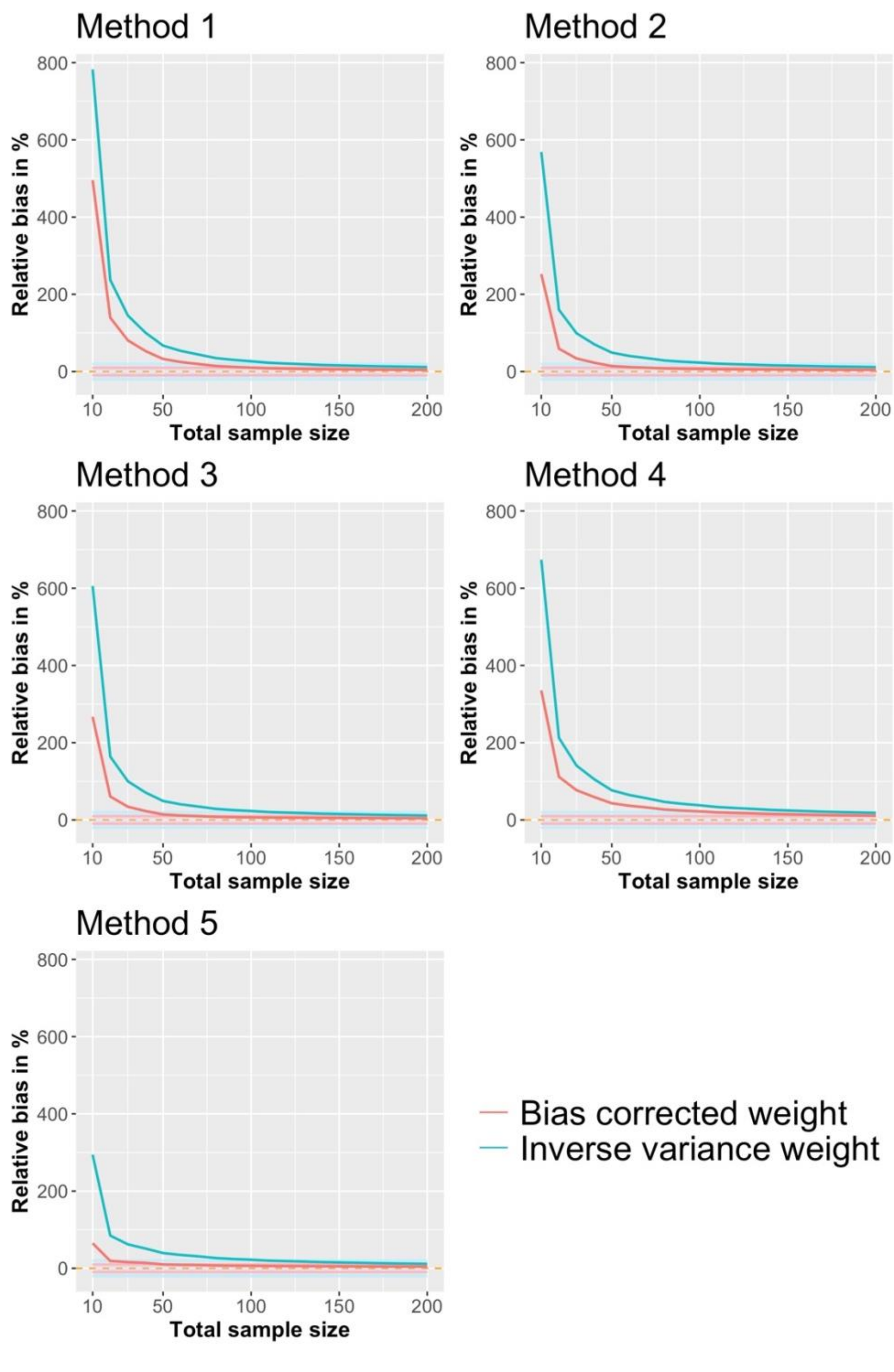

Figure 3.3.10: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.1, \pi_2 = 0.2$

4. Simulation Studies for Meta-Analyses

Simulation studies for meta-analyses with two studies were conducted to investigate the impact of bias correction and zero modifications to the summary effects and the variances of summary effects. The simulation procedure is as the following:

1. Set sample sizes n_{11}, n_{12}, n_{21}, n_{22}, and event rates π_{11}, π_{12}, π_{21} and π_{22}. In all cases, the true effect sizes are set to be 0 for simplicity. Since different effect measures do not vary in the same scale when sample sizes and event rates change, it is much more complicated to set different effect sizes and to clearly demonstrate the combinations of sample sizes and event rates.
2. Generate number of events in treatment and control group for each study from Binomial distributions. For study 1, the number of events in treatment group is $X_1 \sim Bin(n_{11}, \pi_{11})$ and number of events in control group $X_2 \sim Bin(n_{12}, \pi_{12})$. Similarly, for study 2, the number of events in treatment group is $Y_1 \sim Bin(n_{21}, \pi_{21})$ and number of events in control group $Y_2 \sim Bin(n_{22}, \pi_{22})$.
3. Apply the zero modification methods to the generated data.
4. Calculate the summary effects and variances of summary effects using the inverse variance method and bias corrected method for each effect measure.
5. Calculate the difference (D) between the summary effect sTE_{BC} using the bias corrected weight and the summary effect sTE_{IVW} using the inverse variance weight, $D = sTE_{BC} - sTE_{IVW}$.
6. Calculate the ratio (VR) of the variance of summary effect using bias corrected weight $Var(sTE_{BC})$ and the variance of summary effect using inverse variance weight $Var(sTE_{IVW})$, $VR = Var(sTE_{BC})/Var(sTE_{IVW})$.
7. Repeat steps 2 - 6 for $R = 1000$ times.
8. Calculate the average of sTE_{BC}, sTE_{IVW}, $Var(sTE_{BC})$, $Var(sTE_{IVW})$, D, and VR over the 1000 replications.

4.1. Risk Difference

Tables 4.1.1 – 4.1.8 shows the simulation results for risk difference with various sample sizes and equal event rates 0.5 or 0.1. The least biased methods within one setting are marked red. Results for meta-analyses with other event rates are in Appendix B. In general, the estimated summary effects and variances given by inverse variance weighting method and bias corrected weighting method do not differ enormously. The average variance ratio VR is only slightly greater than 1 for all the cases. When the two studies have different total sample sizes, the variances of summary effects estimated by the bias corrected weights tend to be slightly less biased than the standard estimates.

In practice, since estimations for risk differences are only affected by double zeros, zero modification methods 6.1 and 6.2 are more common choices to deal with discontinuity. Simulation results show that methods 6.1 and 6.2 do not necessarily produce less biased summary effect estimates than the other methods; in particular the estimated variances can be more biased than the other methods, when event rates are moderate to large. But when the event rates are small, variances of summary effects estimated by methods 6.1 and 6.2 tend to be less biased than the other methods. Therefore, zero modification methods 6.1 and 6.2 are recommended when the event rates are small or the sample sizes are large. For cases with large event rates and small sample sizes, method 2 gives less biased estimates.

Table 4.1.1: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	3	3	0.5	0.5	0.5	0.5	0.0090	0.0634	0.0091	0.0634	0.0001	1.0001	-23.92%	-23.92%
3	3	3	3	3	0.5	0.5	0.5	0.5	0.0094	0.0574	0.0095	0.0574	0.0002	1.0014	-31.12%	-31.12%
4	3	3	3	3	0.5	0.5	0.5	0.5	0.0085	0.0500	0.0085	0.0500	0.0000	1.0000	-40.00%	-40.00%
5	3	3	3	3	0.5	0.5	0.5	0.5	0.0102	0.0567	0.0104	0.0568	0.0001	1.0008	-31.96%	-31.84%
6.1	3	3	3	3	0.5	0.5	0.5	0.5	-0.0085	0.0545	-0.0085	0.0545	0.0000	1.0001	-34.60%	-34.60%
6.2	3	3	3	3	0.5	0.5	0.5	0.5	-0.0086	0.0537	-0.0086	0.0537	0.0000	1.0003	-35.56%	-35.56%
2	5	5	5	5	0.5	0.5	0.5	0.5	-0.0018	0.0404	-0.0018	0.0404	0.0000	1.0000	-19.20%	-19.20%
3	5	5	5	5	0.5	0.5	0.5	0.5	-0.0015	0.0397	-0.0014	0.0397	0.0000	1.0001	-20.60%	-20.60%
4	5	5	5	5	0.5	0.5	0.5	0.5	-0.0008	0.0355	-0.0008	0.0355	0.0000	1.0000	-29.00%	-29.00%
5	5	5	5	5	0.5	0.5	0.5	0.5	-0.0009	0.0394	-0.0009	0.0394	0.0000	1.0000	-21.20%	-21.20%
6.1	5	5	5	5	0.5	0.5	0.5	0.5	0.0064	0.0391	0.0064	0.0391	0.0000	1.0000	-21.80%	-21.80%
6.2	5	5	5	5	0.5	0.5	0.5	0.5	0.0065	0.0391	0.0065	0.0391	0.0000	1.0000	-21.80%	-21.80%
2	10	10	10	10	0.5	0.5	0.5	0.5	0.0021	0.0224	0.0021	0.0224	0.0000	1.0000	-10.40%	-10.40%
3	10	10	10	10	0.5	0.5	0.5	0.5	0.0022	0.0224	0.0022	0.0224	0.0000	1.0000	-10.40%	-10.40%
4	10	10	10	10	0.5	0.5	0.5	0.5	0.0020	0.0208	0.0020	0.0208	0.0000	1.0000	-16.80%	-16.80%
5	10	10	10	10	0.5	0.5	0.5	0.5	0.0022	0.0223	0.0022	0.0223	0.0000	1.0000	-10.80%	-10.80%
6.1	10	10	10	10	0.5	0.5	0.5	0.5	-0.0011	0.0224	-0.0011	0.0224	0.0000	1.0000	-10.40%	-10.40%
6.2	10	10	10	10	0.5	0.5	0.5	0.5	-0.0011	0.0224	-0.0011	0.0224	0.0000	1.0000	-10.40%	-10.40%
2	20	20	20	20	0.5	0.5	0.5	0.5	-0.0017	0.0119	-0.0017	0.0119	0.0000	1.0000	-4.80%	-4.80%
3	20	20	20	20	0.5	0.5	0.5	0.5	-0.0017	0.0119	-0.0017	0.0119	0.0000	1.0000	-4.80%	-4.80%
4	20	20	20	20	0.5	0.5	0.5	0.5	-0.0016	0.0113	-0.0016	0.0113	0.0000	1.0000	-9.60%	-9.60%
5	20	20	20	20	0.5	0.5	0.5	0.5	-0.0017	0.0119	-0.0017	0.0119	0.0000	1.0000	-4.80%	-4.80%
6.1	20	20	20	20	0.5	0.5	0.5	0.5	-0.0039	0.0119	-0.0039	0.0119	0.0000	1.0000	-4.80%	-4.80%
6.2	20	20	20	20	0.5	0.5	0.5	0.5	-0.0039	0.0119	-0.0039	0.0119	0.0000	1.0000	-4.80%	-4.80%

Table 4.1.2: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	**Mean of** sTE_{IVW}	**Mean of** $Var(sTE_{IVW})$	**Mean of** sTE_{BC}	**Mean of** $Var(sTE_{BC})$	**Mean of** D	**Mean of** VR	**Relative bias of** $Var(sTE_{IVW})$	**Relative bias of** $Var(sTE_{BC})$
2	3	6	3	6	0.5	0.5	0.5	0.5	-0.0026	0.0483	-0.0026	0.0483	0.0000	1.0006	-22.72%	-22.72%
3	3	6	3	6	0.5	0.5	0.5	0.5	-0.0022	0.0459	-0.0022	0.0459	0.0000	1.0012	-26.56%	-26.56%
4	3	6	3	6	0.5	0.5	0.5	0.5	-0.0016	0.0400	-0.0015	0.0400	0.0000	1.0001	-36.00%	-36.00%
5	3	6	3	6	0.5	0.5	0.5	0.5	-0.0016	0.0433	-0.0015	0.0433	0.0001	1.0010	-30.72%	-30.72%
6.1	3	6	3	6	0.5	0.5	0.5	0.5	0.0027	0.0414	0.0032	0.0415	0.0005	1.0015	-33.76%	-33.60%
6.2	3	6	3	6	0.5	0.5	0.5	0.5	0.0025	0.0414	0.0030	0.0414	0.0005	1.0015	-33.76%	-33.76%
2	5	10	5	10	0.5	0.5	0.5	0.5	-0.0002	0.0314	-0.0001	0.0314	0.0001	1.0001	-16.27%	-16.27%
3	5	10	5	10	0.5	0.5	0.5	0.5	0.0000	0.0312	0.0001	0.0312	0.0001	1.0001	-16.80%	-16.80%
4	5	10	5	10	0.5	0.5	0.5	0.5	0.0006	0.0281	0.0007	0.0281	0.0000	1.0000	-25.07%	-25.07%
5	5	10	5	10	0.5	0.5	0.5	0.5	0.0012	0.0307	0.0013	0.0307	0.0001	1.0001	-18.13%	-18.13%
6.1	5	10	5	10	0.5	0.5	0.5	0.5	0.0155	0.0300	0.0156	0.0300	0.0001	1.0002	-20.00%	-20.00%
6.2	5	10	5	10	0.5	0.5	0.5	0.5	0.0155	0.0300	0.0156	0.0300	0.0001	1.0002	-20.00%	-20.00%
2	10	20	10	20	0.5	0.5	0.5	0.5	-0.0095	0.0172	-0.0095	0.0172	0.0000	1.0000	-8.27%	-8.27%
3	10	20	10	20	0.5	0.5	0.5	0.5	-0.0095	0.0172	-0.0095	0.0172	0.0000	1.0000	-8.27%	-8.27%
4	10	20	10	20	0.5	0.5	0.5	0.5	-0.0088	0.0161	-0.0088	0.0161	0.0000	1.0000	-14.13%	-14.13%
5	10	20	10	20	0.5	0.5	0.5	0.5	-0.0096	0.0172	-0.0096	0.0172	0.0000	1.0000	-8.27%	-8.27%
6.1	10	20	10	20	0.5	0.5	0.5	0.5	0.0002	0.0171	0.0002	0.0171	0.0000	1.0000	-8.80%	-8.80%
6.2	10	20	10	20	0.5	0.5	0.5	0.5	0.0002	0.0171	0.0002	0.0171	0.0000	1.0000	-8.80%	-8.80%

Table 4.1.3: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	5	5	0.5	0.5	0.5	0.5	0.0075	0.0491	0.0072	0.0494	-0.0003	1.0065	-21.44%	-20.96%
3	3	3	5	5	0.5	0.5	0.5	0.5	0.0074	0.0465	0.0070	0.0467	-0.0004	1.0045	-25.60%	-25.28%
4	3	3	5	5	0.5	0.5	0.5	0.5	0.0078	0.0413	0.0076	0.0414	-0.0002	1.0026	-33.92%	-33.76%
5	3	3	5	5	0.5	0.5	0.5	0.5	0.0089	0.0460	0.0085	0.0463	-0.0004	1.0049	-26.40%	-25.92%
6.1	3	3	5	5	0.5	0.5	0.5	0.5	0.0050	0.0456	0.0050	0.0460	0.0000	1.0071	-27.04%	-26.40%
6.2	3	3	5	5	0.5	0.5	0.5	0.5	0.0043	0.0452	0.0042	0.0456	-0.0001	1.0069	-27.68%	-27.04%
2	3	3	6	6	0.5	0.5	0.5	0.5	-0.0077	0.0448	-0.0077	0.0453	0.0000	1.0094	-19.36%	-18.46%
3	3	3	6	6	0.5	0.5	0.5	0.5	-0.0065	0.0428	-0.0065	0.0431	0.0000	1.0067	-22.96%	-22.42%
4	3	3	6	6	0.5	0.5	0.5	0.5	-0.0050	0.0383	-0.0052	0.0385	-0.0001	1.0040	-31.06%	-30.70%
5	3	3	6	6	0.5	0.5	0.5	0.5	-0.0059	0.0425	-0.0059	0.0429	0.0000	1.0074	-23.50%	-22.78%
6.1	3	3	6	6	0.5	0.5	0.5	0.5	-0.0105	0.0422	-0.0094	0.0426	0.0011	1.0104	-24.04%	-23.32%
6.2	3	3	6	6	0.5	0.5	0.5	0.5	-0.0112	0.0419	-0.0102	0.0423	0.0010	1.0102	-24.58%	-23.86%
2	3	3	9	9	0.5	0.5	0.5	0.5	0.0018	0.0354	0.0017	0.0359	-0.0001	1.0133	-15.04%	-13.84%
3	3	3	9	9	0.5	0.5	0.5	0.5	0.0023	0.0343	0.0021	0.0346	-0.0002	1.0103	-17.68%	-16.96%
4	3	3	9	9	0.5	0.5	0.5	0.5	0.0025	0.0312	0.0023	0.0314	-0.0002	1.0066	-25.12%	-24.64%
5	3	3	9	9	0.5	0.5	0.5	0.5	0.0025	0.0341	0.0023	0.0345	-0.0002	1.0114	-18.16%	-17.20%
6.1	3	3	9	9	0.5	0.5	0.5	0.5	0.0033	0.0337	0.0029	0.0343	-0.0004	1.0151	-19.12%	-17.68%
6.2	3	3	9	9	0.5	0.5	0.5	0.5	0.0032	0.0336	0.0028	0.0341	-0.0004	1.0149	-19.36%	-18.16%
2	3	3	15	15	0.5	0.5	0.5	0.5	-0.0045	0.0249	-0.0040	0.0253	0.0005	1.0135	-10.36%	-8.92%
3	3	3	15	15	0.5	0.5	0.5	0.5	-0.0044	0.0243	-0.0040	0.0246	0.0004	1.0111	-12.52%	-11.44%
4	3	3	15	15	0.5	0.5	0.5	0.5	-0.0039	0.0227	-0.0037	0.0229	0.0003	1.0077	-18.28%	-17.56%
5	3	3	15	15	0.5	0.5	0.5	0.5	-0.0043	0.0243	-0.0038	0.0246	0.0005	1.0122	-12.52%	-11.44%
6.1	3	3	15	15	0.5	0.5	0.5	0.5	-0.0052	0.0241	-0.0045	0.0244	0.0007	1.0158	-13.24%	-12.16%
6.2	3	3	15	15	0.5	0.5	0.5	0.5	-0.0050	0.0240	-0.0043	0.0244	0.0007	1.0156	-13.60%	-12.16%

Table 4.1.4: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	**Mean of** sTE_{IVW}	**Mean of** $Var(sTE_{IVW})$	**Mean of** sTE_{BC}	**Mean of** $Var(sTE_{BC})$	**Mean of** D	**Mean of** VR	**Relative bias of** $Var(sTE_{IVW})$	**Relative bias of** $Var(sTE_{BC})$
2	5	5	10	10	0.5	0.5	0.5	0.5	-0.0012	0.0289	-0.0009	0.0290	0.0002	1.0030	-13.30%	-13.00%
3	5	5	10	10	0.5	0.5	0.5	0.5	-0.0016	0.0287	-0.0014	0.0288	0.0002	1.0028	-13.90%	-13.60%
4	5	5	10	10	0.5	0.5	0.5	0.5	-0.0015	0.0263	-0.0014	0.0263	0.0002	1.0017	-21.10%	-21.10%
5	5	5	10	10	0.5	0.5	0.5	0.5	-0.0020	0.0286	-0.0018	0.0287	0.0003	1.0029	-14.20%	-13.90%
6.1	5	5	10	10	0.5	0.5	0.5	0.5	-0.0034	0.0284	-0.0034	0.0285	0.0000	1.0031	-14.80%	-14.50%
6.2	5	5	10	10	0.5	0.5	0.5	0.5	-0.0034	0.0284	-0.0033	0.0285	0.0000	1.0031	-14.80%	-14.50%
2	5	5	15	15	0.5	0.5	0.5	0.5	-0.0096	0.0224	-0.0099	0.0225	-0.0003	1.0044	-10.40%	-10.00%
3	5	5	15	15	0.5	0.5	0.5	0.5	-0.0096	0.0223	-0.0098	0.0224	-0.0003	1.0042	-10.80%	-10.40%
4	5	5	15	15	0.5	0.5	0.5	0.5	-0.0087	0.0208	-0.0089	0.0209	-0.0002	1.0027	-16.80%	-16.40%
5	5	5	15	15	0.5	0.5	0.5	0.5	-0.0094	0.0223	-0.0097	0.0224	-0.0003	1.0043	-10.80%	-10.40%
6.1	5	5	15	15	0.5	0.5	0.5	0.5	-0.0096	0.0222	-0.0099	0.0223	-0.0003	1.0045	-11.20%	-10.80%
6.2	5	5	15	15	0.5	0.5	0.5	0.5	-0.0095	0.0222	-0.0098	0.0223	-0.0003	1.0044	-11.20%	-10.80%
2	5	5	20	20	0.5	0.5	0.5	0.5	0.0055	0.0183	0.0051	0.0183	-0.0004	1.0047	-8.50%	-8.50%
3	5	5	20	20	0.5	0.5	0.5	0.5	0.0053	0.0182	0.0049	0.0183	-0.0004	1.0044	-9.00%	-8.50%
4	5	5	20	20	0.5	0.5	0.5	0.5	0.0049	0.0172	0.0046	0.0172	-0.0003	1.0030	-14.00%	-14.00%
5	5	5	20	20	0.5	0.5	0.5	0.5	0.0058	0.0181	0.0054	0.0182	-0.0004	1.0046	-9.50%	-9.00%
6.1	5	5	20	20	0.5	0.5	0.5	0.5	0.0061	0.0181	0.0056	0.0182	-0.0005	1.0048	-9.50%	-9.00%
6.2	5	5	20	20	0.5	0.5	0.5	0.5	0.0061	0.0181	0.0056	0.0182	-0.0005	1.0048	-9.50%	-9.00%
2	10	10	20	20	0.5	0.5	0.5	0.5	-0.0040	0.0155	-0.0040	0.0155	0.0000	1.0006	-7.00%	-7.00%
3	10	10	20	20	0.5	0.5	0.5	0.5	-0.0040	0.0155	-0.0041	0.0155	0.0000	1.0006	-7.00%	-7.00%
4	10	10	20	20	0.5	0.5	0.5	0.5	-0.0037	0.0147	-0.0037	0.0147	0.0000	1.0005	-11.80%	-11.80%
5	10	10	20	20	0.5	0.5	0.5	0.5	-0.0040	0.0155	-0.0041	0.0155	0.0000	1.0006	-7.00%	-7.00%
6.1	10	10	20	20	0.5	0.5	0.5	0.5	-0.0021	0.0155	-0.0019	0.0155	0.0002	1.0006	-7.00%	-7.00%
6.2	10	10	20	20	0.5	0.5	0.5	0.5	-0.0021	0.0155	-0.0019	0.0155	0.0002	1.0006	-7.00%	-7.00%

Table 4.1.5: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IV}$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	3	3	0.1	0.1	0.1	0.1	0.0039	0.0441	0.0038	0.0441	0.0000	1.0003	47.00%	47.00%
3	3	3	3	3	0.1	0.1	0.1	0.1	0.0042	0.0352	0.0042	0.0353	-0.0001	1.0004	17.33%	17.67%
4	3	3	3	3	0.1	0.1	0.1	0.1	0.0042	0.0346	0.0042	0.0346	0.0000	1.0000	15.33%	15.33%
5	3	3	3	3	0.1	0.1	0.1	0.1	0.0045	0.0318	0.0045	0.0318	-0.0001	1.0002	6.00%	6.00%
6.1	3	3	3	3	0.1	0.1	0.1	0.1	0.0016	0.0378	0.0014	0.0379	-0.0002	1.0006	26.00%	26.33%
6.2	3	3	3	3	0.1	0.1	0.1	0.1	0.0009	0.0331	0.0006	0.0332	-0.0003	1.0016	10.33%	10.67%
2	5	5	5	5	0.1	0.1	0.1	0.1	0.0002	0.0222	0.0002	0.0222	0.0000	1.0000	23.33%	23.33%
3	5	5	5	5	0.1	0.1	0.1	0.1	0.0003	0.0201	0.0003	0.0201	0.0000	1.0001	11.67%	11.67%
4	5	5	5	5	0.1	0.1	0.1	0.1	0.0002	0.0200	0.0002	0.0200	0.0000	1.0000	11.11%	11.11%
5	5	5	5	5	0.1	0.1	0.1	0.1	0.0013	0.0156	0.0013	0.0156	0.0000	1.0000	-13.33%	-13.33%
6.1	5	5	5	5	0.1	0.1	0.1	0.1	0.0019	0.0184	0.0019	0.0184	0.0000	1.0001	2.22%	2.22%
6.2	5	5	5	5	0.1	0.1	0.1	0.1	0.0018	0.0173	0.0018	0.0173	0.0000	1.0002	-3.89%	-3.89%
2	10	10	10	10	0.1	0.1	0.1	0.1	0.0016	0.0089	0.0016	0.0089	0.0000	1.0000	-1.11%	-1.11%
3	10	10	10	10	0.1	0.1	0.1	0.1	0.0022	0.0090	0.0022	0.0090	0.0000	1.0000	0.00%	0.00%
4	10	10	10	10	0.1	0.1	0.1	0.1	0.0022	0.0094	0.0022	0.0094	0.0000	1.0000	4.44%	4.44%
5	10	10	10	10	0.1	0.1	0.1	0.1	0.0024	0.0072	0.0024	0.0072	0.0000	1.0000	-20.00%	-20.00%
6.1	10	10	10	10	0.1	0.1	0.1	0.1	-0.0014	0.0076	-0.0014	0.0076	0.0000	1.0000	-15.56%	-15.56%
6.2	10	10	10	10	0.1	0.1	0.1	0.1	-0.0014	0.0075	-0.0014	0.0075	0.0000	1.0000	-16.67%	-16.67%
2	20	20	20	20	0.1	0.1	0.1	0.1	0.0040	0.0041	0.0040	0.0041	0.0000	1.0000	-8.89%	-8.89%
3	20	20	20	20	0.1	0.1	0.1	0.1	0.0042	0.0042	0.0042	0.0042	0.0000	1.0000	-6.67%	-6.67%
4	20	20	20	20	0.1	0.1	0.1	0.1	0.0041	0.0046	0.0041	0.0046	0.0000	1.0000	2.22%	2.22%
5	20	20	20	20	0.1	0.1	0.1	0.1	0.0042	0.0039	0.0042	0.0039	0.0000	1.0000	-13.33%	-13.33%
6.1	20	20	20	20	0.1	0.1	0.1	0.1	-0.0014	0.0039	-0.0014	0.0039	0.0000	1.0000	-13.33%	-13.33%
6.2	20	20	20	20	0.1	0.1	0.1	0.1	-0.0014	0.0039	-0.0014	0.0039	0.0000	1.0000	-13.33%	-13.33%

Table 4.1.6: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	**Mean of** sTE_{IVW}	**Mean of** $Var(sTE_{IVW})$	**Mean of** sTE_{BC}	**Mean of** $Var(sTE_{BC})$	**Mean of** D	**Mean of** VR	**Relative bias of** $Var(sTE_{IVW})$	**Relative bias of** $Var(sTE_{BC})$
2	3	6	3	6	0.1	0.1	0.1	0.1	0.0508	0.0304	0.0487	0.0304	-0.0021	1.0006	35.11%	35.11%
3	3	6	3	6	0.1	0.1	0.1	0.1	0.0291	0.0257	0.0273	0.0258	-0.0018	1.0006	14.22%	14.67%
4	3	6	3	6	0.1	0.1	0.1	0.1	0.0295	0.0253	0.0282	0.0253	-0.0012	1.0001	12.44%	12.44%
5	3	6	3	6	0.1	0.1	0.1	0.1	-0.0254	0.0192	-0.0286	0.0192	-0.0032	1.0008	-14.67%	-14.67%
6.1	3	6	3	6	0.1	0.1	0.1	0.1	-0.0176	0.0221	-0.0237	0.0221	-0.0061	1.0023	-1.78%	-1.78%
6.2	3	6	3	6	0.1	0.1	0.1	0.1	-0.0203	0.0202	-0.0259	0.0203	-0.0057	1.0021	-10.22%	-9.78%
2	5	10	5	10	0.1	0.1	0.1	0.1	0.0270	0.0155	0.0260	0.0155	-0.0010	1.0002	14.81%	14.81%
3	5	10	5	10	0.1	0.1	0.1	0.1	0.0138	0.0147	0.0127	0.0147	-0.0011	1.0002	8.89%	8.89%
4	5	10	5	10	0.1	0.1	0.1	0.1	0.0166	0.0146	0.0157	0.0146	-0.0008	1.0001	8.15%	8.15%
5	5	10	5	10	0.1	0.1	0.1	0.1	-0.0244	0.0102	-0.0262	0.0102	-0.0018	1.0004	-24.44%	-24.44%
6.1	5	10	5	10	0.1	0.1	0.1	0.1	-0.0194	0.0112	-0.0217	0.0112	-0.0023	1.0007	-17.04%	-17.04%
6.2	5	10	5	10	0.1	0.1	0.1	0.1	-0.0199	0.0109	-0.0221	0.0109	-0.0022	1.0007	-19.26%	-19.26%
2	10	20	10	20	0.1	0.1	0.1	0.1	0.0078	0.0065	0.0074	0.0065	-0.0004	1.0000	-3.70%	-3.70%
3	10	20	10	20	0.1	0.1	0.1	0.1	0.0029	0.0065	0.0024	0.0065	-0.0004	1.0000	-3.70%	-3.70%
4	10	20	10	20	0.1	0.1	0.1	0.1	0.0102	0.0069	0.0098	0.0069	-0.0003	1.0000	2.22%	2.22%
5	10	20	10	20	0.1	0.1	0.1	0.1	-0.0128	0.0053	-0.0134	0.0053	-0.0006	1.0001	-21.48%	-21.48%
6.1	10	20	10	20	0.1	0.1	0.1	0.1	-0.0153	0.0053	-0.0159	0.0053	-0.0007	1.0001	-21.48%	-21.48%
6.2	10	20	10	20	0.1	0.1	0.1	0.1	-0.0153	0.0053	-0.0160	0.0053	-0.0007	1.0001	-21.48%	-21.48%

Table 4.1.7: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	5	5	0.1	0.1	0.1	0.1	0.0018	0.0296	0.0015	0.0298	-0.0004	1.0044	31.56%	32.44%
3	3	3	5	5	0.1	0.1	0.1	0.1	0.0008	0.0257	0.0004	0.0258	-0.0004	1.0026	14.22%	14.67%
4	3	3	5	5	0.1	0.1	0.1	0.1	0.0007	0.0254	0.0004	0.0255	-0.0004	1.0024	12.89%	13.33%
5	3	3	5	5	0.1	0.1	0.1	0.1	0.0000	0.0213	-0.0004	0.0213	-0.0004	1.0027	-5.33%	-5.33%
6.1	3	3	5	5	0.1	0.1	0.1	0.1	0.0010	0.0247	0.0016	0.0248	0.0006	1.0049	9.78%	10.22%
6.2	3	3	5	5	0.1	0.1	0.1	0.1	0.0011	0.0226	0.0016	0.0227	0.0005	1.0041	0.44%	0.89%
2	3	3	6	6	0.1	0.1	0.1	0.1	0.0054	0.0251	0.0051	0.0252	-0.0003	1.0060	25.50%	26.00%
3	3	3	6	6	0.1	0.1	0.1	0.1	0.0062	0.0225	0.0060	0.0225	-0.0003	1.0037	12.50%	12.50%
4	3	3	6	6	0.1	0.1	0.1	0.1	0.0061	0.0223	0.0059	0.0224	-0.0002	1.0036	11.50%	12.00%
5	3	3	6	6	0.1	0.1	0.1	0.1	0.0063	0.0184	0.0060	0.0185	-0.0003	1.0040	-8.00%	-7.50%
6.1	3	3	6	6	0.1	0.1	0.1	0.1	-0.0029	0.0213	-0.0027	0.0215	0.0001	1.0067	6.50%	7.50%
6.2	3	3	6	6	0.1	0.1	0.1	0.1	-0.0028	0.0200	-0.0028	0.0201	0.0001	1.0056	0.00%	0.50%
2	3	3	9	9	0.1	0.1	0.1	0.1	0.0027	0.0170	0.0027	0.0171	0.0000	1.0077	13.33%	14.00%
3	3	3	9	9	0.1	0.1	0.1	0.1	0.0026	0.0161	0.0025	0.0162	-0.0001	1.0053	7.33%	8.00%
4	3	3	9	9	0.1	0.1	0.1	0.1	0.0023	0.0164	0.0022	0.0165	-0.0001	1.0054	9.33%	10.00%
5	3	3	9	9	0.1	0.1	0.1	0.1	0.0022	0.0136	0.0022	0.0137	-0.0001	1.0062	-9.33%	-8.67%
6.1	3	3	9	9	0.1	0.1	0.1	0.1	0.0024	0.0149	0.0023	0.0151	-0.0002	1.0083	-0.67%	0.67%
6.2	3	3	9	9	0.1	0.1	0.1	0.1	0.0024	0.0143	0.0022	0.0144	-0.0002	1.0072	-4.67%	-4.00%
2	3	3	15	15	0.1	0.1	0.1	0.1	-0.0031	0.0105	-0.0032	0.0106	-0.0001	1.0069	5.00%	6.00%
3	3	3	15	15	0.1	0.1	0.1	0.1	-0.0040	0.0103	-0.0041	0.0103	-0.0001	1.0054	3.00%	3.00%
4	3	3	15	15	0.1	0.1	0.1	0.1	-0.0040	0.0108	-0.0041	0.0109	-0.0001	1.0056	8.00%	9.00%
5	3	3	15	15	0.1	0.1	0.1	0.1	-0.0044	0.0094	-0.0045	0.0095	-0.0001	1.0067	-6.00%	-5.00%
6.1	3	3	15	15	0.1	0.1	0.1	0.1	-0.0046	0.0097	-0.0047	0.0098	-0.0001	1.0080	-3.00%	-2.00%
6.2	3	3	15	15	0.1	0.1	0.1	0.1	-0.0045	0.0095	-0.0046	0.0096	-0.0001	1.0074	-5.00%	-4.00%

Table 4.1.8: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	5	5	10	10	0.1	0.1	0.1	0.1	-0.0059	0.0130	-0.0060	0.0130	-0.0001	1.0022	8.33%	8.33%
3	5	5	10	10	0.1	0.1	0.1	0.1	-0.0062	0.0126	-0.0063	0.0126	-0.0001	1.0016	5.00%	5.00%
4	5	5	10	10	0.1	0.1	0.1	0.1	-0.0061	0.0129	-0.0061	0.0129	-0.0001	1.0015	7.50%	7.50%
5	5	5	10	10	0.1	0.1	0.1	0.1	-0.0059	0.0101	-0.0060	0.0101	-0.0001	1.0020	-15.83%	-15.83%
6.1	5	5	10	10	0.1	0.1	0.1	0.1	-0.0016	0.0110	-0.0019	0.0110	-0.0003	1.0023	-8.33%	-8.33%
6.2	5	5	10	10	0.1	0.1	0.1	0.1	-0.0016	0.0107	-0.0018	0.0107	-0.0003	1.0021	-10.83%	-10.83%
2	5	5	15	15	0.1	0.1	0.1	0.1	-0.0006	0.0092	-0.0008	0.0092	-0.0001	1.0030	2.22%	2.22%
3	5	5	15	15	0.1	0.1	0.1	0.1	-0.0003	0.0091	-0.0004	0.0091	-0.0001	1.0023	1.11%	1.11%
4	5	5	15	15	0.1	0.1	0.1	0.1	-0.0002	0.0095	-0.0004	0.0095	-0.0001	1.0023	5.56%	5.56%
5	5	5	15	15	0.1	0.1	0.1	0.1	0.0001	0.0077	0.0000	0.0077	-0.0002	1.0032	-14.44%	-14.44%
6.1	5	5	15	15	0.1	0.1	0.1	0.1	-0.0005	0.0084	-0.0007	0.0084	-0.0002	1.0033	-6.67%	-6.67%
6.2	5	5	15	15	0.1	0.1	0.1	0.1	-0.0004	0.0082	-0.0006	0.0082	-0.0002	1.0031	-8.89%	-8.89%
2	5	5	20	20	0.1	0.1	0.1	0.1	-0.0019	0.0071	-0.0020	0.0072	0.0000	1.0031	-1.39%	0.00%
3	5	5	20	20	0.1	0.1	0.1	0.1	-0.0023	0.0070	-0.0023	0.0071	0.0000	1.0025	-2.78%	-1.39%
4	5	5	20	20	0.1	0.1	0.1	0.1	-0.0024	0.0075	-0.0024	0.0075	0.0000	1.0026	4.17%	4.17%
5	5	5	20	20	0.1	0.1	0.1	0.1	-0.0029	0.0062	-0.0029	0.0063	0.0000	1.0037	-13.89%	-12.50%
6.1	5	5	20	20	0.1	0.1	0.1	0.1	-0.0027	0.0067	-0.0027	0.0068	0.0000	1.0035	-6.94%	-5.56%
6.2	5	5	20	20	0.1	0.1	0.1	0.1	-0.0028	0.0066	-0.0028	0.0067	0.0000	1.0033	-8.33%	-6.94%
2	10	10	20	20	0.1	0.1	0.1	0.1	-0.0011	0.0056	-0.0011	0.0056	0.0000	1.0006	-6.67%	-6.67%
3	10	10	20	20	0.1	0.1	0.1	0.1	-0.0016	0.0057	-0.0016	0.0057	0.0000	1.0005	-5.00%	-5.00%
4	10	10	20	20	0.1	0.1	0.1	0.1	-0.0018	0.0060	-0.0017	0.0060	0.0000	1.0004	0.00%	0.00%
5	10	10	20	20	0.1	0.1	0.1	0.1	-0.0017	0.0049	-0.0017	0.0049	0.0000	1.0005	-18.33%	-18.33%
6.1	10	10	20	20	0.1	0.1	0.1	0.1	-0.0003	0.0053	-0.0003	0.0053	0.0000	1.0006	-11.67%	-11.67%
6.2	10	10	20	20	0.1	0.1	0.1	0.1	-0.0003	0.0052	-0.0004	0.0052	0.0000	1.0006	-13.33%	-13.33%

4.2. Log Relative Risk

Table 4.2.1 – 4.2.4 shows the simulation results for log relative risk with various sample sizes and equal event rates 0.5 or 0.1. Summary effects estimated by the standard method and bias corrected method are both close to the true value for each parameter setting. Since the true variance of the log relative risk is unknown, the true variance of the summary effect is unavailable here, so we only compare the estimated variance of summary effect to the second order approximation. The "relative biases" are calculated by the second order approximation. Lower relative bias here does not necessarily imply that the estimate is closer to the true value. The better methods within one setting are marked red.

The variance ratio VR tends to be large when the sample sizes are small. In most of the cases, the variances estimated by inverse variance weights are negatively biased, whereas the variances estimated by the bias corrected weights are positively or ness negatively biased. The bias corrected weight with zero modification method 4 gives the least biased variance estimate relative to the second order approximation in majority of the settings, and is likely to slightly overestimate the variances, which is better than underestimating the variances. Underestimating the variance can cause the confidence interval to be narrower than the actual length at the confidence level, which underestimates the coverage probability, and can lead to an increase in false positive rate. For the other zero modification methods, the estimated variances using the bias corrected weights are more biased than the standard estimates when the sample sizes are too small. In addition, the summary effects given by zero modification method 4 are also the ones that are closest to the true value 0 among the four methods for most of the cases with both bias corrected weighting and inverse variance weighting. Therefore, bias corrected weighting with zero modification method 4 has the most advantages for meta-analyses using log relative risk as the risk measure.

Table 4.2.1: simulation results of estimated summary effects and variances of summary effects for log relative risk

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	3	3	0.5	0.5	0.5	0.5	0.0110	0.4195	0.0095	0.9994	-0.0016	2.1080	-31.35%	63.54%
3	3	3	3	3	0.5	0.5	0.5	0.5	0.0100	0.3952	0.0084	0.9273	-0.0015	2.0428	-35.33%	51.74%
4	3	3	3	3	0.5	0.5	0.5	0.5	0.0066	0.3198	0.0046	0.6697	-0.0019	1.8243	-47.67%	9.59%
5	3	3	3	3	0.5	0.5	0.5	0.5	0.0077	0.4408	0.0057	1.1745	-0.0019	2.1316	-27.87%	92.19%
2	5	5	5	5	0.5	0.5	0.5	0.5	-0.0120	0.2450	-0.0140	0.4445	-0.0020	1.6470	-18.33%	48.17%
3	5	5	5	5	0.5	0.5	0.5	0.5	-0.0116	0.2424	-0.0140	0.4389	-0.0024	1.6399	-19.20%	46.30%
4	5	5	5	5	0.5	0.5	0.5	0.5	-0.0097	0.1937	-0.0118	0.3100	-0.0021	1.5054	-35.43%	3.33%
5	5	5	5	5	0.5	0.5	0.5	0.5	-0.0141	0.2538	-0.0165	0.4900	-0.0024	1.6481	-15.40%	63.33%
2	10	10	10	10	0.5	0.5	0.5	0.5	0.0044	0.1150	0.0030	0.1533	-0.0014	1.2985	-8.00%	22.64%
3	10	10	10	10	0.5	0.5	0.5	0.5	0.0045	0.1150	0.0030	0.1532	-0.0015	1.2985	-8.00%	22.56%
4	10	10	10	10	0.5	0.5	0.5	0.5	0.0044	0.1018	0.0034	0.1310	-0.0010	1.2641	-18.56%	4.80%
5	10	10	10	10	0.5	0.5	0.5	0.5	0.0042	0.1151	0.0028	0.1534	-0.0014	1.2981	-7.92%	22.72%
2	20	20	20	20	0.5	0.5	0.5	0.5	-0.0043	0.0523	-0.0045	0.0597	-0.0003	1.1355	-7.02%	6.13%
3	20	20	20	20	0.5	0.5	0.5	0.5	-0.0043	0.0523	-0.0045	0.0597	-0.0003	1.1355	-7.02%	6.13%
4	20	20	20	20	0.5	0.5	0.5	0.5	-0.0040	0.0496	-0.0042	0.0562	-0.0002	1.1281	-11.82%	-0.09%
5	20	20	20	20	0.5	0.5	0.5	0.5	-0.0043	0.0523	-0.0045	0.0597	-0.0003	1.1355	-7.02%	6.13%
2	3	6	3	6	0.5	0.5	0.5	0.5	0.0328	0.3113	0.0600	0.6624	0.0272	1.8497	-26.51%	56.37%
3	3	6	3	6	0.5	0.5	0.5	0.5	0.0329	0.3033	0.0635	0.6440	0.0306	1.8282	-28.40%	52.03%
4	3	6	3	6	0.5	0.5	0.5	0.5	0.0319	0.2435	0.0574	0.4592	0.0255	1.6461	-42.52%	8.40%
5	3	6	3	6	0.5	0.5	0.5	0.5	0.0586	0.3684	0.0998	1.2124	0.0412	1.9435	-13.03%	186.21%
2	5	10	5	10	0.5	0.5	0.5	0.5	0.0431	0.1758	0.0635	0.2813	0.0205	1.4852	-17.27%	32.38%
3	5	10	5	10	0.5	0.5	0.5	0.5	0.0434	0.1751	0.0642	0.2801	0.0208	1.4831	-17.60%	31.81%
4	5	10	5	10	0.5	0.5	0.5	0.5	0.0350	0.1448	0.0487	0.2104	0.0137	1.3959	-31.86%	-0.99%
5	5	10	5	10	0.5	0.5	0.5	0.5	0.0549	0.1780	0.0745	0.2844	0.0196	1.4793	-16.24%	33.84%
2	10	20	10	20	0.5	0.5	0.5	0.5	0.0070	0.0809	0.0137	0.1012	0.0067	1.2277	-10.73%	11.67%
3	10	20	10	20	0.5	0.5	0.5	0.5	0.0071	0.0809	0.0137	0.1012	0.0067	1.2277	-10.73%	11.67%
4	10	20	10	20	0.5	0.5	0.5	0.5	0.0034	0.0738	0.0081	0.0902	0.0047	1.2060	-18.57%	-0.47%
5	10	20	10	20	0.5	0.5	0.5	0.5	0.0074	0.0809	0.0139	0.1012	0.0065	1.2276	-10.73%	11.67%

Table 4.2.2: estimated summary effects and variances of summary effects for log relative risk

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	5	5	0.5	0.5	0.5	0.5	0.0000	0.3213	-0.0033	0.6635	-0.0033	1.8293	-20.16%	64.87%
3	3	3	5	5	0.5	0.5	0.5	0.5	-0.0008	0.3101	-0.0041	0.6353	-0.0034	1.8020	-22.94%	57.86%
4	3	3	5	5	0.5	0.5	0.5	0.5	0.0021	0.2468	-0.0008	0.4418	-0.0029	1.6269	-38.67%	9.78%
5	3	3	5	5	0.5	0.5	0.5	0.5	-0.0014	0.3350	-0.0055	0.7507	-0.0041	1.8334	-16.76%	86.54%
2	3	3	6	6	0.5	0.5	0.5	0.5	-0.0190	0.2707	-0.0195	0.5132	-0.0005	1.6984	-20.53%	50.67%
3	3	3	6	6	0.5	0.5	0.5	0.5	-0.0183	0.2622	-0.0193	0.4918	-0.0010	1.6766	-23.02%	44.38%
4	3	3	6	6	0.5	0.5	0.5	0.5	-0.0143	0.2142	-0.0154	0.3605	-0.0011	1.5469	-37.11%	5.84%
5	3	3	6	6	0.5	0.5	0.5	0.5	-0.0185	0.2788	-0.0194	0.5722	-0.0009	1.6972	-18.15%	67.99%
2	3	3	9	9	0.5	0.5	0.5	0.5	0.0067	0.1956	0.0078	0.3107	0.0011	1.4817	-15.11%	34.84%
3	3	3	9	9	0.5	0.5	0.5	0.5	0.0077	0.1911	0.0085	0.3019	0.0008	1.4731	-17.06%	31.02%
4	3	3	9	9	0.5	0.5	0.5	0.5	0.0068	0.1624	0.0074	0.2371	0.0005	1.4024	-29.52%	2.90%
5	3	3	9	9	0.5	0.5	0.5	0.5	0.0086	0.1950	0.0094	0.3086	0.0007	1.4731	-15.37%	33.93%
2	3	3	15	15	0.5	0.5	0.5	0.5	-0.0082	0.1250	-0.0075	0.1649	0.0008	1.2886	-9.42%	19.50%
3	3	3	15	15	0.5	0.5	0.5	0.5	-0.0083	0.1230	-0.0077	0.1620	0.0006	1.2867	-10.86%	17.40%
4	3	3	15	15	0.5	0.5	0.5	0.5	-0.0077	0.1110	-0.0074	0.1425	0.0003	1.2632	-19.56%	3.27%
5	3	3	15	15	0.5	0.5	0.5	0.5	-0.0084	0.1242	-0.0078	0.1631	0.0006	1.2853	-10.00%	18.19%
2	5	5	10	10	0.5	0.5	0.5	0.5	-0.0062	0.1570	-0.0058	0.2331	0.0004	1.4004	-11.03%	32.09%
3	5	5	10	10	0.5	0.5	0.5	0.5	-0.0070	0.1565	-0.0067	0.2322	0.0003	1.3990	-11.32%	31.58%
4	5	5	10	10	0.5	0.5	0.5	0.5	-0.0067	0.1336	-0.0068	0.1868	-0.0001	1.3424	-24.29%	5.85%
5	5	5	10	10	0.5	0.5	0.5	0.5	-0.0093	0.1600	-0.0084	0.2626	0.0009	1.4041	-9.33%	48.81%
2	5	5	15	15	0.5	0.5	0.5	0.5	-0.0173	0.1132	-0.0177	0.1480	-0.0004	1.2769	-8.36%	19.81%
3	5	5	15	15	0.5	0.5	0.5	0.5	-0.0174	0.1128	-0.0178	0.1474	-0.0004	1.2762	-8.69%	19.32%
4	5	5	15	15	0.5	0.5	0.5	0.5	-0.0161	0.1010	-0.0164	0.1283	-0.0003	1.2501	-18.24%	3.86%
5	5	5	15	15	0.5	0.5	0.5	0.5	-0.0176	0.1135	-0.0179	0.1480	-0.0003	1.2749	-8.12%	19.81%
2	5	5	20	20	0.5	0.5	0.5	0.5	0.0072	0.0886	0.0060	0.1088	-0.0012	1.2122	-6.48%	14.84%
3	5	5	20	20	0.5	0.5	0.5	0.5	0.0074	0.0884	0.0062	0.1085	-0.0011	1.2118	-6.69%	14.53%
4	5	5	20	20	0.5	0.5	0.5	0.5	0.0070	0.0811	0.0061	0.0982	-0.0009	1.1978	-14.39%	3.66%
5	5	5	20	20	0.5	0.5	0.5	0.5	0.0070	0.0887	0.0060	0.1087	-0.0010	1.2108	-6.37%	14.74%
2	10	10	20	20	0.5	0.5	0.5	0.5	-0.0048	0.0722	-0.0046	0.0863	0.0002	1.1843	-6.94%	11.23%
3	10	10	20	20	0.5	0.5	0.5	0.5	-0.0048	0.0722	-0.0046	0.0863	0.0002	1.1843	-6.94%	11.23%
4	10	10	20	20	0.5	0.5	0.5	0.5	-0.0048	0.0670	-0.0046	0.0790	0.0002	1.1713	-13.64%	1.82%
5	10	10	20	20	0.5	0.5	0.5	0.5	-0.0049	0.0722	-0.0047	0.0863	0.0003	1.1842	-6.94%	11.23%

Table 4.2.3: estimated summary effects and variances of summary effects for log relative risk

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	3	3	0.1	0.1	0.1	0.1	0.0167	1.3647	0.0171	4.8914	0.0004	3.5017	-92.20%	-72.05%
3	3	3	3	3	0.1	0.1	0.1	0.1	0.0192	1.3345	0.0197	4.8268	0.0005	3.5300	-92.37%	-72.42%
4	3	3	3	3	0.1	0.1	0.1	0.1	0.0189	1.3003	0.0193	4.6946	0.0004	3.4576	-92.57%	-73.17%
5	3	3	3	3	0.1	0.1	0.1	0.1	0.0238	1.9875	0.0246	9.9204	0.0007	4.7593	-88.64%	-43.31%
2	5	5	5	5	0.1	0.1	0.1	0.1	-0.0112	1.2946	-0.0130	4.4409	-0.0019	3.3174	-81.56%	-36.74%
3	5	5	5	5	0.1	0.1	0.1	0.1	-0.0135	1.2365	-0.0156	4.2665	-0.0021	3.3401	-82.39%	-39.22%
4	5	5	5	5	0.1	0.1	0.1	0.1	-0.0145	1.1613	-0.0166	3.9679	-0.0022	3.1872	-83.46%	-43.48%
5	5	5	5	5	0.1	0.1	0.1	0.1	-0.0249	2.7199	-0.0287	20.0017	-0.0037	6.3514	-61.25%	184.92%
2	10	10	10	10	0.1	0.1	0.1	0.1	0.0119	1.0230	0.0118	3.0933	-0.0001	2.8334	-53.61%	40.29%
3	10	10	10	10	0.1	0.1	0.1	0.1	0.0182	0.9824	0.0186	2.9782	0.0003	2.8521	-55.45%	35.07%
4	10	10	10	10	0.1	0.1	0.1	0.1	0.0187	0.8439	0.0193	2.4479	0.0006	2.5676	-61.73%	11.02%
5	10	10	10	10	0.1	0.1	0.1	0.1	0.0473	2.7603	0.0499	33.4489	0.0026	6.8424	25.18%	1416.96%
2	20	20	20	20	0.1	0.1	0.1	0.1	0.0488	0.6092	0.0470	1.4025	-0.0018	2.0889	-21.52%	80.68%
3	20	20	20	20	0.1	0.1	0.1	0.1	0.0509	0.6024	0.0490	1.3874	-0.0019	2.0952	-22.40%	78.73%
4	20	20	20	20	0.1	0.1	0.1	0.1	0.0420	0.4768	0.0399	0.9856	-0.0022	1.8429	-38.58%	26.97%
5	20	20	20	20	0.1	0.1	0.1	0.1	0.0572	1.2110	0.0524	18.8529	-0.0048	3.4670	56.01%	2328.71%
2	3	6	3	6	0.1	0.1	0.1	0.1	0.3676	1.3023	0.3641	4.5245	-0.0035	3.3700	-88.49%	-60.00%
3	3	6	3	6	0.1	0.1	0.1	0.1	0.2415	1.2496	0.2393	4.3745	-0.0022	3.3957	-88.95%	-61.33%
4	3	6	3	6	0.1	0.1	0.1	0.1	0.2326	1.1965	0.2299	4.1640	-0.0027	3.2821	-89.42%	-63.19%
5	3	6	3	6	0.1	0.1	0.1	0.1	-0.0884	2.7490	0.0017	21.0802	0.0901	6.6734	-75.70%	86.34%
2	5	10	5	10	0.1	0.1	0.1	0.1	0.2807	1.1473	0.2851	3.7234	0.0044	3.0984	-75.13%	-19.28%
3	5	10	5	10	0.1	0.1	0.1	0.1	0.1768	1.0929	0.1849	3.5637	0.0081	3.1212	-76.31%	-22.74%
4	5	10	5	10	0.1	0.1	0.1	0.1	0.1795	0.9931	0.1895	3.1694	0.0100	2.9104	-78.47%	-31.29%
5	5	10	5	10	0.1	0.1	0.1	0.1	-0.1218	3.2761	0.0035	38.1280	0.1253	8.1284	-28.97%	726.62%
2	10	20	10	20	0.1	0.1	0.1	0.1	0.1572	0.8012	0.1758	2.1512	0.0185	2.4770	-46.25%	44.32%
3	10	20	10	20	0.1	0.1	0.1	0.1	0.1140	0.7816	0.1376	2.1016	0.0236	2.4904	-47.57%	40.99%
4	10	20	10	20	0.1	0.1	0.1	0.1	0.1551	0.6382	0.1817	1.5867	0.0266	2.1849	-57.19%	6.45%
5	10	20	10	20	0.1	0.1	0.1	0.1	-0.0179	2.3356	0.0493	45.3508	0.0671	6.2255	56.69%	2942.40%

Table 4.2.4: estimated summary effects and variances of summary effects for log relative risk

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	5	5	0.1	0.1	0.1	0.1	0.0145	1.3220	0.0155	4.6162	0.0010	3.3898	-86.81%	-53.93%
3	3	3	5	5	0.1	0.1	0.1	0.1	0.0104	1.2765	0.0113	4.4892	0.0010	3.4133	-87.26%	-55.20%
4	3	3	5	5	0.1	0.1	0.1	0.1	0.0085	1.2169	0.0091	4.2537	0.0006	3.2914	-87.86%	-57.55%
5	3	3	5	5	0.1	0.1	0.1	0.1	0.0143	2.2585	0.0245	12.7601	0.0102	5.1626	-77.46%	27.34%
2	3	3	6	6	0.1	0.1	0.1	0.1	0.0339	1.2994	0.0344	4.4951	0.0005	3.3419	-83.61%	-43.30%
3	3	3	6	6	0.1	0.1	0.1	0.1	0.0390	1.2557	0.0396	4.3723	0.0006	3.3652	-84.16%	-44.85%
4	3	3	6	6	0.1	0.1	0.1	0.1	0.0383	1.1862	0.0388	4.0937	0.0005	3.2226	-85.04%	-48.37%
5	3	3	6	6	0.1	0.1	0.1	0.1	0.0556	2.3191	0.0581	13.3750	0.0025	5.1513	-70.75%	68.70%
2	3	3	9	9	0.1	0.1	0.1	0.1	0.0170	1.2044	0.0171	3.9809	0.0001	3.1567	-73.50%	-12.40%
3	3	3	9	9	0.1	0.1	0.1	0.1	0.0170	1.1670	0.0165	3.8749	-0.0005	3.1763	-74.32%	-14.73%
4	3	3	9	9	0.1	0.1	0.1	0.1	0.0107	1.0662	0.0093	3.4690	-0.0014	2.9714	-76.54%	-23.66%
5	3	3	9	9	0.1	0.1	0.1	0.1	0.0203	2.2182	0.0327	12.4659	0.0124	4.6715	-51.19%	174.33%
2	3	3	15	15	0.1	0.1	0.1	0.1	-0.0177	0.9939	-0.0169	2.9689	0.0009	2.7595	-55.05%	34.28%
3	3	3	15	15	0.1	0.1	0.1	0.1	-0.0239	0.9678	-0.0228	2.8994	0.0010	2.7759	-56.23%	31.14%
4	3	3	15	15	0.1	0.1	0.1	0.1	-0.0238	0.8452	-0.0227	2.4229	0.0011	2.5173	-61.77%	9.59%
5	3	3	15	15	0.1	0.1	0.1	0.1	-0.0142	1.7420	0.0090	8.6870	0.0232	3.6172	-21.21%	292.91%
2	5	5	10	10	0.1	0.1	0.1	0.1	-0.0160	1.1462	-0.0156	3.6960	0.0004	3.0461	-65.85%	10.13%
3	5	5	10	10	0.1	0.1	0.1	0.1	-0.0226	1.0979	-0.0223	3.5542	0.0004	3.0665	-67.28%	5.91%
4	5	5	10	10	0.1	0.1	0.1	0.1	-0.0208	0.9897	-0.0204	3.1279	0.0005	2.8431	-70.51%	-6.79%
5	5	5	10	10	0.1	0.1	0.1	0.1	-0.0263	2.7428	-0.0087	23.2254	0.0176	6.1256	-18.27%	592.08%
2	5	5	15	15	0.1	0.1	0.1	0.1	-0.0006	0.9824	-0.0020	2.8972	-0.0014	2.7322	-51.38%	43.40%
3	5	5	15	15	0.1	0.1	0.1	0.1	0.0004	0.9495	-0.0013	2.8051	-0.0017	2.7490	-53.00%	38.84%
4	5	5	15	15	0.1	0.1	0.1	0.1	-0.0005	0.8178	-0.0025	2.2985	-0.0020	2.4763	-59.52%	13.77%
5	5	5	15	15	0.1	0.1	0.1	0.1	0.0056	2.1643	0.0093	16.7427	0.0038	4.6588	7.12%	728.69%
2	5	5	20	20	0.1	0.1	0.1	0.1	-0.0073	0.8533	-0.0046	2.3277	0.0027	2.4741	-38.96%	66.51%
3	5	5	20	20	0.1	0.1	0.1	0.1	-0.0070	0.8323	-0.0035	2.2742	0.0036	2.4885	-40.46%	62.68%
4	5	5	20	20	0.1	0.1	0.1	0.1	-0.0053	0.7030	-0.0015	1.7981	0.0038	2.2226	-49.71%	28.63%
5	5	5	20	20	0.1	0.1	0.1	0.1	0.0197	1.7235	0.0395	11.9321	0.0198	3.6624	23.29%	753.56%
2	10	10	20	20	0.1	0.1	0.1	0.1	-0.0146	0.7837	-0.0118	2.0366	0.0027	2.3742	-31.75%	77.36%
3	10	10	20	20	0.1	0.1	0.1	0.1	-0.0188	0.7654	-0.0154	1.9937	0.0033	2.3881	-33.34%	73.63%
4	10	10	20	20	0.1	0.1	0.1	0.1	-0.0146	0.6246	-0.0105	1.4874	0.0041	2.0987	-45.60%	29.53%
5	10	10	20	20	0.1	0.1	0.1	0.1	-0.0163	1.7624	-0.0117	20.6395	0.0046	4.2494	53.48%	1697.45%

4.3. Log Odds Ratio

Table 4.2.1 – 4.2.4 shows the simulation results for log odds ratio with various sample sizes and equal event rates 0.5 or 0.1. Similar to log relative risk, since the true variance of the measure can only be approximated, the relative biases of variances of summary effect are calculated relative to the second order approximated variance as a way to compare the two variance estimates.

In almost all settings, the variances estimated by inverse variance weights are negatively biased, which underestimate the variances of summary effects. In contrast, the variances estimated by the bias corrected weights are mostly positively biased. For the few cases where the bias corrected weights give negative bias in variances of summary effects, they tend to be a lot less negatively biased than variances estimated by the inverse variance weights. In many of the settings, bias corrected weight with zero modification method 4 gives the least biased variance estimate relative to the second order approximation, with a few exceptions where the standard estimates with zero modification method 5 being better when the sample sizes are small, and the treatment arms are imbalanced. Hence, zero modification method 4 is recommended for relatively large sample sizes. For small sample sizes with imbalanced arms, zero modification method 5 works better.

Table 4.3.1: estimated summary effects and variances of summary effects for log odds ratio

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	3	3	0.5	0.5	0.5	0.5	0.0335	1.6849	0.0302	3.8413	-0.0032	2.2471	-24.18%	72.86%
3	3	3	3	3	0.5	0.5	0.5	0.5	0.0341	1.6021	0.0304	3.6785	-0.0037	2.2760	-27.91%	65.53%
4	3	3	3	3	0.5	0.5	0.5	0.5	0.0293	1.3176	0.0251	2.7531	-0.0042	2.0070	-40.71%	23.89%
5	3	3	3	3	0.5	0.5	0.5	0.5	0.0350	1.8205	0.0287	4.9097	-0.0063	2.5724	-18.08%	120.94%
2	5	5	5	5	0.5	0.5	0.5	0.5	-0.0126	1.0225	-0.0151	1.8393	-0.0025	1.7577	-8.71%	64.22%
3	5	5	5	5	0.5	0.5	0.5	0.5	-0.0105	1.0137	-0.0133	1.8283	-0.0029	1.7649	-9.49%	63.24%
4	5	5	5	5	0.5	0.5	0.5	0.5	-0.0075	0.8137	-0.0104	1.3036	-0.0030	1.5607	-27.35%	16.39%
5	5	5	5	5	0.5	0.5	0.5	0.5	-0.0109	1.1031	-0.0154	2.2484	-0.0045	1.8360	-1.51%	100.75%
2	10	10	10	10	0.5	0.5	0.5	0.5	0.0095	0.4551	0.0072	0.5903	-0.0023	1.2879	-5.19%	22.98%
3	10	10	10	10	0.5	0.5	0.5	0.5	0.0096	0.4551	0.0073	0.5903	-0.0023	1.2880	-5.19%	22.98%
4	10	10	10	10	0.5	0.5	0.5	0.5	0.0085	0.4027	0.0069	0.5028	-0.0016	1.2437	-16.10%	4.75%
5	10	10	10	10	0.5	0.5	0.5	0.5	0.0086	0.4564	0.0061	0.5913	-0.0025	1.2867	-4.92%	23.19%
2	20	20	20	20	0.5	0.5	0.5	0.5	-0.0074	0.2115	-0.0075	0.2367	-0.0001	1.1182	-3.86%	7.59%
3	20	20	20	20	0.5	0.5	0.5	0.5	-0.0074	0.2115	-0.0075	0.2367	-0.0001	1.1182	-3.86%	7.59%
4	20	20	20	20	0.5	0.5	0.5	0.5	-0.0070	0.2003	-0.0070	0.2225	0.0000	1.1106	-8.95%	1.14%
5	20	20	20	20	0.5	0.5	0.5	0.5	-0.0074	0.2115	-0.0075	0.2367	-0.0001	1.1182	-3.86%	7.59%
2	3	6	3	6	0.5	0.5	0.5	0.5	-0.0090	1.2673	-0.0075	2.6307	0.0015	2.0397	-18.53%	69.12%
3	3	6	3	6	0.5	0.5	0.5	0.5	-0.0057	1.2418	-0.0045	2.5973	0.0012	2.0610	-20.17%	66.97%
4	3	6	3	6	0.5	0.5	0.5	0.5	-0.0044	1.0064	-0.0040	1.8787	0.0004	1.7956	-35.30%	20.77%
5	3	6	3	6	0.5	0.5	0.5	0.5	-0.0047	1.5770	-0.0074	4.9067	-0.0027	2.4920	1.38%	215.43%
2	5	10	5	10	0.5	0.5	0.5	0.5	-0.0050	0.7337	-0.0091	1.1824	-0.0041	1.5750	-8.29%	47.80%
3	5	10	5	10	0.5	0.5	0.5	0.5	-0.0045	0.7326	-0.0088	1.1818	-0.0043	1.5770	-8.43%	47.73%
4	5	10	5	10	0.5	0.5	0.5	0.5	-0.0020	0.6042	-0.0064	0.8813	-0.0044	1.4297	-24.48%	10.16%
5	5	10	5	10	0.5	0.5	0.5	0.5	-0.0090	0.7934	-0.0160	1.6163	-0.0070	1.6169	-0.83%	102.04%
2	10	20	10	20	0.5	0.5	0.5	0.5	-0.0326	0.3306	-0.0306	0.4067	0.0020	1.2240	-5.54%	16.20%
3	10	20	10	20	0.5	0.5	0.5	0.5	-0.0326	0.3306	-0.0306	0.4067	0.0020	1.2240	-5.54%	16.20%
4	10	20	10	20	0.5	0.5	0.5	0.5	-0.0310	0.2998	-0.0296	0.3588	0.0014	1.1938	-14.34%	2.51%
5	10	20	10	20	0.5	0.5	0.5	0.5	-0.0312	0.3310	-0.0296	0.4070	0.0016	1.2234	-5.43%	16.29%

Table 4.3.2: estimated summary effects and variances of summary effects for log odds ratio

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	5	5	0.5	0.5	0.5	0.5	0.0268	1.2764	0.0223	2.5140	-0.0045	1.9255	-14.30%	68.80%
3	3	3	5	5	0.5	0.5	0.5	0.5	0.0270	1.2438	0.0220	2.4661	-0.0049	1.9444	-16.49%	65.58%
4	3	3	5	5	0.5	0.5	0.5	0.5	0.0275	1.0075	0.0232	1.7722	-0.0043	1.7060	-32.35%	18.99%
5	3	3	5	5	0.5	0.5	0.5	0.5	0.0260	1.3766	0.0131	3.0745	-0.0129	2.0667	-7.57%	106.43%
2	3	3	6	6	0.5	0.5	0.5	0.5	0.0101	1.1155	0.0100	2.0423	0.0000	1.7836	-12.15%	60.83%
3	3	3	6	6	0.5	0.5	0.5	0.5	0.0118	1.0930	0.0113	2.0132	-0.0005	1.7989	-13.93%	58.54%
4	3	3	6	6	0.5	0.5	0.5	0.5	0.0138	0.8946	0.0129	1.4773	-0.0009	1.6049	-29.55%	16.34%
5	3	3	6	6	0.5	0.5	0.5	0.5	0.0152	1.1898	0.0132	2.4263	-0.0020	1.8728	-6.30%	91.07%
2	3	3	9	9	0.5	0.5	0.5	0.5	0.0129	0.7895	0.0128	1.1956	-0.0002	1.4878	-9.57%	36.95%
3	3	3	9	9	0.5	0.5	0.5	0.5	0.0154	0.7800	0.0144	1.1887	-0.0010	1.4978	-10.65%	36.16%
4	3	3	9	9	0.5	0.5	0.5	0.5	0.0146	0.6663	0.0134	0.9444	-0.0011	1.4025	-23.68%	8.18%
5	3	3	9	9	0.5	0.5	0.5	0.5	0.0169	0.8076	0.0152	1.2455	-0.0017	1.4998	-7.49%	42.67%
2	3	3	15	15	0.5	0.5	0.5	0.5	-0.0196	0.4922	-0.0180	0.6240	0.0016	1.2602	-7.50%	17.28%
3	3	3	15	15	0.5	0.5	0.5	0.5	-0.0199	0.4886	-0.0183	0.6222	0.0016	1.2663	-8.17%	16.94%
4	3	3	15	15	0.5	0.5	0.5	0.5	-0.0180	0.4433	-0.0170	0.5530	0.0010	1.2406	-16.69%	3.93%
5	3	3	15	15	0.5	0.5	0.5	0.5	-0.0217	0.4988	-0.0208	0.6433	0.0008	1.2638	-6.25%	20.90%
2	5	5	10	10	0.5	0.5	0.5	0.5	-0.0037	0.6267	-0.0004	0.8894	0.0033	1.4012	-6.74%	32.35%
3	5	5	10	10	0.5	0.5	0.5	0.5	-0.0047	0.6254	-0.0010	0.8887	0.0037	1.4031	-6.93%	32.25%
4	5	5	10	10	0.5	0.5	0.5	0.5	-0.0046	0.5355	-0.0018	0.7173	0.0028	1.3279	-20.31%	6.74%
5	5	5	10	10	0.5	0.5	0.5	0.5	-0.0046	0.6400	0.0003	0.9325	0.0048	1.4025	-4.76%	38.76%
2	5	5	15	15	0.5	0.5	0.5	0.5	-0.0430	0.4488	-0.0442	0.5684	-0.0012	1.2613	-5.71%	19.41%
3	5	5	15	15	0.5	0.5	0.5	0.5	-0.0431	0.4483	-0.0443	0.5682	-0.0012	1.2624	-5.82%	19.37%
4	5	5	15	15	0.5	0.5	0.5	0.5	-0.0388	0.4007	-0.0399	0.4940	-0.0011	1.2296	-15.82%	3.78%
5	5	5	15	15	0.5	0.5	0.5	0.5	-0.0439	0.4531	-0.0448	0.5720	-0.0010	1.2575	-4.81%	20.17%
2	5	5	20	20	0.5	0.5	0.5	0.5	0.0178	0.3512	0.0152	0.4206	-0.0026	1.1948	-4.50%	14.37%
3	5	5	20	20	0.5	0.5	0.5	0.5	0.0177	0.3508	0.0151	0.4205	-0.0025	1.1958	-4.61%	14.34%
4	5	5	20	20	0.5	0.5	0.5	0.5	0.0165	0.3216	0.0146	0.3795	-0.0019	1.1780	-12.55%	3.19%
5	5	5	20	20	0.5	0.5	0.5	0.5	0.0170	0.3540	0.0144	0.4226	-0.0026	1.1914	-3.74%	14.91%
2	10	10	20	20	0.5	0.5	0.5	0.5	-0.0127	0.2885	-0.0117	0.3371	0.0010	1.1665	-4.38%	11.73%
3	10	10	20	20	0.5	0.5	0.5	0.5	-0.0127	0.2885	-0.0117	0.3371	0.0010	1.1665	-4.38%	11.73%
4	10	10	20	20	0.5	0.5	0.5	0.5	-0.0122	0.2674	-0.0115	0.3082	0.0006	1.1515	-11.37%	2.15%
5	10	10	20	20	0.5	0.5	0.5	0.5	-0.0126	0.2888	-0.0116	0.3372	0.0010	1.1661	-4.28%	11.76%

Table 4.3.3: estimated summary effects and variances of summary effects for log odds ratio

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	**Mean of** sTE_{IVW}	**Mean of** $Var(sTE_{IVW})$	**Mean of** sTE_{BC}	**Mean of** $Var(sTE_{BC})$	**Mean of** D	**Mean of** VR	**Relative bias of** $Var(sTE_{IVW})$	**Relative bias of** $Var(sTE_{BC})$
2	3	3	3	3	0.1	0.1	0.1	0.1	0.0224	2.0896	0.0234	6.2796	0.0011	2.9727	-89.20%	-67.53%
3	3	3	3	3	0.1	0.1	0.1	0.1	0.0253	1.9606	0.0264	6.0023	0.0011	3.0240	-89.86%	-68.97%
4	3	3	3	3	0.1	0.1	0.1	0.1	0.0250	1.9135	0.0261	5.8231	0.0011	2.9719	-90.11%	-69.89%
5	3	3	3	3	0.1	0.1	0.1	0.1	0.0305	2.6745	0.0324	11.4272	0.0019	4.1504	-86.17%	-40.92%
2	5	5	5	5	0.1	0.1	0.1	0.1	-0.0120	1.7359	-0.0151	5.2214	-0.0030	2.9373	-77.89%	-33.50%
3	5	5	5	5	0.1	0.1	0.1	0.1	-0.0147	1.6433	-0.0181	4.9754	-0.0034	2.9600	-79.07%	-36.63%
4	5	5	5	5	0.1	0.1	0.1	0.1	-0.0158	1.5639	-0.0195	4.6568	-0.0036	2.8401	-80.08%	-40.69%
5	5	5	5	5	0.1	0.1	0.1	0.1	-0.0275	3.1940	-0.0337	21.1233	-0.0062	5.8592	-59.32%	169.02%
2	10	10	10	10	0.1	0.1	0.1	0.1	0.0131	1.2510	0.0123	3.4595	-0.0007	2.6230	-50.33%	37.36%
3	10	10	10	10	0.1	0.1	0.1	0.1	0.0204	1.2031	0.0200	3.3299	-0.0004	2.6371	-52.23%	32.22%
4	10	10	10	10	0.1	0.1	0.1	0.1	0.0205	1.0639	0.0206	2.7885	0.0000	2.3836	-57.76%	10.72%
5	10	10	10	10	0.1	0.1	0.1	0.1	0.0482	3.0374	0.0504	34.0598	0.0022	6.5875	20.60%	1252.37%
2	20	20	20	20	0.1	0.1	0.1	0.1	0.0537	0.7271	0.0520	1.5685	-0.0017	1.9893	-19.87%	72.86%
3	20	20	20	20	0.1	0.1	0.1	0.1	0.0561	0.7193	0.0542	1.5522	-0.0019	1.9953	-20.73%	71.06%
4	20	20	20	20	0.1	0.1	0.1	0.1	0.0469	0.5913	0.0448	1.1401	-0.0021	1.7553	-34.84%	25.64%
5	20	20	20	20	0.1	0.1	0.1	0.1	0.0624	1.3513	0.0572	19.0700	-0.0052	3.3606	48.92%	2001.59%
2	3	6	3	6	0.1	0.1	0.1	0.1	0.4390	1.8520	0.4371	5.5495	-0.0020	2.9458	-85.24%	-55.79%
3	3	6	3	6	0.1	0.1	0.1	0.1	0.2872	1.7417	0.2871	5.2792	-0.0001	2.9800	-86.12%	-57.94%
4	3	6	3	6	0.1	0.1	0.1	0.1	0.2821	1.6781	0.2826	5.0274	0.0005	2.8940	-86.63%	-59.95%
5	3	6	3	6	0.1	0.1	0.1	0.1	-0.0960	3.3391	0.0373	22.6504	0.1333	6.1130	-73.40%	80.46%
2	5	10	5	10	0.1	0.1	0.1	0.1	0.3238	1.4843	0.3319	4.3035	0.0081	2.8039	-71.37%	-17.00%
3	5	10	5	10	0.1	0.1	0.1	0.1	0.2051	1.4105	0.2181	4.1050	0.0130	2.8236	-72.80%	-20.83%
4	5	10	5	10	0.1	0.1	0.1	0.1	0.2145	1.3067	0.2314	3.6911	0.0169	2.6486	-74.80%	-28.81%
5	5	10	5	10	0.1	0.1	0.1	0.1	-0.1138	3.6758	0.0484	39.1885	0.1622	7.7368	-29.11%	655.78%
2	10	20	10	20	0.1	0.1	0.1	0.1	0.1753	0.9769	0.1985	2.4220	0.0232	2.3246	-42.97%	41.39%
3	10	20	10	20	0.1	0.1	0.1	0.1	0.1263	0.9539	0.1558	2.3670	0.0295	2.3366	-44.31%	38.18%
4	10	20	10	20	0.1	0.1	0.1	0.1	0.1775	0.8085	0.2119	1.8386	0.0343	2.0569	-52.80%	7.33%
5	10	20	10	20	0.1	0.1	0.1	0.1	0.0008	2.5601	0.0815	45.8140	0.0807	6.0518	49.45%	2574.55%

Table 4.3.4: estimated summary effects and variances of summary effects for log odds ratio

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	5	5	0.1	0.1	0.1	0.1	0.0175	1.8945	0.0199	5.6778	0.0025	2.9420	-83.04%	-49.17%
3	3	3	5	5	0.1	0.1	0.1	0.1	0.0120	1.7859	0.0146	5.4144	0.0026	2.9763	-84.01%	-51.52%
4	3	3	5	5	0.1	0.1	0.1	0.1	0.0101	1.7166	0.0123	5.1426	0.0022	2.8846	-84.63%	-53.96%
5	3	3	5	5	0.1	0.1	0.1	0.1	0.0172	2.8819	0.0333	14.2861	0.0161	4.6380	-74.20%	27.90%
2	3	3	6	6	0.1	0.1	0.1	0.1	-0.0371	1.8186	-0.0381	5.4297	-0.0010	2.9170	-79.52%	-38.84%
3	3	3	6	6	0.1	0.1	0.1	0.1	-0.0436	1.7186	-0.0447	5.1840	-0.0011	2.9488	-80.64%	-41.61%
4	3	3	6	6	0.1	0.1	0.1	0.1	-0.0433	1.6393	-0.0445	4.8721	-0.0012	2.8375	-81.54%	-45.12%
5	3	3	6	6	0.1	0.1	0.1	0.1	-0.0632	2.9039	-0.0705	14.7301	-0.0073	4.6339	-67.29%	65.92%
2	3	3	9	9	0.1	0.1	0.1	0.1	0.0214	1.6291	0.0221	4.7356	0.0007	2.8038	-68.38%	-8.09%
3	3	3	9	9	0.1	0.1	0.1	0.1	0.0222	1.5506	0.0225	4.5416	0.0003	2.8312	-69.91%	-11.86%
4	3	3	9	9	0.1	0.1	0.1	0.1	0.0154	1.4382	0.0146	4.0998	-0.0008	2.6616	-72.09%	-20.43%
5	3	3	9	9	0.1	0.1	0.1	0.1	0.0257	2.7815	0.0404	13.9859	0.0146	4.2687	-46.02%	171.44%
2	3	3	15	15	0.1	0.1	0.1	0.1	-0.0235	1.3054	-0.0212	3.4780	0.0023	2.4891	-48.85%	36.27%
3	3	3	15	15	0.1	0.1	0.1	0.1	-0.0306	1.2544	-0.0280	3.3590	0.0027	2.5120	-50.85%	31.61%
4	3	3	15	15	0.1	0.1	0.1	0.1	-0.0302	1.1161	-0.0274	2.8442	0.0029	2.2914	-56.27%	11.44%
5	3	3	15	15	0.1	0.1	0.1	0.1	-0.0180	2.1907	0.0119	9.7958	0.0299	3.3107	-14.17%	283.81%
2	5	5	10	10	0.1	0.1	0.1	0.1	-0.0203	1.4604	-0.0195	4.2231	0.0008	2.7656	-61.71%	10.73%
3	5	5	10	10	0.1	0.1	0.1	0.1	-0.0279	1.3945	-0.0271	4.0458	0.0008	2.7834	-63.44%	6.08%
4	5	5	10	10	0.1	0.1	0.1	0.1	-0.0261	1.2819	-0.0249	3.6014	0.0012	2.5945	-66.39%	-5.57%
5	5	5	10	10	0.1	0.1	0.1	0.1	-0.0310	3.1306	-0.0093	24.2479	0.0217	5.7798	-17.91%	535.80%
2	5	5	15	15	0.1	0.1	0.1	0.1	-0.0004	1.2304	-0.0011	3.2888	-0.0007	2.5075	-47.14%	41.30%
3	5	5	15	15	0.1	0.1	0.1	0.1	0.0010	1.1865	0.0000	3.1759	-0.0010	2.5230	-49.02%	36.45%
4	5	5	15	15	0.1	0.1	0.1	0.1	0.0002	1.0485	-0.0011	2.6502	-0.0014	2.2851	-54.95%	13.86%
5	5	5	15	15	0.1	0.1	0.1	0.1	0.0093	2.4890	0.0147	17.5632	0.0054	4.3991	6.94%	654.59%
2	5	5	20	20	0.1	0.1	0.1	0.1	-0.0097	1.0537	-0.0054	2.6246	0.0042	2.2902	-35.23%	61.33%
3	5	5	20	20	0.1	0.1	0.1	0.1	-0.0096	1.0256	-0.0042	2.5587	0.0054	2.3038	-36.96%	57.28%
4	5	5	20	20	0.1	0.1	0.1	0.1	-0.0078	0.8888	-0.0021	2.0646	0.0057	2.0676	-45.37%	26.91%
5	5	5	20	20	0.1	0.1	0.1	0.1	0.0216	1.9810	0.0459	12.5431	0.0244	3.4641	21.77%	671.02%
2	10	10	20	20	0.1	0.1	0.1	0.1	-0.0174	0.9411	-0.0145	2.2706	0.0028	2.2363	-29.46%	70.19%
3	10	10	20	20	0.1	0.1	0.1	0.1	-0.0223	0.9200	-0.0187	2.2231	0.0036	2.2482	-31.04%	66.63%
4	10	10	20	20	0.1	0.1	0.1	0.1	-0.0182	0.7779	-0.0135	1.7075	0.0047	1.9813	-41.69%	27.99%
5	10	10	20	20	0.1	0.1	0.1	0.1	-0.0191	1.9619	-0.0132	21.0290	0.0060	4.1013	47.05%	1476.23%

5. Cochrane Data Examples

Table 5.1 shows 4 examples of meta-analyses from the Cochrane Database [30 – 32], where r_1 and r_2 donote the number of events in the treatment group and control group respectively, and n_1 and n_2 donote the sample size of the treatment group and control group respectively. Since at least one study in each meta-analysis has zero event in at least one group, some measures cannot be calculated directly from the original data. Tables 5.2 – 5.4 present the impact of bias correction and zero modifications.

In Table 5.2, the bias correction of risk difference affects the summary effects more than the variances. The change in the summary effects vary from 1.87% to 51.52%, whereas the change in the variance is only up to 6.81%. Table 5.3 and 5.4 show the opposite situation to Table 5.2, where for log relative risk and log odds ratio, the changes in variances are much larger than the changes in summary effects. The change in variance can be several hundred percent, which will influence the confidence intervals and results for significance tests.

Table 5.1: effect measures and study weights of meta-analyses

Analysis	Study	r_1	r_2	n_1	n_2	RD: Inverse variance weight	RD: Second-order bias-corrected weight	RD: Treatment effect	*ln*RR: First-order inverse variance weight	*ln*RR: Second-order bias-corrected weight	*ln*RR: Treatment effect	*ln*OR: First-order inverse variance weight	*ln*OR: Second-order bias-corrected weight	*ln*OR: Treatment effect
Tammenmaa-Aho 1.2.2	1	1	2	4	2	21.33	16.00	-0.75	1.33	1.31	1.39	—	—	—
	2	3	0	4	1	21.33	16.00	0.75	—	—	—	—	—	—
Tammenmaa-Aho 1.2.4	1	0	2	3	3	13.50	9.00	-0.67	—	—	—	—	—	—
	2	13	13	15	15	64.90	60.58	0	48.75	46.31	0	0.87	0.87	0
Bergman 1.3	1	1	0	5	4	31.25	25.00	0.20	—	—	—	—	—	—
	2	0	2	4	4	16.00	12.00	-0.50	—	—	—	—	—	—
Wojcieszek 8.6	1	0	1	2	3	13.50	9.00	-0.33	—	—	—	—	—	—
	2	0	0	1	1	—	—	0	—	—	—	—	—	—

Table 5.2: Impact of bias correction on the summary treatment effect and its estimated variance in a sample of meta-analyses, for risk difference

	Method 2				Method 3				Method 4				Method 5			
Analysis	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)
Tammenmaa-Aho 1.2.2	-0.20	-0.29	44.36	3.63	-0.15	-0.19	32.70	0.98	-0.15	-0.19	32.70	0.98	-0.19	-0.28	51.52	3.62
Tammenmaa-Aho 1.2.4	-0.06	-0.05	-24.41	0.84	-0.08	-0.06	-17.17	0.53	-0.08	-0.07	-17.34	0.58	-0.08	-0.07	-19.36	0.67
Bergman 1.3	-0.10	-0.09	-5.06	0.04	-0.08	-0.08	-4.31	0.02	-0.08	-0.08	-4.31	0.02	-0.06	-0.05	-9.47	0.03
Wojcieszek 8.6	-0.09	-0.11	17.81	6.81	-0.13	-0.15	12.01	2.58	-0.13	-0.15	12.01	2.58	-0.15	-0.15	1.87	0.05

	Method 6.1				Method 6.2			
Analysis	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(sTE) (%)	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(sTE) (%)
Wojcieszek 8.6	-0.27	-0.30	11.11	4.94	-0.24	-0.26	7.62	1.47

Table 5.3: Impact of bias correction on the summary treatment effect and its estimated variance in a sample of meta-analyses, for log relative risk

	Method 2				Method 3				Method 4				Method 5			
Analysis	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)
Tammenmaa-Aho 1.2.2	-0.42	-0.44	3.95	172.70	-0.51	-0.50	-0.78	129.60	-0.50	-0.50	-0.78	129.60	-0.78	-0.98	26.29	105.61
Tammenmaa-Aho 1.2.4	-0.02	-0.02	3.29	11.17	-0.02	-0.02	4.04	11.22	-0.02	-0.02	3.43	11.34	-0.01	-0.01	4.39	11.34
Bergman 1.3	-0.58	-0.58	-0.51	252.87	-0.43	-0.43	-0.43	257.08	-0.43	-0.43	-0.43	257.08	-0.58	-0.57	-0.36	605.12
Wojcieszek 8.6	-0.28	-0.28	2.50	250.01	-0.48	-0.48	0.70	256.67	-0.48	-0.48	0.70	256.67	-0.33	-0.34	1.94	212.82

Table 5.4: Impact of bias correction on the summary treatment effect and its estimated variance in a sample of meta-analyses, for log odd ratio

	Method 2				Method 3				Method 4				Method 5			
Analysis	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)	Old *sTE*	New *sTE*	Change in *sTE* (%)	Change in Var(*sTE*) (%)
Tammenmaa-Aho 1.2.2	-0.48	-0.49	3.58	167.03	-0.34	-0.35	2.67	172.40	-0.34	-0.35	2.67	172.40	-0.41	0.17	-142.29	431.28
Tammenmaa-Aho 1.2.4	-0.57	-0.57	-0.63	87.17	-0.63	-0.63	-0.41	91.57	-0.54	-0.54	-0.42	76.41	-0.59	-0.37	-36.63	85.35
Bergman 1.3	-0.74	-0.74	-0.29	192.68	-0.57	-0.57	-0.24	198.41	-0.57	-0.57	-0.24	198.41	-0.74	-0.96	30.17	512.76
Wojcieszek 8.6	-0.42	-0.42	-0.83	174.47	-0.67	-0.67	0.35	184.98	-0.67	-0.67	0.35	184.98	-0.57	-0.40	-30.25	142.40

6. Conclusion and Discussion

We conducted simulations to assess the accuracy of the proposed weights at the individual study level, then assessed the accuracy of estimated summary effects and variances of summary effects of meta-analyses. There is no one method that is superior for all event rates and sample sizes. One continuity correction method that gives high accuracy for study weights does not necessarily lead to a more accurate summary effect and variance of summary effect.

For one study weight, the inverse variance weight is always positively biased for all measures and all simulation settings. The bias corrections lower the weights, and in most of the situations, improves the accuracy of estimated weights. Only in a few situations with small sample sizes, the bias corrected weights lower the weights too much and produce negative biases. Otherwise, the bias corrected weights are uniformly less biased than the inverse variance weights if they are positively biased for all sample sizes. In either situation, the bias corrected weights converge to the true value faster than the inverse variance weight, while both converge to the true value as the sample size gets larger. For risk difference, zero modification method 2 and 3 perform better when the event rates are moderate to large. Method 4 gives the least biased the weights when the event rates are small. For log relative risk, zero modification method 2, 3, and 5 are generally less biased than method 4 for moderate to large event rates. Method 5 is particularly more accurate for small event rates. For log odds ratio, in very few situations, the bias corrected weight is less accurate than the inverse variance weight when sample size is small, where there might be negative biases. But in most of the cases, the bias corrected weights with zero modification method 2, 3 and 5 have high accuracy for moderate to large event rates. Bias corrected weights with zero modification method 5 is much less biased than the other methods.

In meta-analyses, differences between the summary effects estimated by inverse variance weighting and bias corrected weighting are not obvious. However, the variances of summary effect estimated by the bias corrected weights are always greater than with the uncorrected method.

For risk difference, the impact of bias corrected weight on the summary effect and variance of summary effect is small. The average ratio of new variance estimate over standard variance estimate is close to 1. When the sample sizes are small the event rates are moderate to large, zero modification method 2 is showing better variance estimations than other methods, even though it is not necessary to have continuity correction when there is only one zero cell in a study for risk difference. Method 6.1 and 6.2 are more common choices for risk difference since the zero modifications are only made when double zero cells occur, but they tend to underestimate the variance of the summary effect when the sample sizes are large, or the event rates are small. So there is a trade-off between accuracies of summary effect and variance of summary effect.

For log relative risk, the new variance estimate tends to be much larger than the standard estimate. In some cases where the event rates are moderate to large, the variance estimated by the bias corrected weight deviates from the second order approximated variance with true parameter values more than the standard variance estimate. Yet variance estimated by bias corrected weight with zero modification method 4 seems to be always less biased than the standard estimate, which is also the least biased on the absolute among all methods in most cases, and can improve the issue in underestimation of variances given by inverse variance weights. Therefore, in general method 4 is recommended along with the bias corrected weights for log relative risk.

For log odds ratio, the ratio of new variance estimate over standard variance estimate is around 2-4 when sample sizes are very small. The variance estimated by bias corrected weight can be more biased for some zero modification methods when event rates are moderate to large. Similar to the situation for log relative risk, variance of summary effect estimated by bias corrected weight with zero modification method 4 is less biased than using inverse variance weighting. Moreover, it is likely less biased than other methods if the sample sizes are not too small and can improve the underestimation of variances caused by inverse variance weights. In some situations where the sample sizes are very small and event rates are moderate to large, method 5 with inverse variance weight gives the lowest bias. Hence, method 4 with bias corrected weights or method 5 with inverse variance weights are better choices depending on the specific situations.

One limitation of the work is that the simulation studies only covered relatively simple parameter settings, which might not be sufficient to make conclusions for all possible situations. In addition, alternative variance estimations based on certain continuity corrections were proposed for variance of empirical logit and logarithm of a binomial variate were proposed to provide more accuracy [27 - 29]. Since currently our work is based on the usual variances, further work could be extended to developing bias corrections from the various alternative variance formulae.

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Appendix A

In the appendix, relative bias of study weights of studies with moderate event rates are plotted by different methods.

A.1. Relative bias

A.1.1. Risk difference

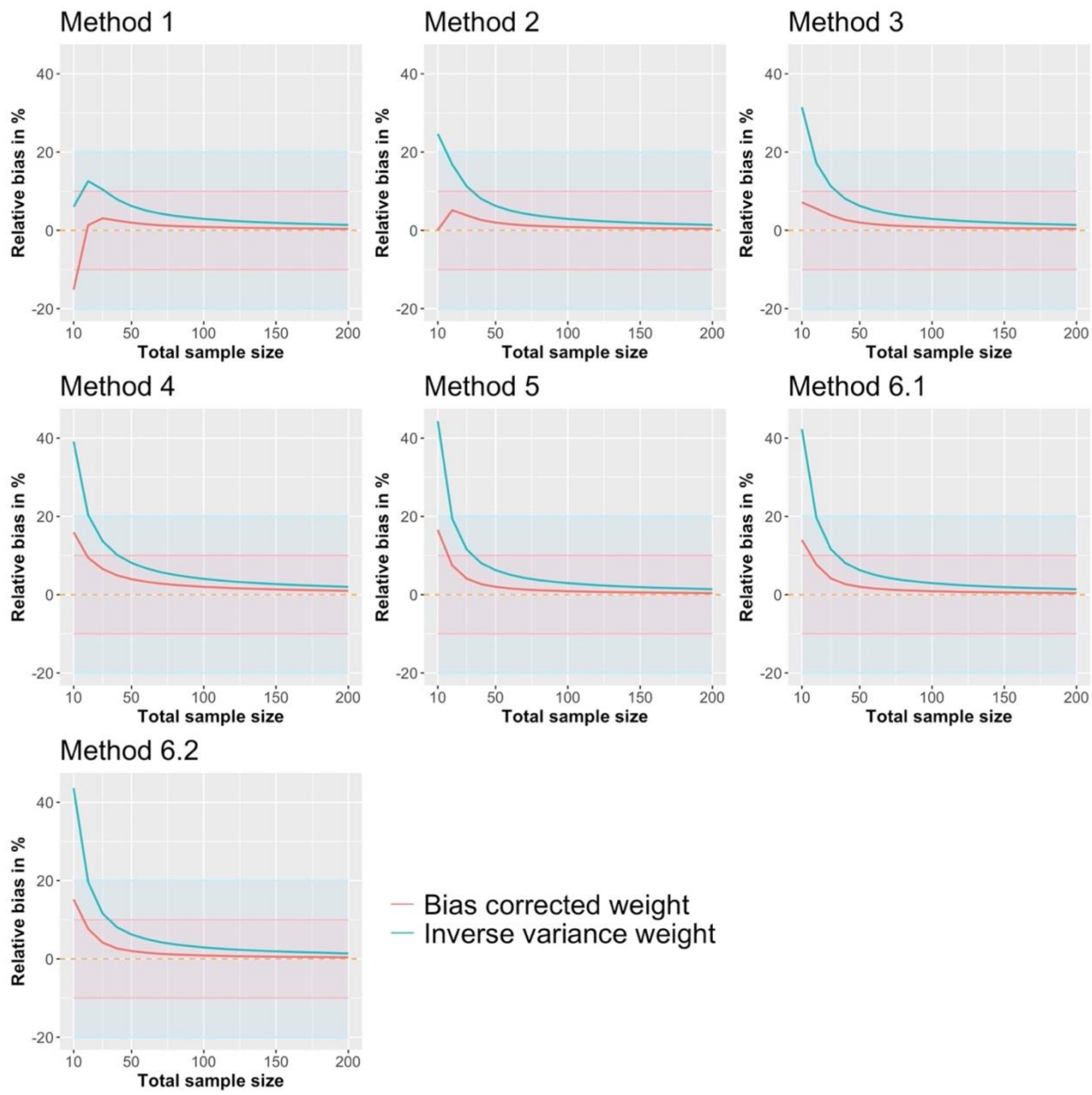

Figure A.1.1: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.3$

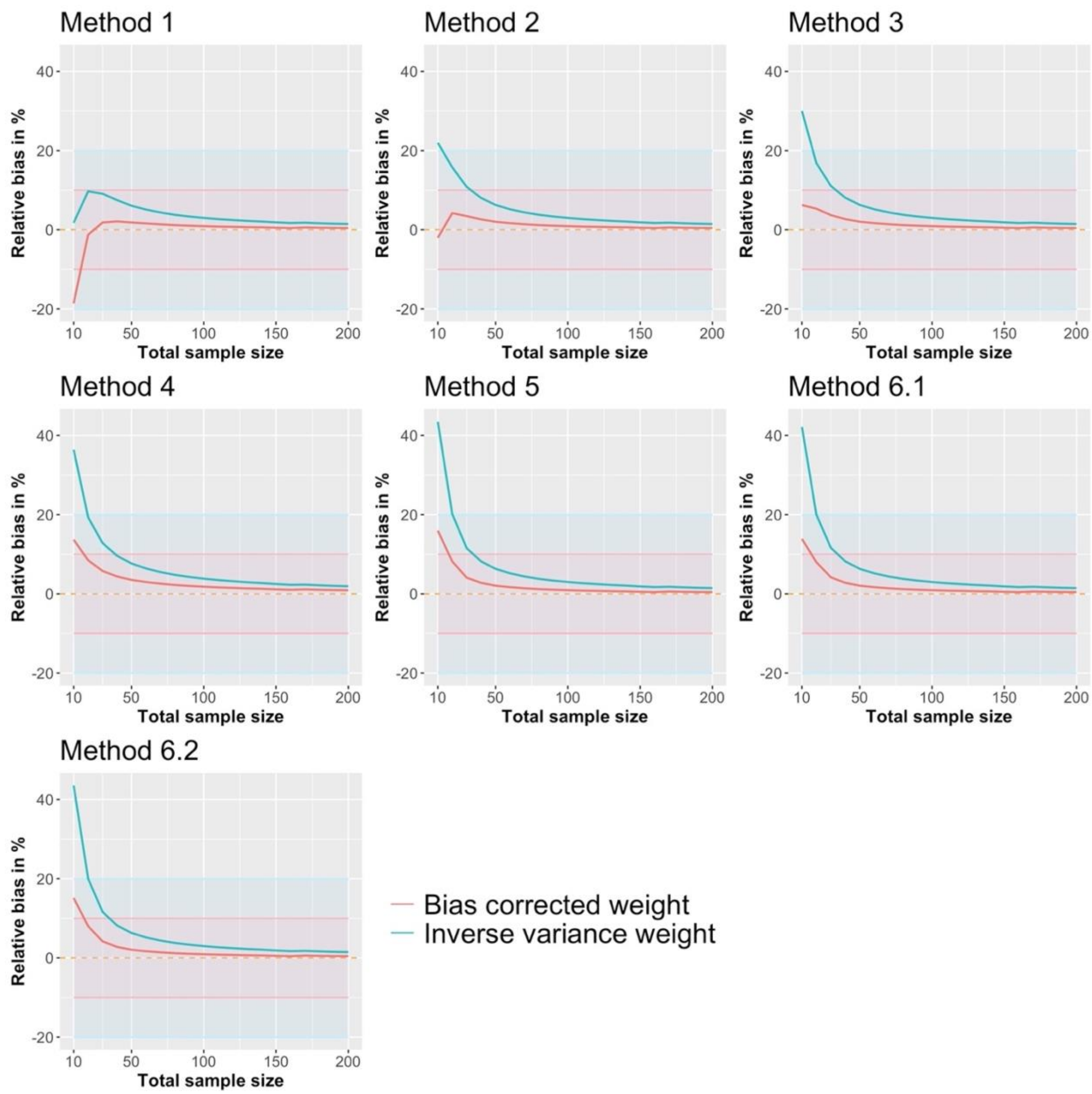

Figure A.1.2: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $n_1 = n_2$, with unequal event rates $\pi_1 = 0.4, \pi_2 = 0.2$

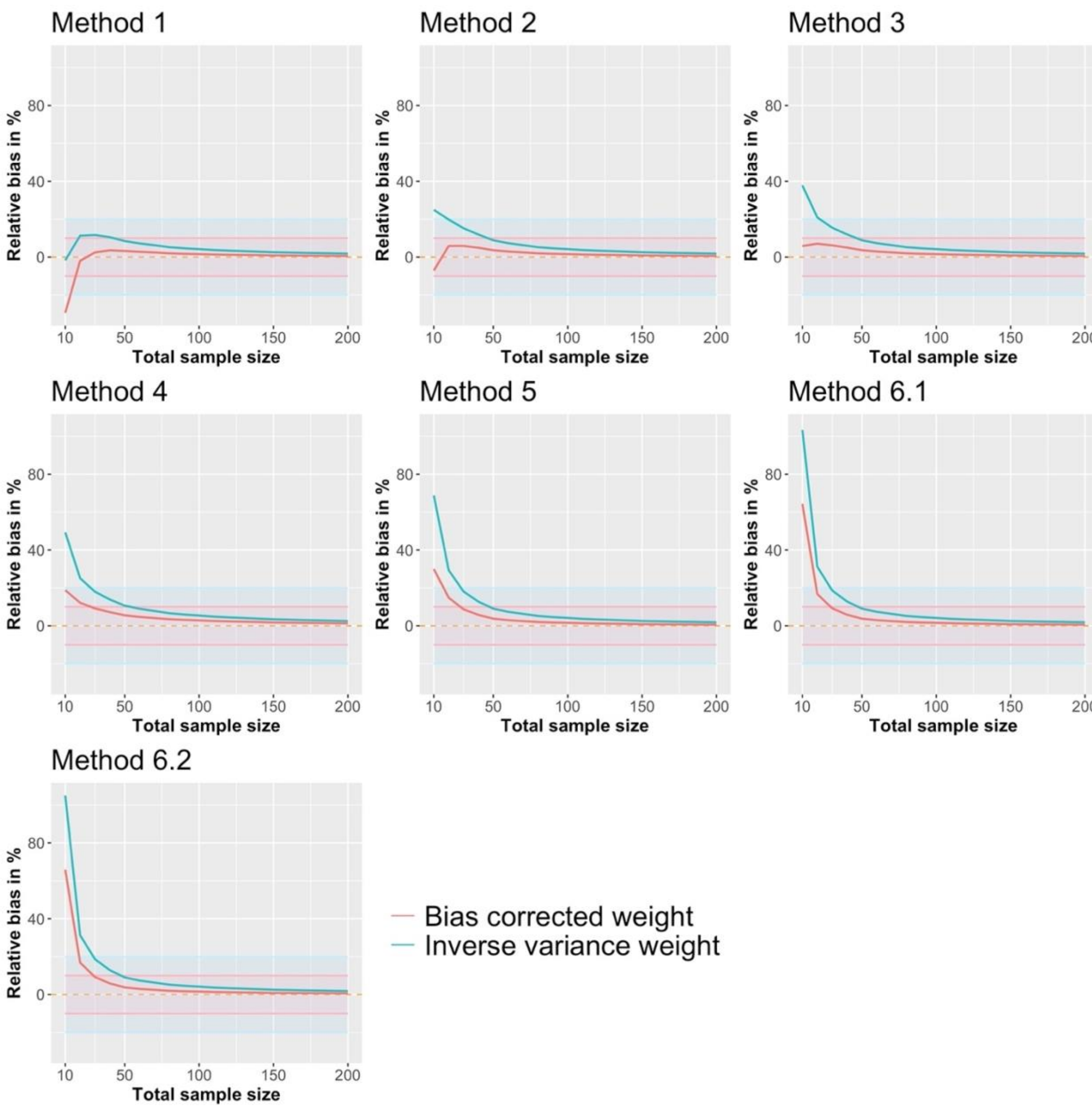

Figure A.1.3: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $2n_1 \approx n_2$, with equal event rates $\pi_1 = \pi_2 = 0.3$

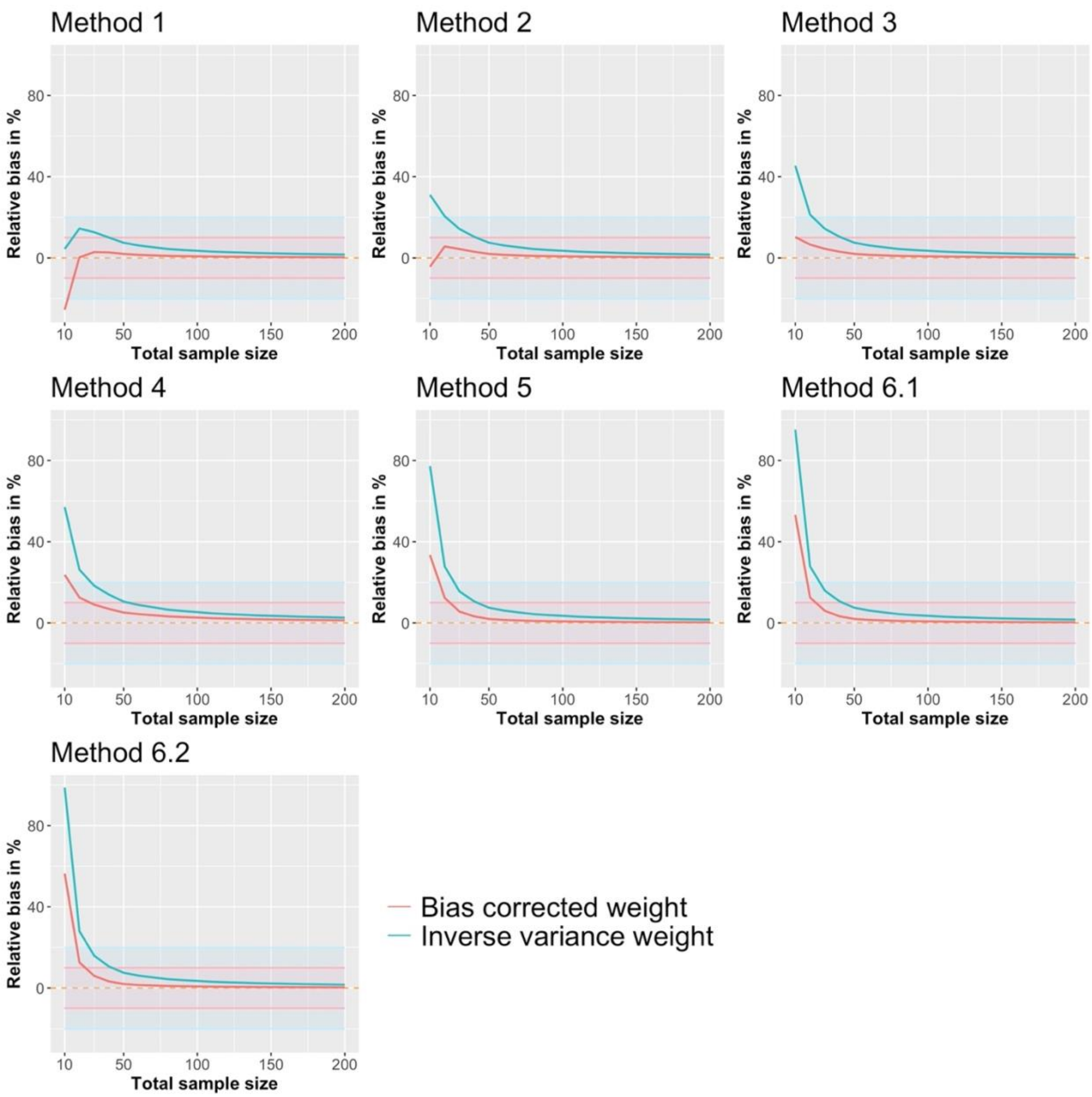

Figure A.1.4: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.4, \pi_2 = 0.2$

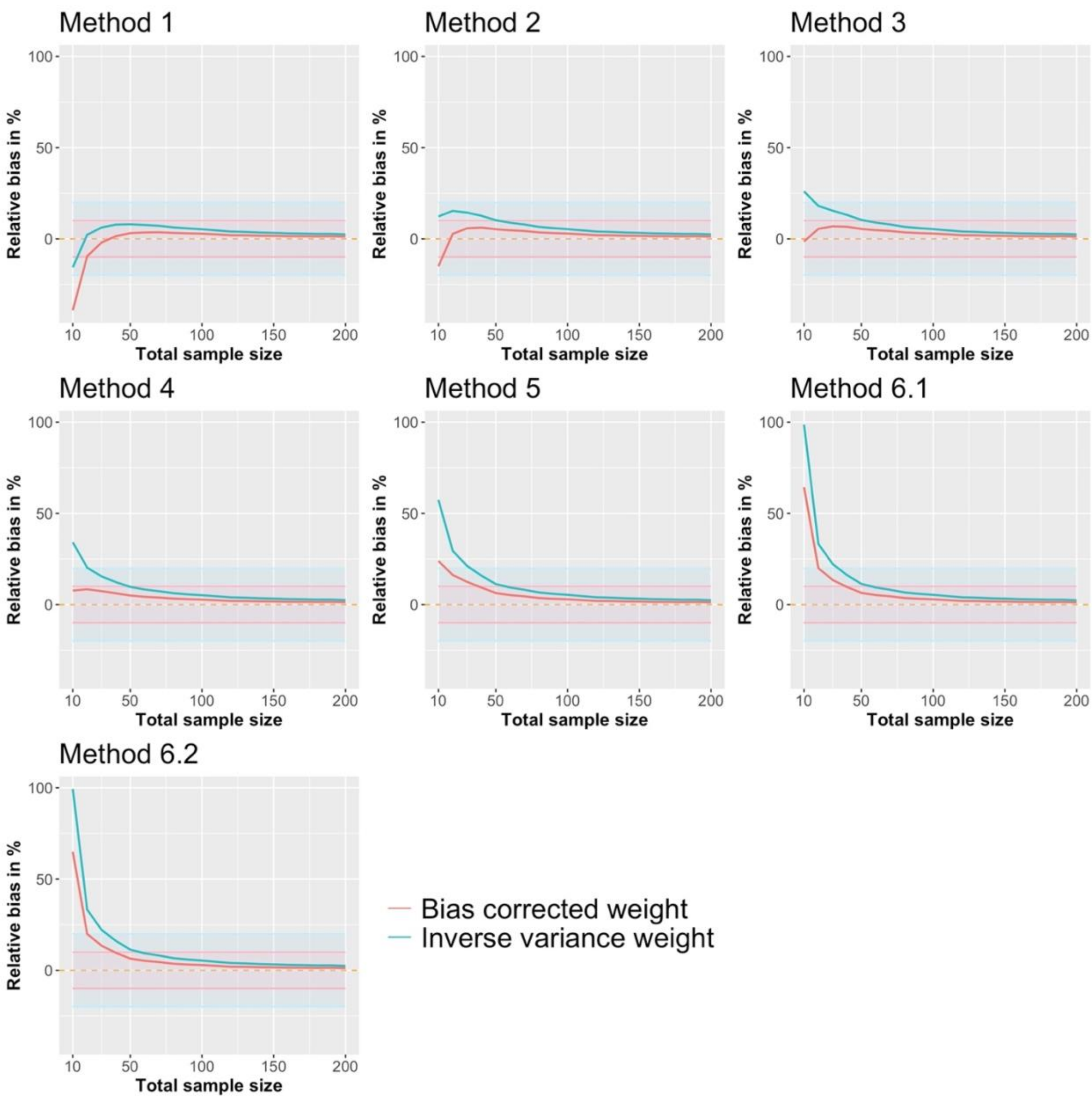

Figure A.1.5: Relative bias of various corrected weights and inverse variance weights for risk difference, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.2, \pi_2 = 0.4$

A.1.2. Log relative risk

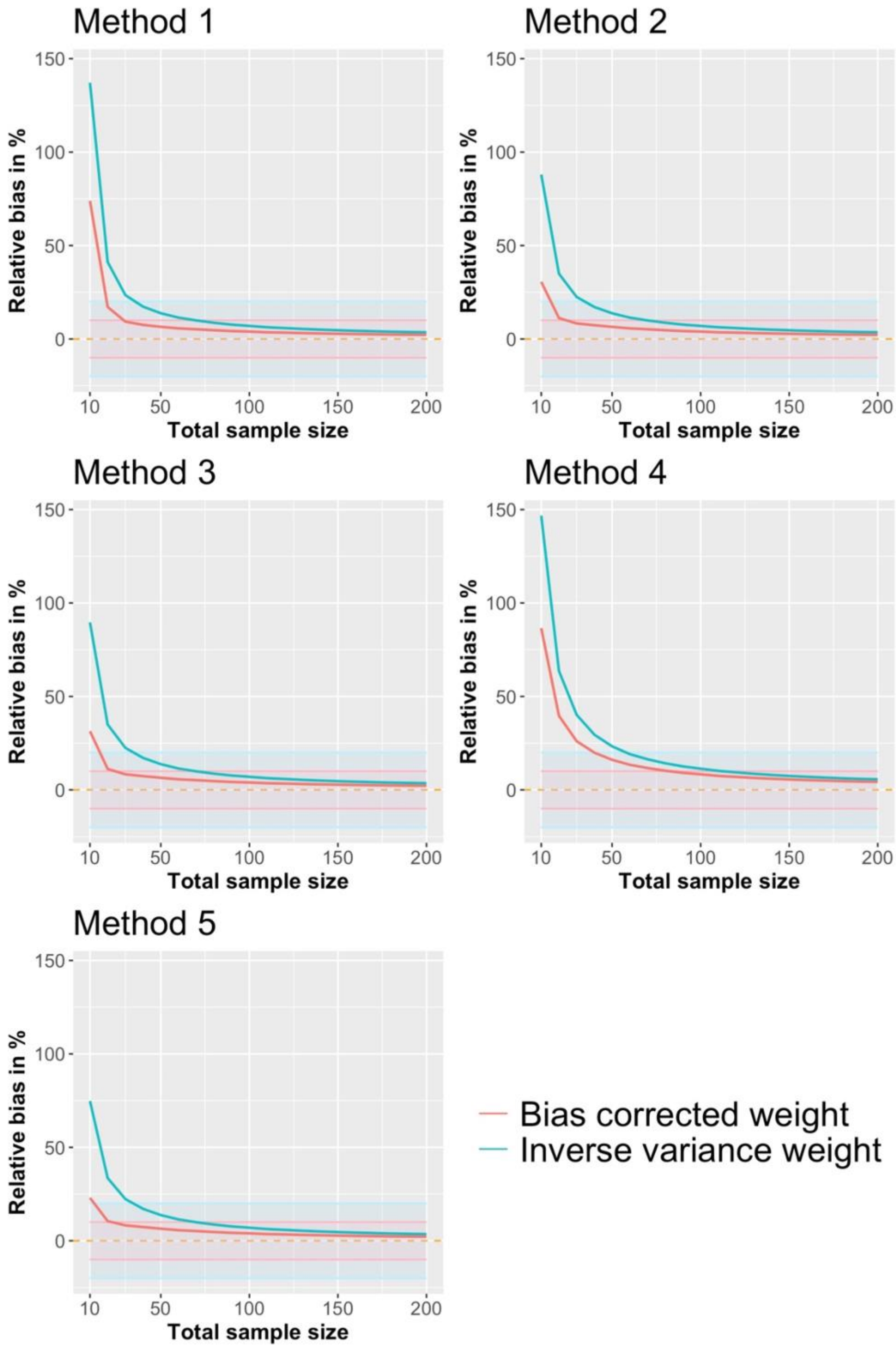

Figure A.1.6: Relative bias of various corrected weights and inverse variance weights log relative risk, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.3$

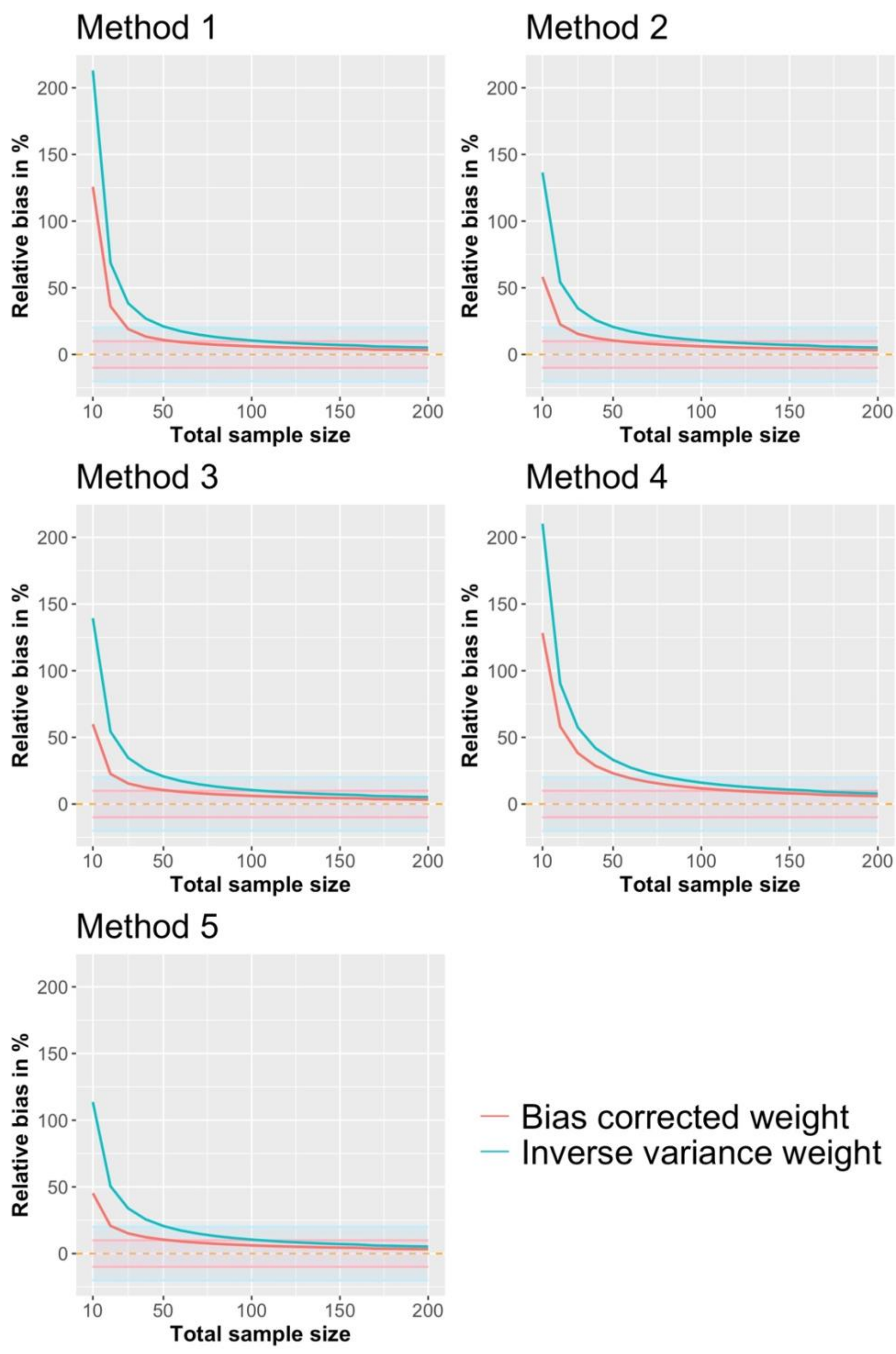

Figure A.1.7: Relative bias of various corrected weights and inverse variance weights log relative risk, varying sample sizes $n_1 = n_2$*, with unequal event rates* $\pi_1 = 0.4, \pi_2 = 0.2$

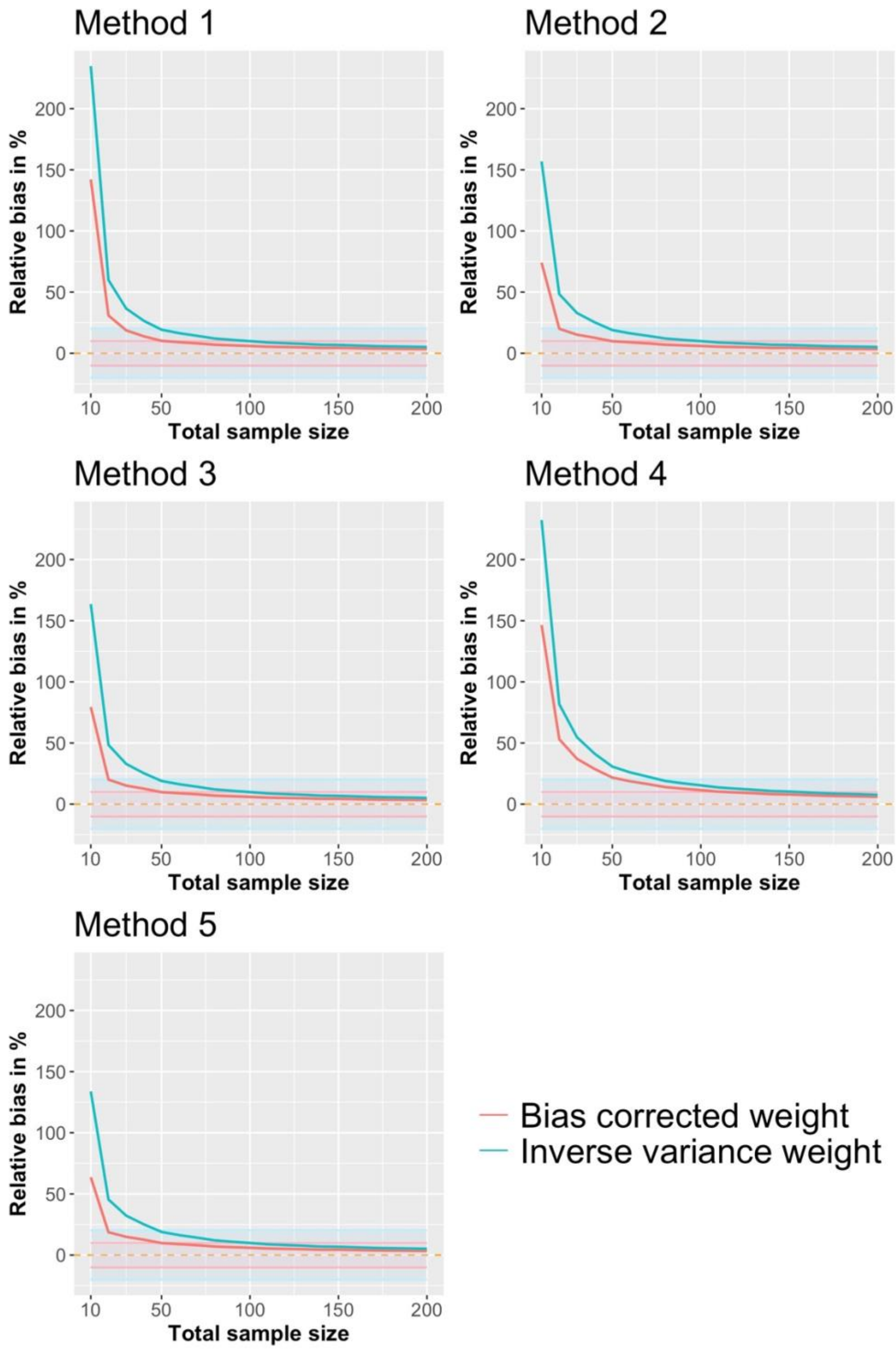

Figure A.1.8: Relative bias of various corrected weights and inverse variance weights log relative risk, varying sample sizes $2n_1 \approx n_2$, with equal event rates $\pi_1 = \pi_2 = 0.3$

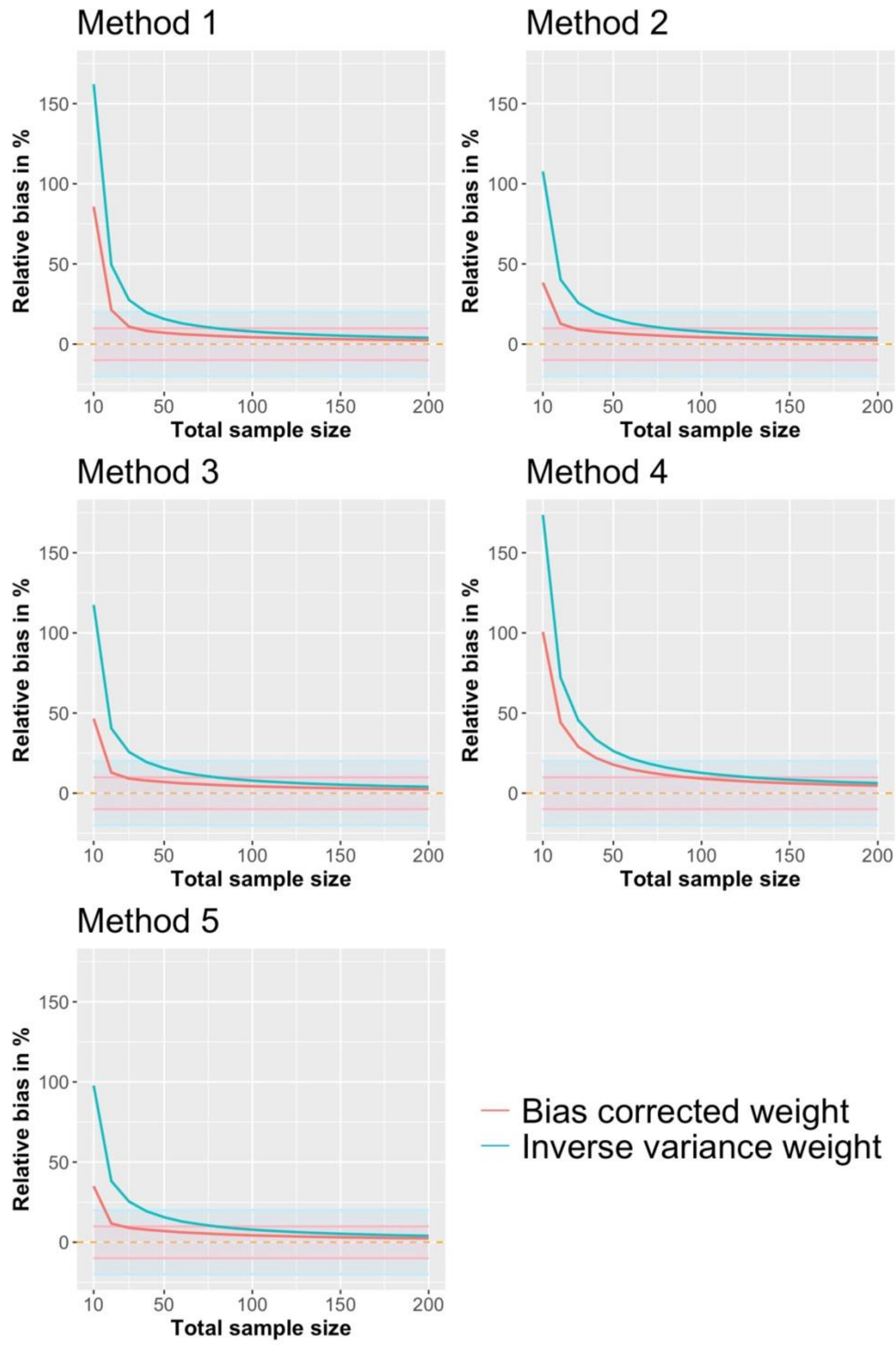

Figure A.1.9: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.4, \pi_2 = 0.2$

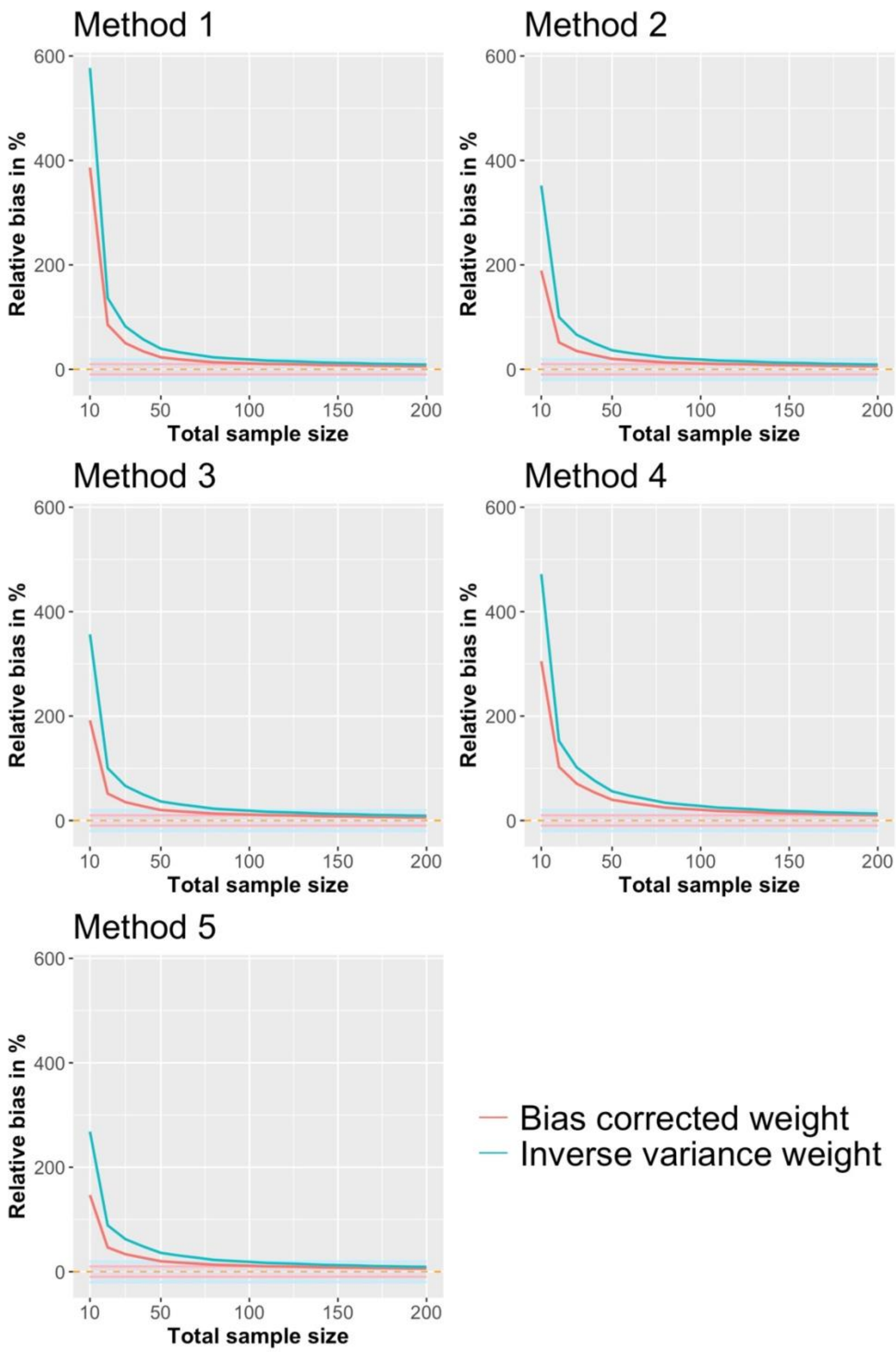

Figure A.1.10: Relative bias of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.2, \pi_2 = 0.4$

A.1.3. Log odds ratio

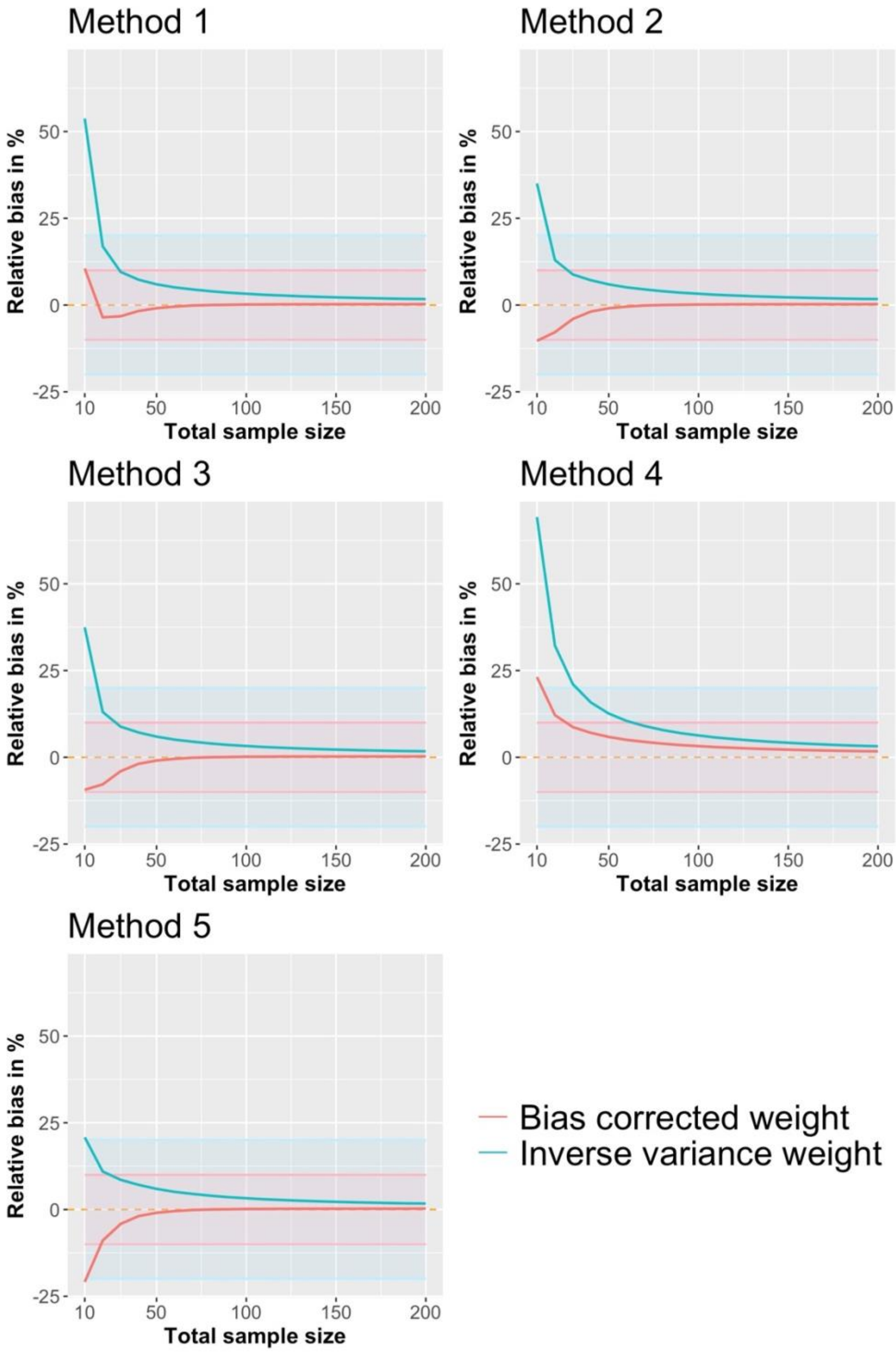

Figure A.1.11: Relative bias of various corrected weights and inverse variance weights odds ratio, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.3$

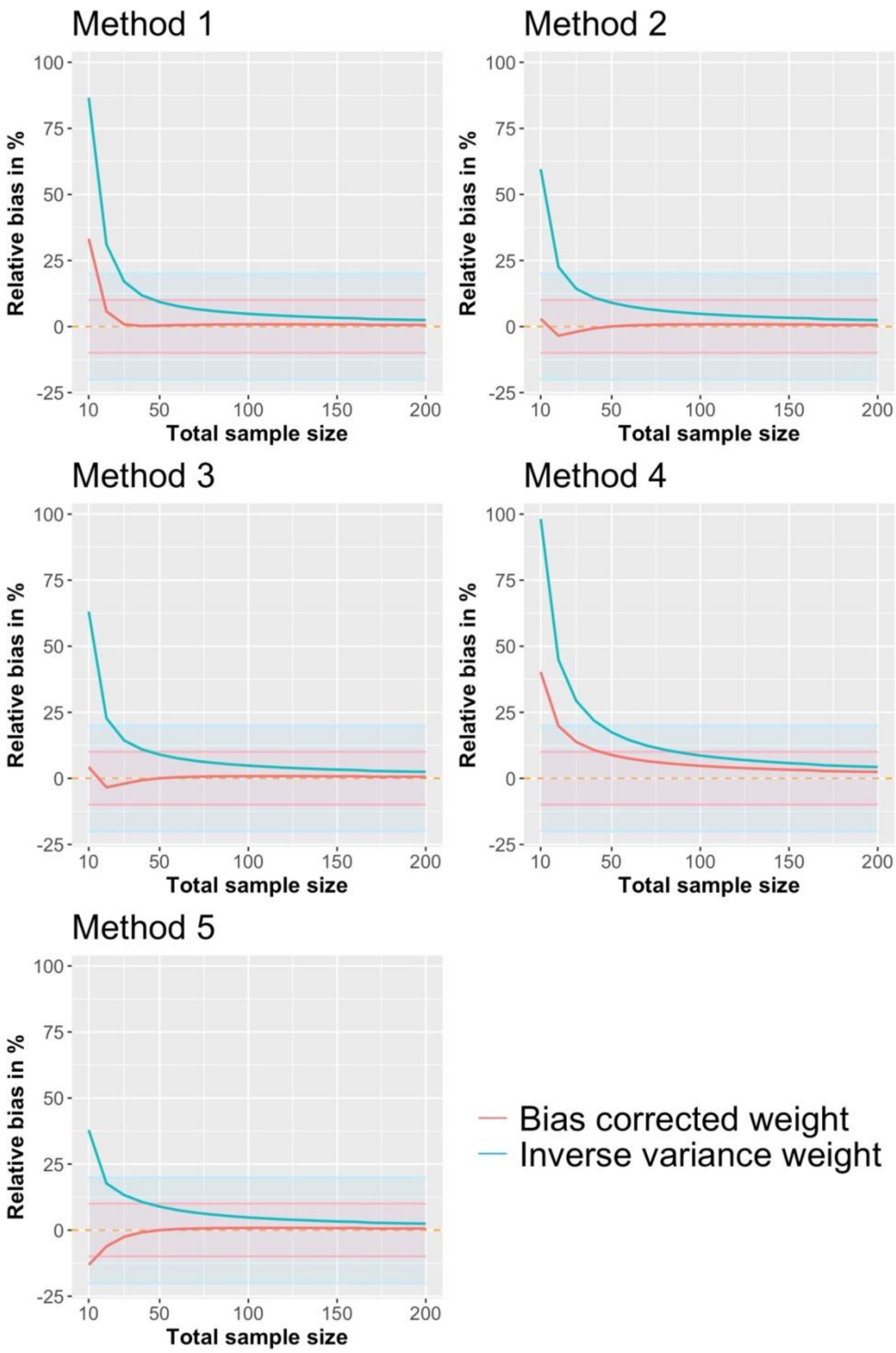

Figure A.1.12: Relative bias of various corrected weights and inverse variance weights log odds ratio, varying sample sizes $n_1 = n_2$, with unequal event rates $\pi_1 = 0.4, \pi_2 = 0.2$

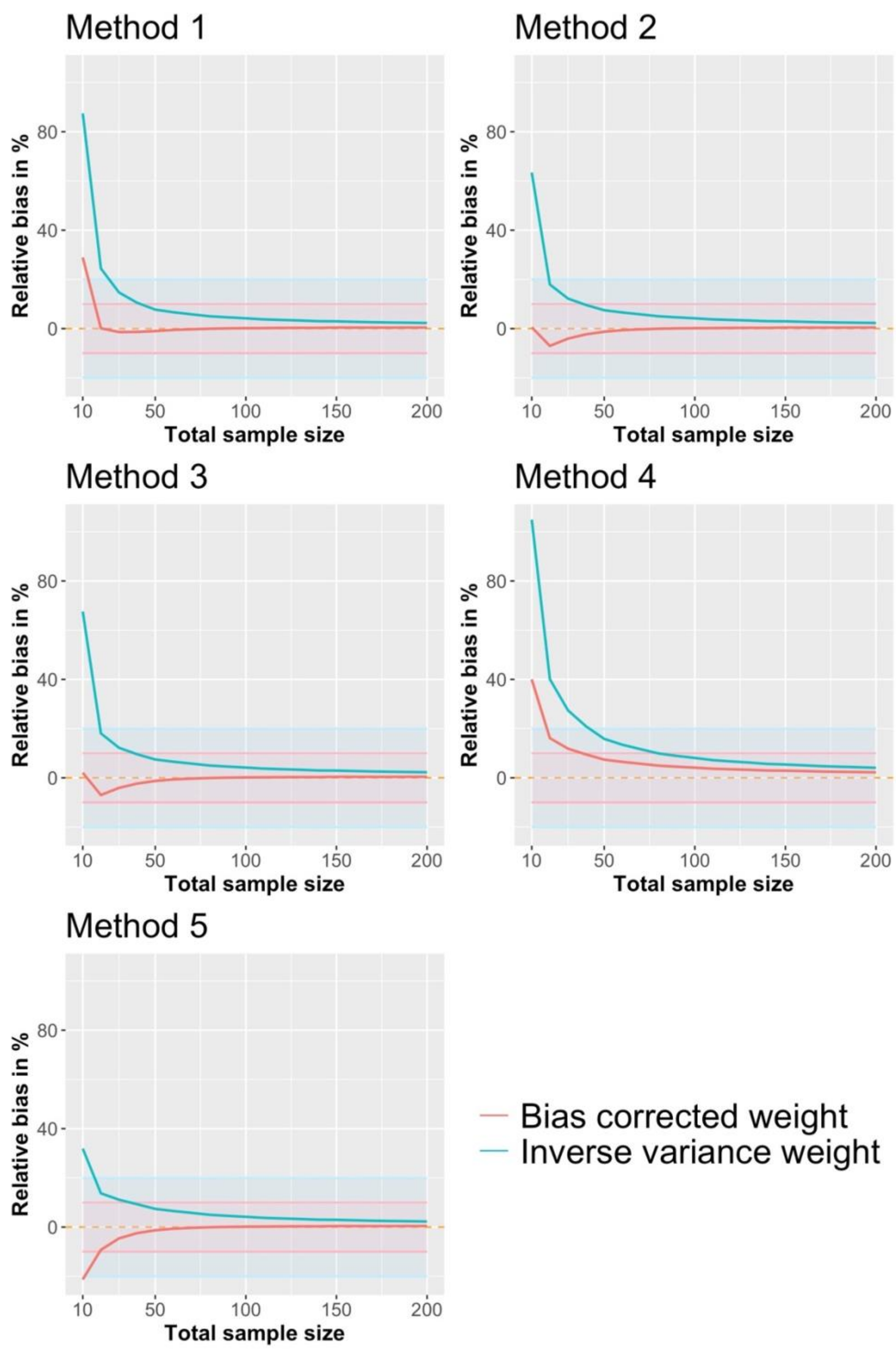

Figure A.1.13: Relative bias of various corrected weights and inverse variance weights log odds ratio, varying sample sizes $2n_1 \approx n_2$, with equal event rates $\pi_1 = \pi_2 = 0.3$

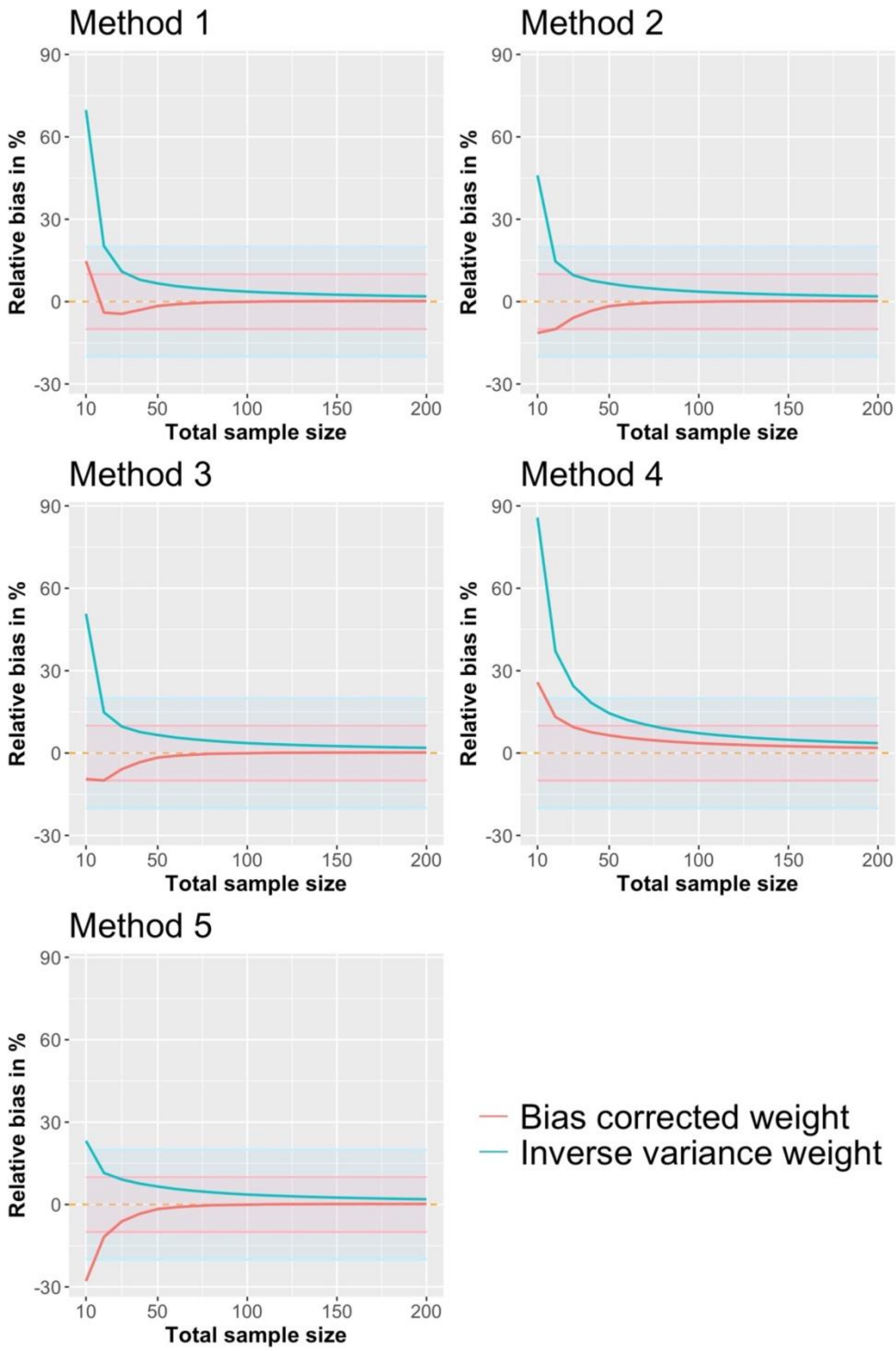

Figure A.1.14: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.4, \pi_2 = 0.2$

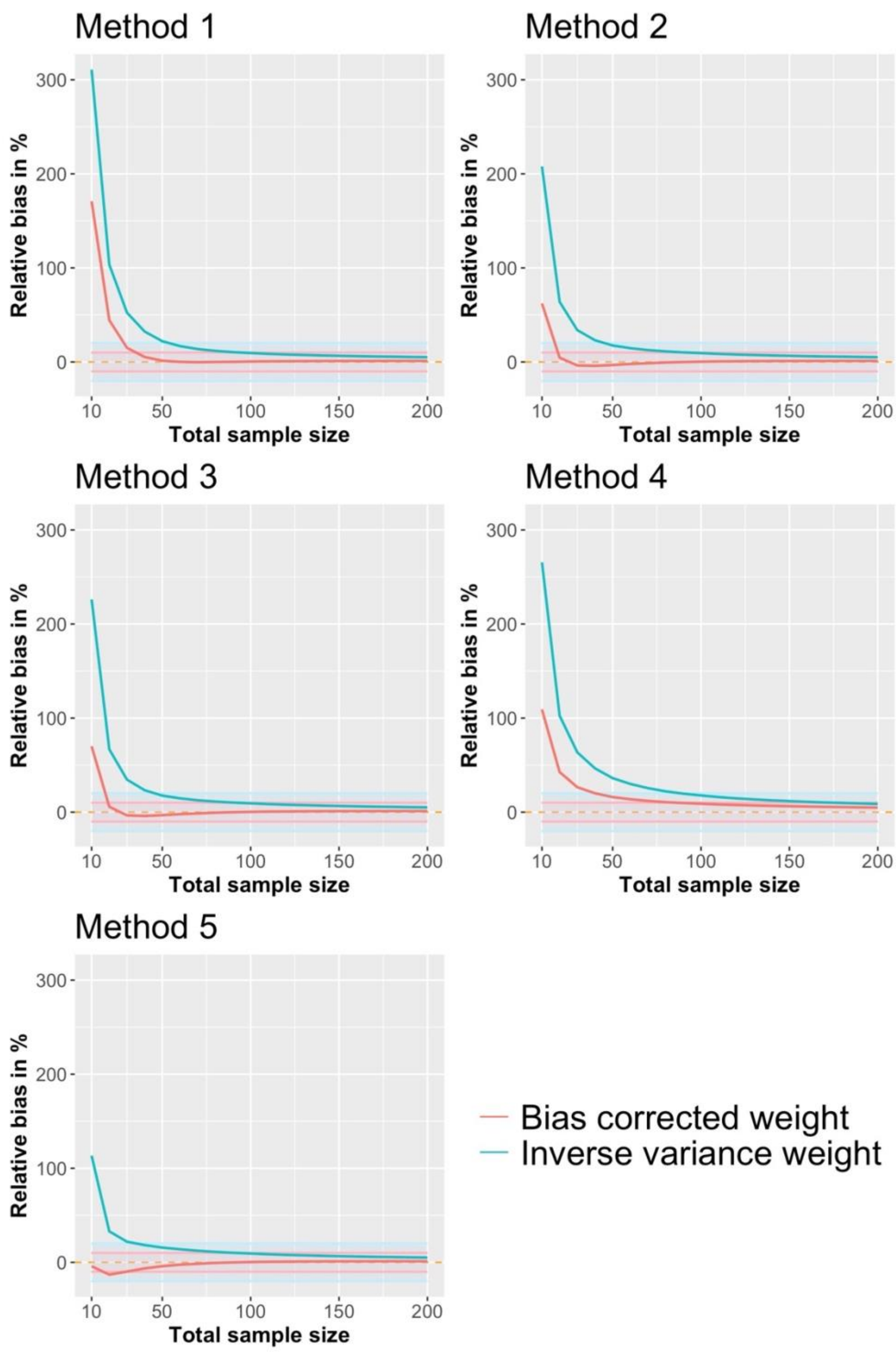

Figure A.1.0.15: Relative bias of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $2n_1 \approx n_2$, with unequal event rates $\pi_1 = 0.2, \pi_2 = 0.4$

A.2. Relative root mean squared error

A.2.1. Risk difference

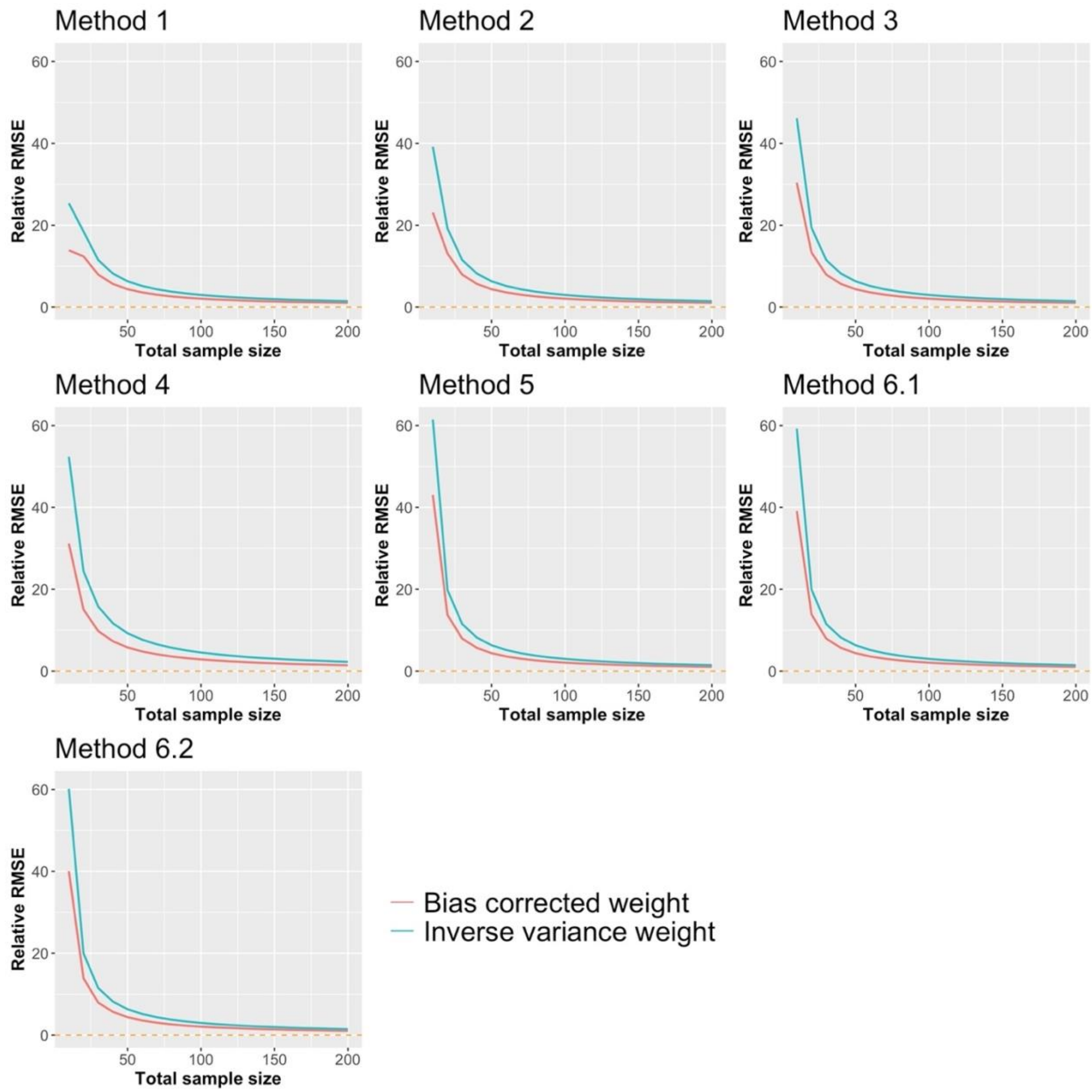

Figure A.2.1: Relative root mean squared error of various corrected weights and inverse variance weights for risk difference, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.5$

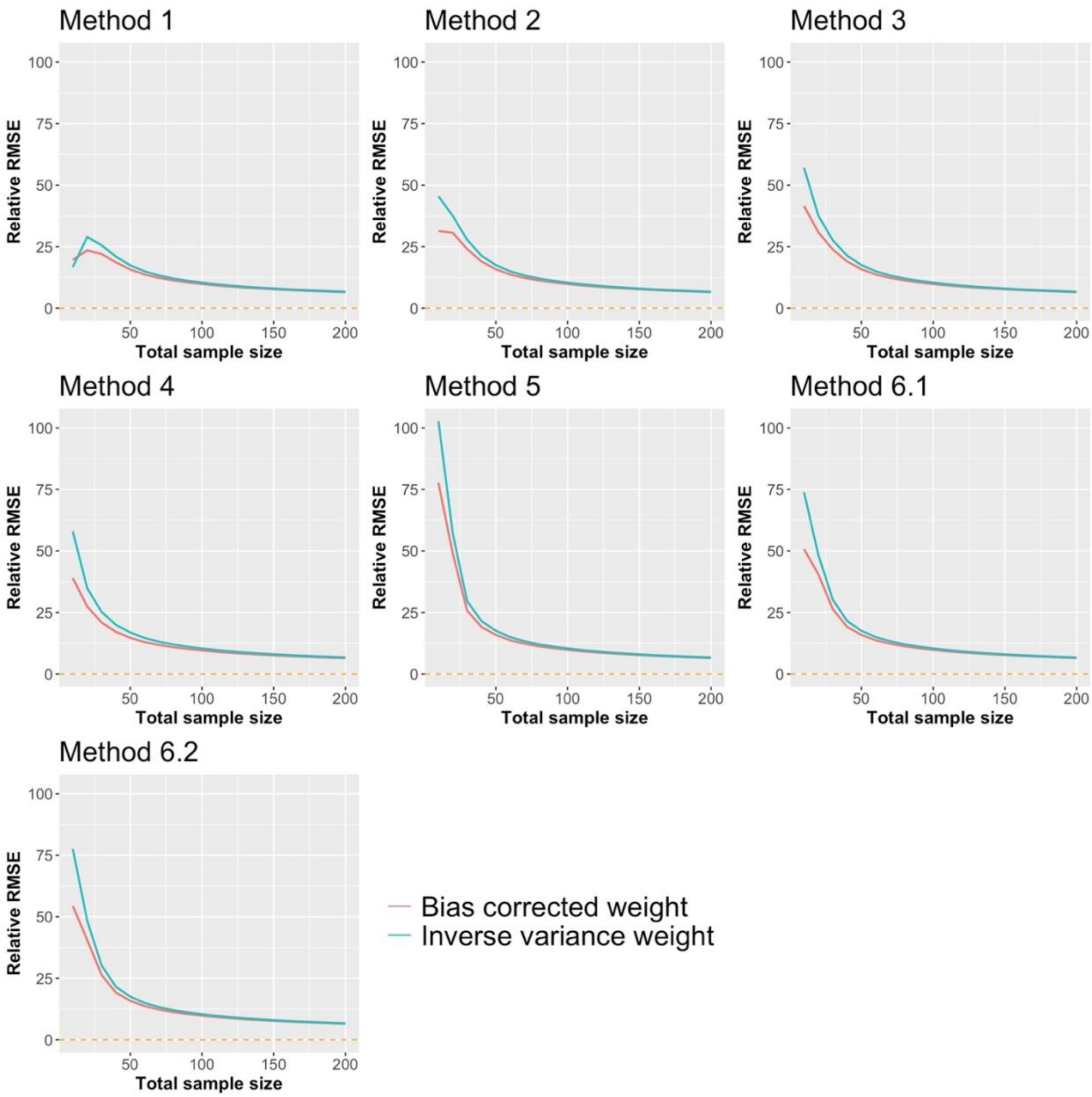

Figure A.2.2: Relative root mean squared error of various corrected weights and inverse variance weights for risk difference, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.3$

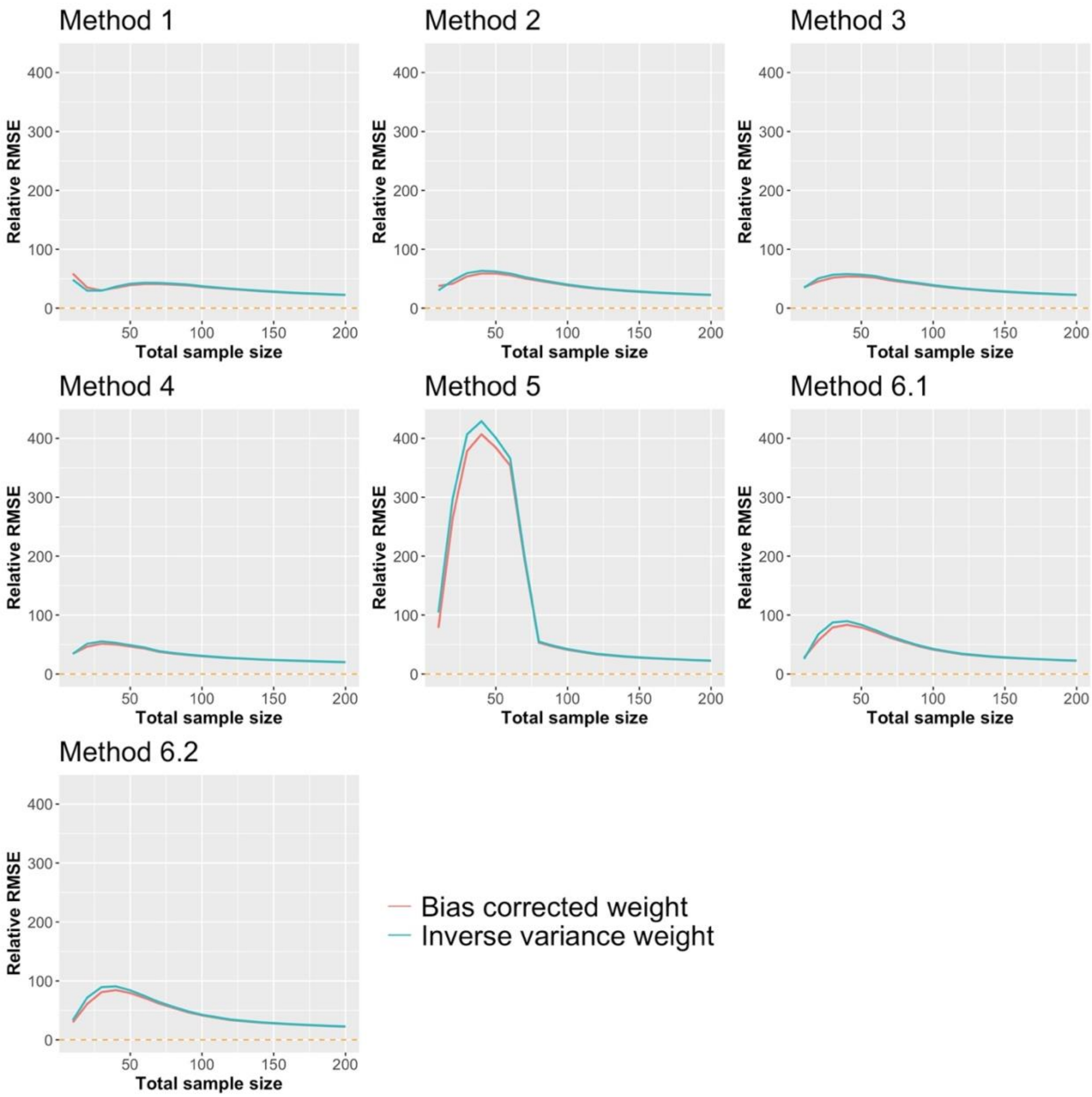

Figure A.2.3: Relative root mean squared error of various corrected weights and inverse variance weights for risk difference, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.1$

A.2.2. Log relative risk

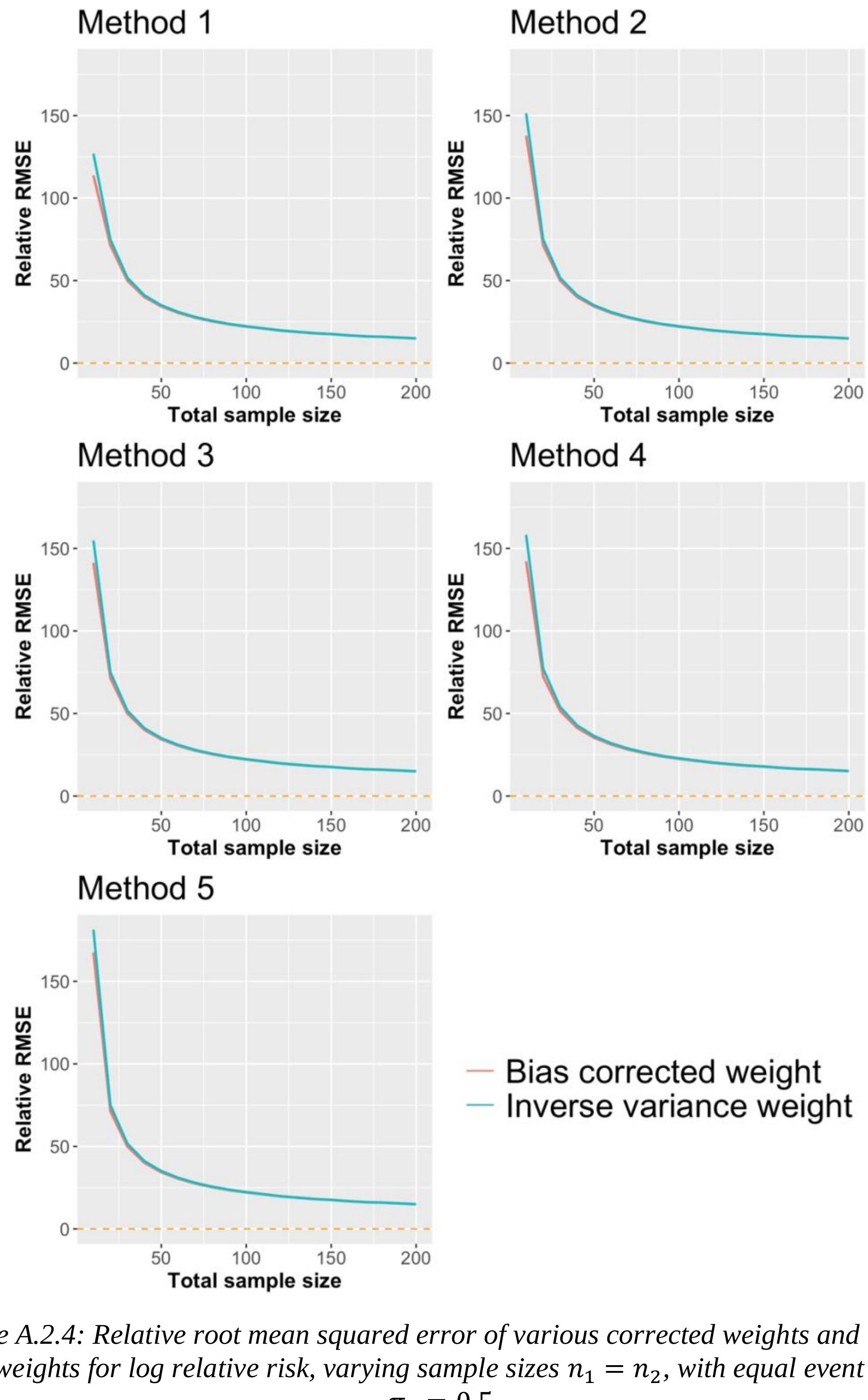

Figure A.2.4: Relative root mean squared error of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.5$

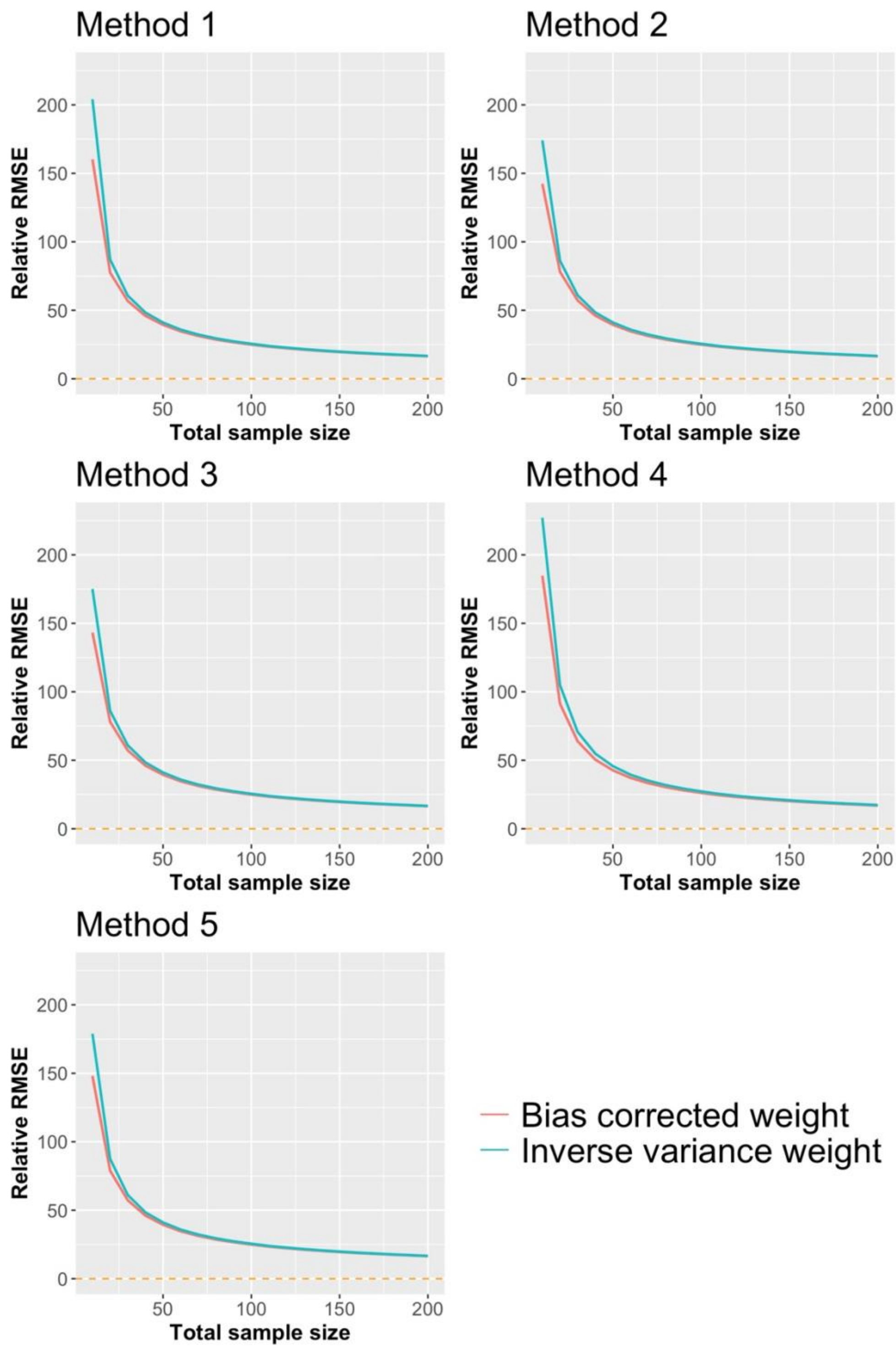

Figure A.2.5: Relative root mean squared error of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.3$

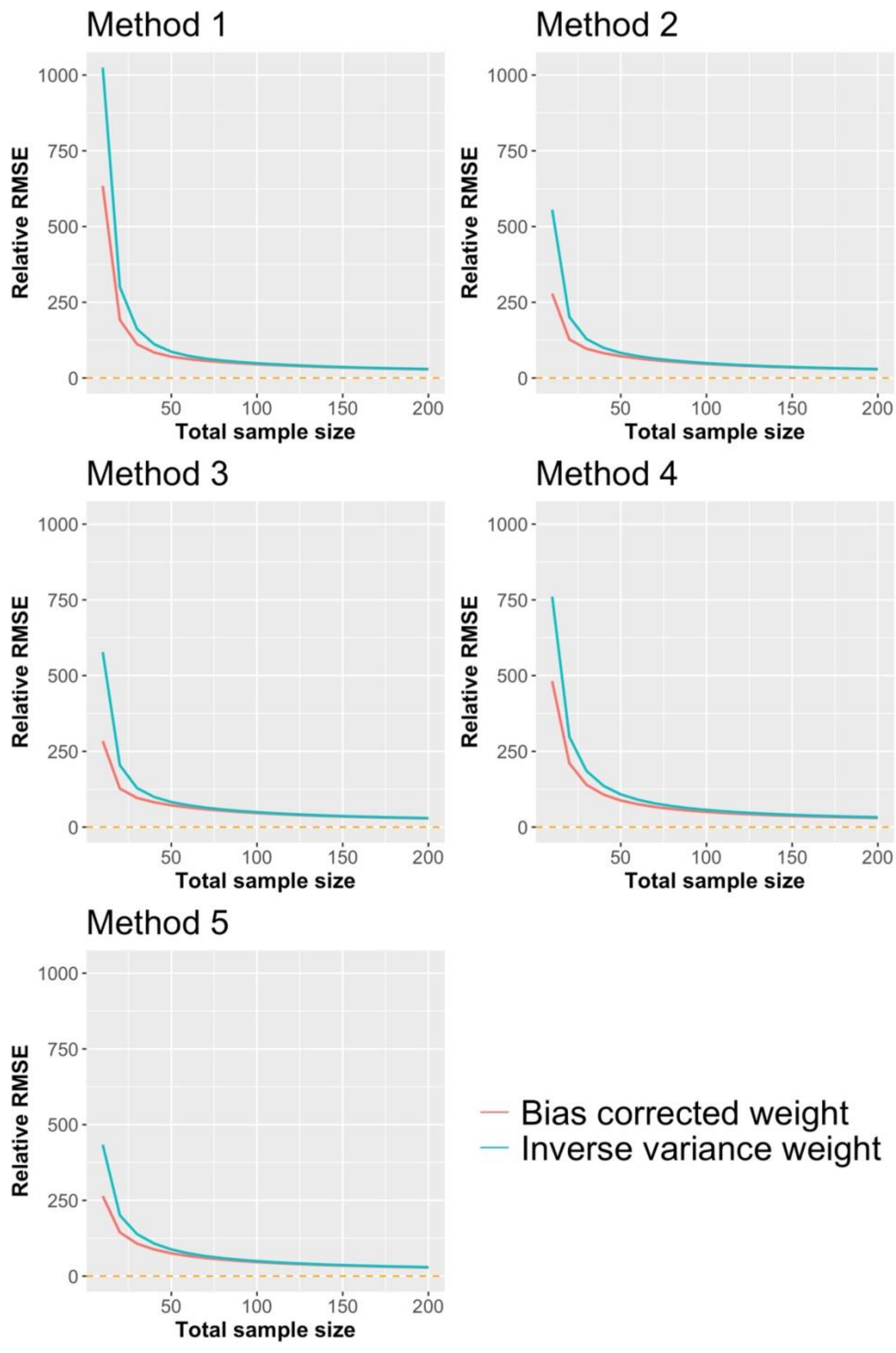

Figure A.2.6: Relative root mean squared error of various corrected weights and inverse variance weights for log relative risk, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.1$

A.2.3. Log odds ratio

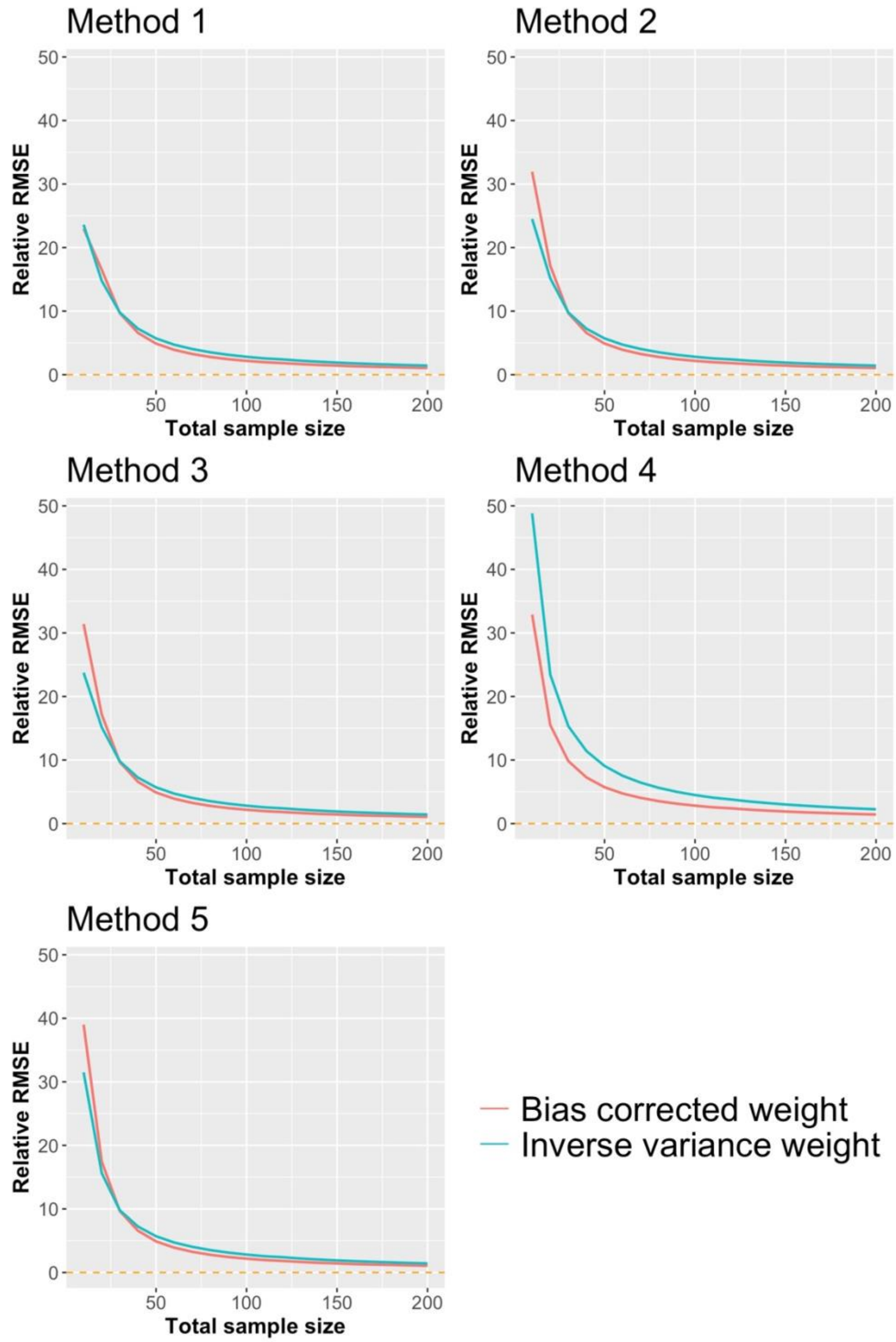

Figure A.2.7: Relative root mean squared error of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.5$

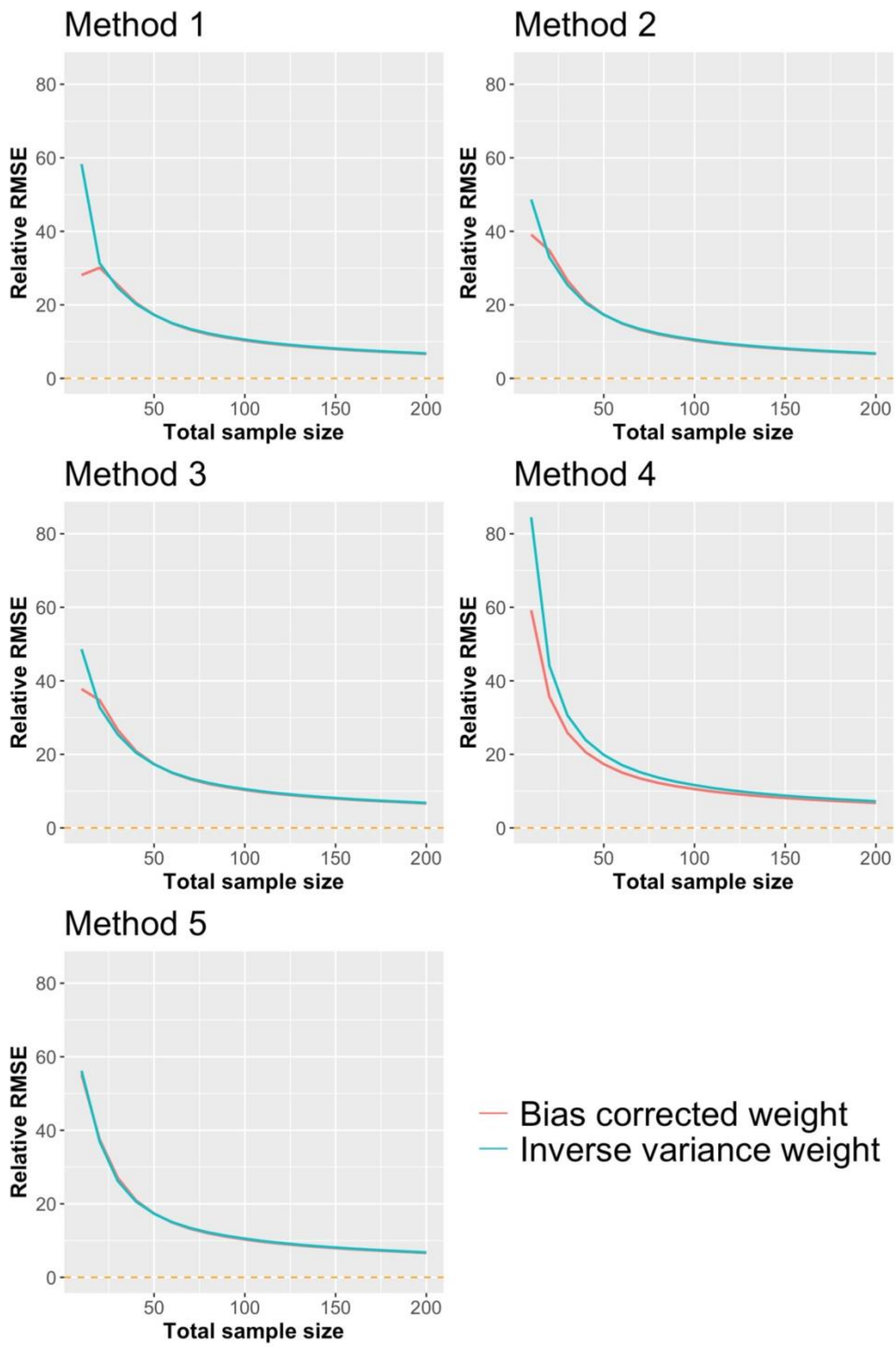

Figure A.2.8: Relative root mean squared error of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.3$

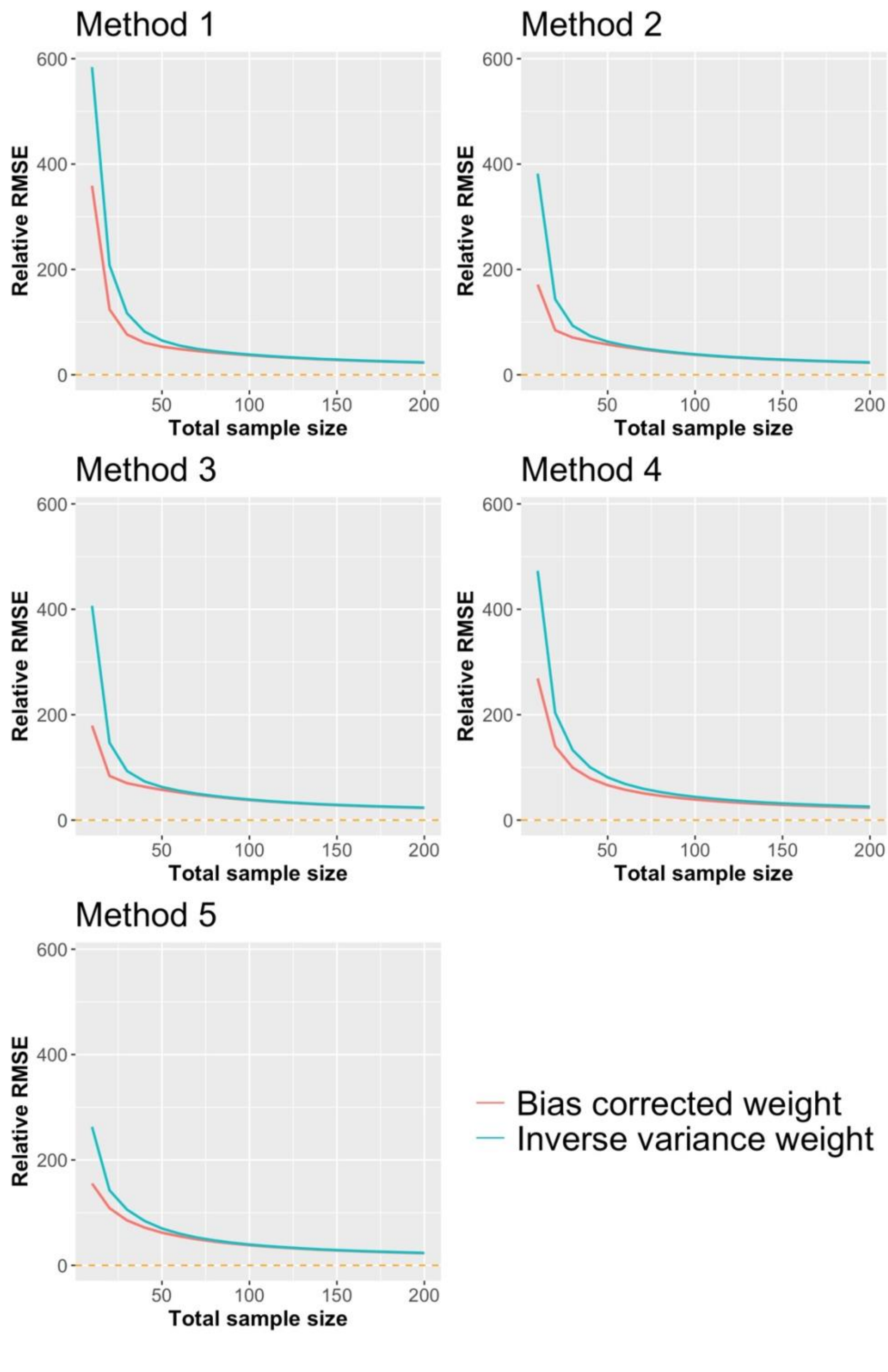

Figure A.2.9: Relative root mean squared error of various corrected weights and inverse variance weights for log odds ratio, varying sample sizes $n_1 = n_2$, with equal event rates $\pi_1 = \pi_2 = 0.1$

Appendix B

Table B.1: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	3	3	0.3	0.3	0.3	0.3	-0.0044	0.0584	-0.0045	0.0584	-0.0001	1.0002	-16.57%	-16.57%
3	3	3	3	3	0.3	0.3	0.3	0.3	-0.0060	0.0506	-0.0063	0.0507	-0.0003	1.0015	-27.71%	-27.57%
4	3	3	3	3	0.3	0.3	0.3	0.3	-0.0057	0.0460	-0.0057	0.0460	0.0000	1.0000	-34.29%	-34.29%
5	3	3	3	3	0.3	0.3	0.3	0.3	-0.0067	0.0494	-0.0069	0.0495	-0.0002	1.0008	-29.43%	-29.29%
6.1	3	3	3	3	0.3	0.3	0.3	0.3	0.0056	0.0485	0.0056	0.0485	0.0000	1.0002	-30.71%	-30.71%
6.2	3	3	3	3	0.3	0.3	0.3	0.3	0.0055	0.0470	0.0055	0.0471	-0.0001	1.0007	-32.86%	-32.71%
2	5	5	5	5	0.3	0.3	0.3	0.3	0.0105	0.0351	0.0105	0.0351	0.0000	1.0000	-16.43%	-16.43%
3	5	5	5	5	0.3	0.3	0.3	0.3	0.0107	0.0338	0.0107	0.0338	0.0000	1.0002	-19.52%	-19.52%
4	5	5	5	5	0.3	0.3	0.3	0.3	0.0093	0.0314	0.0093	0.0314	0.0000	1.0000	-25.24%	-25.24%
5	5	5	5	5	0.3	0.3	0.3	0.3	0.0110	0.0326	0.0110	0.0326	0.0000	1.0000	-22.38%	-22.38%
6.1	5	5	5	5	0.3	0.3	0.3	0.3	-0.0033	0.0316	-0.0033	0.0316	0.0000	1.0000	-24.76%	-24.76%
6.2	5	5	5	5	0.3	0.3	0.3	0.3	-0.0034	0.0315	-0.0034	0.0315	0.0000	1.0000	-25.00%	-25.00%
2	10	10	10	10	0.3	0.3	0.3	0.3	-0.0024	0.0185	-0.0024	0.0185	0.0000	1.0000	-11.90%	-11.90%
3	10	10	10	10	0.3	0.3	0.3	0.3	-0.0025	0.0184	-0.0025	0.0184	0.0000	1.0000	-12.38%	-12.38%
4	10	10	10	10	0.3	0.3	0.3	0.3	-0.0024	0.0178	-0.0024	0.0178	0.0000	1.0000	-15.24%	-15.24%
5	10	10	10	10	0.3	0.3	0.3	0.3	-0.0026	0.0183	-0.0026	0.0183	0.0000	1.0000	-12.86%	-12.86%
6.1	10	10	10	10	0.3	0.3	0.3	0.3	-0.0048	0.0183	-0.0048	0.0183	0.0000	1.0000	-12.86%	-12.86%
6.2	10	10	10	10	0.3	0.3	0.3	0.3	-0.0048	0.0183	-0.0048	0.0183	0.0000	1.0000	-12.86%	-12.86%
2	20	20	20	20	0.3	0.3	0.3	0.3	-0.0047	0.0099	-0.0047	0.0099	0.0000	1.0000	-5.71%	-5.71%
3	20	20	20	20	0.3	0.3	0.3	0.3	-0.0047	0.0099	-0.0047	0.0099	0.0000	1.0000	-5.71%	-5.71%
4	20	20	20	20	0.3	0.3	0.3	0.3	-0.0044	0.0096	-0.0044	0.0096	0.0000	1.0000	-8.57%	-8.57%
5	20	20	20	20	0.3	0.3	0.3	0.3	-0.0047	0.0098	-0.0047	0.0098	0.0000	1.0000	-6.67%	-6.67%
6.1	20	20	20	20	0.3	0.3	0.3	0.3	-0.0028	0.0099	-0.0028	0.0099	0.0000	1.0000	-5.71%	-5.71%
6.2	20	20	20	20	0.3	0.3	0.3	0.3	-0.0028	0.0099	-0.0028	0.0099	0.0000	1.0000	-5.71%	-5.71%

Table B.2: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	6	3	6	0.3	0.3	0.3	0.3	0.0310	0.0436	0.0280	0.0436	-0.0030	1.0007	-16.95%	-16.95%
3	3	6	3	6	0.3	0.3	0.3	0.3	0.0142	0.0403	0.0109	0.0404	-0.0034	1.0013	-23.24%	-23.05%
4	3	6	3	6	0.3	0.3	0.3	0.3	0.0141	0.0363	0.0127	0.0363	-0.0014	1.0001	-30.86%	-30.86%
5	3	6	3	6	0.3	0.3	0.3	0.3	-0.0192	0.0370	-0.0235	0.0370	-0.0044	1.0011	-29.52%	-29.52%
6.1	3	6	3	6	0.3	0.3	0.3	0.3	-0.0242	0.0340	-0.0305	0.0340	-0.0063	1.0021	-35.24%	-35.24%
6.2	3	6	3	6	0.3	0.3	0.3	0.3	-0.0246	0.0337	-0.0309	0.0337	-0.0063	1.0022	-35.81%	-35.81%
2	5	10	5	10	0.3	0.3	0.3	0.3	0.0006	0.0264	-0.0008	0.0264	-0.0014	1.0001	-16.19%	-16.19%
3	5	10	5	10	0.3	0.3	0.3	0.3	-0.0060	0.0259	-0.0076	0.0259	-0.0016	1.0002	-17.78%	-17.78%
4	5	10	5	10	0.3	0.3	0.3	0.3	0.0016	0.0242	0.0008	0.0242	-0.0008	1.0001	-23.17%	-23.17%
5	5	10	5	10	0.3	0.3	0.3	0.3	-0.0244	0.0244	-0.0264	0.0245	-0.0020	1.0003	-22.54%	-22.22%
6.1	5	10	5	10	0.3	0.3	0.3	0.3	-0.0240	0.0243	-0.0262	0.0243	-0.0021	1.0004	-22.86%	-22.86%
6.2	5	10	5	10	0.3	0.3	0.3	0.3	-0.0240	0.0243	-0.0262	0.0243	-0.0021	1.0004	-22.86%	-22.86%
2	10	20	10	20	0.3	0.3	0.3	0.3	-0.0083	0.0142	-0.0087	0.0142	-0.0004	1.0000	-9.84%	-9.84%
3	10	20	10	20	0.3	0.3	0.3	0.3	-0.0088	0.0142	-0.0092	0.0142	-0.0004	1.0000	-9.84%	-9.84%
4	10	20	10	20	0.3	0.3	0.3	0.3	0.0017	0.0138	0.0014	0.0138	-0.0003	1.0000	-12.38%	-12.38%
5	10	20	10	20	0.3	0.3	0.3	0.3	-0.0106	0.0141	-0.0110	0.0141	-0.0004	1.0000	-10.48%	-10.48%
6.1	10	20	10	20	0.3	0.3	0.3	0.3	-0.0200	0.0138	-0.0205	0.0138	-0.0005	1.0000	-12.38%	-12.38%
6.2	10	20	10	20	0.3	0.3	0.3	0.3	-0.0200	0.0138	-0.0205	0.0138	-0.0005	1.0000	-12.38%	-12.38%

Table B.3: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
3	3	3	5	5	0.3	0.3	0.3	0.3	-0.0077	0.0408	-0.0069	0.0409	0.0008	1.0039	-22.29%	-22.10%
4	3	3	5	5	0.3	0.3	0.3	0.3	-0.0071	0.0374	-0.0065	0.0375	0.0006	1.0026	-28.76%	-28.57%
5	3	3	5	5	0.3	0.3	0.3	0.3	-0.0078	0.0396	-0.0069	0.0398	0.0009	1.0042	-24.57%	-24.19%
6.1	3	3	5	5	0.3	0.3	0.3	0.3	-0.0003	0.0386	-0.0011	0.0389	-0.0008	1.0066	-26.48%	-25.90%
6.2	3	3	5	5	0.3	0.3	0.3	0.3	-0.0002	0.0380	-0.0010	0.0382	-0.0008	1.0063	-27.62%	-27.24%
2	3	3	6	6	0.3	0.3	0.3	0.3	0.0002	0.0391	-0.0004	0.0394	-0.0006	1.0084	-16.21%	-15.57%
3	3	3	6	6	0.3	0.3	0.3	0.3	0.0005	0.0365	0.0002	0.0367	-0.0003	1.0054	-21.79%	-21.36%
4	3	3	6	6	0.3	0.3	0.3	0.3	0.0008	0.0340	0.0003	0.0341	-0.0005	1.0039	-27.14%	-26.93%
5	3	3	6	6	0.3	0.3	0.3	0.3	0.0007	0.0356	0.0003	0.0358	-0.0004	1.0062	-23.71%	-23.29%
6.1	3	3	6	6	0.3	0.3	0.3	0.3	0.0000	0.0350	-0.0007	0.0354	-0.0007	1.0097	-25.00%	-24.14%
6.2	3	3	6	6	0.3	0.3	0.3	0.3	0.0005	0.0346	-0.0001	0.0349	-0.0006	1.0093	-25.86%	-25.21%
2	3	3	9	9	0.3	0.3	0.3	0.3	-0.0017	0.0306	-0.0008	0.0309	0.0008	1.0119	-12.57%	-11.71%
3	3	3	9	9	0.3	0.3	0.3	0.3	-0.0021	0.0292	-0.0015	0.0294	0.0006	1.0084	-16.57%	-16.00%
4	3	3	9	9	0.3	0.3	0.3	0.3	-0.0019	0.0275	-0.0013	0.0277	0.0006	1.0064	-21.43%	-20.86%
5	3	3	9	9	0.3	0.3	0.3	0.3	-0.0020	0.0288	-0.0013	0.0290	0.0007	1.0098	-17.71%	-17.14%
6.1	3	3	9	9	0.3	0.3	0.3	0.3	-0.0049	0.0287	-0.0035	0.0291	0.0014	1.0141	-18.00%	-16.86%
6.2	3	3	9	9	0.3	0.3	0.3	0.3	-0.0046	0.0283	-0.0031	0.0287	0.0015	1.0136	-19.14%	-18.00%
2	3	3	15	15	0.3	0.3	0.3	0.3	-0.0010	0.0212	-0.0011	0.0215	-0.0001	1.0120	-9.14%	-7.86%
3	3	3	15	15	0.3	0.3	0.3	0.3	-0.0010	0.0205	-0.0011	0.0207	-0.0001	1.0093	-12.14%	-11.29%
4	3	3	15	15	0.3	0.3	0.3	0.3	-0.0009	0.0197	-0.0010	0.0198	-0.0001	1.0075	-15.57%	-15.14%
5	3	3	15	15	0.3	0.3	0.3	0.3	-0.0011	0.0203	-0.0012	0.0205	-0.0001	1.0109	-13.00%	-12.14%
6.1	3	3	15	15	0.3	0.3	0.3	0.3	-0.0003	0.0204	-0.0006	0.0207	-0.0003	1.0147	-12.57%	-11.29%
6.2	3	3	15	15	0.3	0.3	0.3	0.3	-0.0004	0.0201	-0.0007	0.0204	-0.0003	1.0142	-13.86%	-12.57%

Table B.4: estimated summary effects and variances of summary effects for risk difference

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	**Mean of** sTE_{IVW}	**Mean of** $Var(sTE_{IVW})$	**Mean of** sTE_{BC}	**Mean of** $Var(sTE_{BC})$	**Mean of** D	**Mean of** VR	**Relative bias of** $Var(sTE_{IVW})$	**Relative bias of** $Var(sTE_{BC})$
2	5	5	10	10	0.3	0.3	0.3	0.3	-0.0070	0.0241	-0.0073	0.0242	-0.0003	1.0028	-13.93%	-13.57%
3	5	5	10	10	0.3	0.3	0.3	0.3	-0.0062	0.0238	-0.0065	0.0238	-0.0002	1.0024	-15.00%	-15.00%
4	5	5	10	10	0.3	0.3	0.3	0.3	-0.0055	0.0226	-0.0057	0.0227	-0.0002	1.0017	-19.29%	-18.93%
5	5	5	10	10	0.3	0.3	0.3	0.3	-0.0058	0.0233	-0.0060	0.0234	-0.0003	1.0027	-16.79%	-16.43%
6.1	5	5	10	10	0.3	0.3	0.3	0.3	-0.0055	0.0232	-0.0058	0.0233	-0.0003	1.0030	-17.14%	-16.79%
6.2	5	5	10	10	0.3	0.3	0.3	0.3	-0.0054	0.0231	-0.0057	0.0232	-0.0003	1.0029	-17.50%	-17.14%
2	5	5	15	15	0.3	0.3	0.3	0.3	0.0015	0.0189	0.0013	0.0189	-0.0002	1.0042	-10.00%	-10.00%
3	5	5	15	15	0.3	0.3	0.3	0.3	0.0017	0.0186	0.0015	0.0187	-0.0002	1.0037	-11.43%	-10.95%
4	5	5	15	15	0.3	0.3	0.3	0.3	0.0019	0.0179	0.0017	0.0179	-0.0002	1.0027	-14.76%	-14.76%
5	5	5	15	15	0.3	0.3	0.3	0.3	0.0024	0.0183	0.0021	0.0184	-0.0003	1.0041	-12.86%	-12.38%
6.1	5	5	15	15	0.3	0.3	0.3	0.3	0.0021	0.0183	0.0018	0.0184	-0.0003	1.0044	-12.86%	-12.38%
6.2	5	5	15	15	0.3	0.3	0.3	0.3	0.0022	0.0183	0.0019	0.0184	-0.0003	1.0044	-12.86%	-12.38%
2	5	5	20	20	0.3	0.3	0.3	0.3	-0.0038	0.0153	-0.0037	0.0154	0.0001	1.0044	-8.93%	-8.33%
3	5	5	20	20	0.3	0.3	0.3	0.3	-0.0036	0.0152	-0.0036	0.0152	0.0001	1.0040	-9.52%	-9.52%
4	5	5	20	20	0.3	0.3	0.3	0.3	-0.0033	0.0147	-0.0033	0.0147	0.0000	1.0030	-12.50%	-12.50%
5	5	5	20	20	0.3	0.3	0.3	0.3	-0.0034	0.0150	-0.0034	0.0150	0.0000	1.0044	-10.71%	-10.71%
6.1	5	5	20	20	0.3	0.3	0.3	0.3	-0.0034	0.0149	-0.0033	0.0150	0.0000	1.0048	-11.31%	-10.71%
6.2	5	5	20	20	0.3	0.3	0.3	0.3	-0.0033	0.0149	-0.0033	0.0150	0.0000	1.0048	-11.31%	-10.71%
2	10	10	20	20	0.3	0.3	0.3	0.3	0.0032	0.0128	0.0032	0.0128	0.0000	1.0006	-8.57%	-8.57%
3	10	10	20	20	0.3	0.3	0.3	0.3	0.0031	0.0127	0.0031	0.0128	0.0000	1.0006	-9.29%	-8.57%
4	10	10	20	20	0.3	0.3	0.3	0.3	0.0028	0.0124	0.0028	0.0124	0.0000	1.0005	-11.43%	-11.43%
5	10	10	20	20	0.3	0.3	0.3	0.3	0.0029	0.0127	0.0030	0.0127	0.0000	1.0006	-9.29%	-9.29%
6.1	10	10	20	20	0.3	0.3	0.3	0.3	0.0030	0.0128	0.0030	0.0128	0.0000	1.0006	-8.57%	-8.57%
6.2	10	10	20	20	0.3	0.3	0.3	0.3	0.0030	0.0128	0.0030	0.0128	0.0000	1.0006	-8.57%	-8.57%

Table B.5: simulation results of estimated summary effects and variances of summary effects for log relative risk

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	3	3	0.3	0.3	0.3	0.3	-0.0108	0.8000	-0.0095	2.3774	0.0013	2.7298	-58.86%	22.27%
3	3	3	3	3	0.3	0.3	0.3	0.3	-0.0162	0.7724	-0.0150	2.3069	0.0012	2.7285	-60.28%	18.64%
4	3	3	3	3	0.3	0.3	0.3	0.3	-0.0165	0.6606	-0.0153	1.8896	0.0012	2.4469	-66.03%	-2.82%
5	3	3	3	3	0.3	0.3	0.3	0.3	-0.0200	0.9906	-0.0180	3.8213	0.0020	3.1796	-49.05%	96.52%
2	5	5	5	5	0.3	0.3	0.3	0.3	0.0346	0.6001	0.0348	1.5011	0.0002	2.2705	-32.32%	69.30%
3	5	5	5	5	0.3	0.3	0.3	0.3	0.0372	0.5913	0.0376	1.4833	0.0004	2.2797	-33.31%	67.29%
4	5	5	5	5	0.3	0.3	0.3	0.3	0.0320	0.4564	0.0323	1.0272	0.0003	1.9664	-48.53%	15.85%
5	5	5	5	5	0.3	0.3	0.3	0.3	0.0452	0.7921	0.0444	3.1342	-0.0007	2.6383	-10.67%	253.48%
2	10	10	10	10	0.3	0.3	0.3	0.3	-0.0088	0.2993	-0.0085	0.5174	0.0003	1.6109	-11.54%	52.93%
3	10	10	10	10	0.3	0.3	0.3	0.3	-0.0090	0.2989	-0.0086	0.5169	0.0004	1.6117	-11.66%	52.78%
4	10	10	10	10	0.3	0.3	0.3	0.3	-0.0072	0.2372	-0.0071	0.3696	0.0001	1.4861	-29.89%	9.24%
5	10	10	10	10	0.3	0.3	0.3	0.3	-0.0080	0.3177	-0.0081	0.6824	-0.0001	1.6219	-6.10%	101.69%
2	20	20	20	20	0.3	0.3	0.3	0.3	-0.0165	0.1320	-0.0161	0.1700	0.0005	1.2667	-7.64%	18.95%
3	20	20	20	20	0.3	0.3	0.3	0.3	-0.0166	0.1320	-0.0161	0.1700	0.0005	1.2667	-7.64%	18.95%
4	20	20	20	20	0.3	0.3	0.3	0.3	-0.0152	0.1178	-0.0148	0.1478	0.0003	1.2396	-17.57%	3.42%
5	20	20	20	20	0.3	0.3	0.3	0.3	-0.0167	0.1321	-0.0161	0.1700	0.0006	1.2663	-7.57%	18.95%
2	3	6	3	6	0.3	0.3	0.3	0.3	0.1566	0.6754	0.1760	1.8348	0.0194	2.4603	-48.54%	39.79%
3	3	6	3	6	0.3	0.3	0.3	0.3	0.1061	0.6577	0.1326	1.7922	0.0265	2.4661	-49.89%	36.55%
4	3	6	3	6	0.3	0.3	0.3	0.3	0.0989	0.5371	0.1258	1.3620	0.0269	2.1649	-59.08%	3.77%
5	3	6	3	6	0.3	0.3	0.3	0.3	0.0649	1.0364	0.1484	5.4529	0.0835	3.2500	-21.04%	315.46%
2	5	10	5	10	0.3	0.3	0.3	0.3	0.0638	0.4523	0.0974	0.9985	0.0336	1.9808	-26.16%	63.02%
3	5	10	5	10	0.3	0.3	0.3	0.3	0.0477	0.4493	0.0854	0.9935	0.0377	1.9846	-26.64%	62.20%
4	5	10	5	10	0.3	0.3	0.3	0.3	0.0715	0.3486	0.1054	0.6838	0.0339	1.7431	-43.09%	11.64%
5	5	10	5	10	0.3	0.3	0.3	0.3	0.0640	0.6303	0.1191	3.2517	0.0551	2.2961	2.91%	430.89%
2	10	20	10	20	0.3	0.3	0.3	0.3	0.0308	0.2076	0.0554	0.3181	0.0246	1.4470	-13.72%	32.20%
3	10	20	10	20	0.3	0.3	0.3	0.3	0.0299	0.2076	0.0549	0.3181	0.0249	1.4470	-13.72%	32.20%
4	10	20	10	20	0.3	0.3	0.3	0.3	0.0511	0.1724	0.0678	0.2446	0.0167	1.3710	-28.35%	1.65%
5	10	20	10	20	0.3	0.3	0.3	0.3	0.0407	0.2123	0.0628	0.3236	0.0221	1.4396	-11.77%	34.48%

Table B.6: estimated summary effects and variances of summary effects for log relative risk

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	5	5	0.3	0.3	0.3	0.3	-0.0260	0.6896	-0.0236	1.8903	0.0025	2.4679	-43.38%	55.20%
3	3	3	5	5	0.3	0.3	0.3	0.3	-0.0285	0.6721	-0.0254	1.8478	0.0030	2.4719	-44.82%	51.71%
4	3	3	5	5	0.3	0.3	0.3	0.3	-0.0239	0.5495	-0.0208	1.4130	0.0031	2.1771	-54.88%	16.01%
5	3	3	5	5	0.3	0.3	0.3	0.3	-0.0332	0.8987	-0.0310	3.4978	0.0022	2.8836	-26.21%	187.19%
2	3	3	6	6	0.3	0.3	0.3	0.3	-0.0022	0.6498	-0.0055	1.7157	-0.0033	2.3657	-35.55%	70.17%
3	3	3	6	6	0.3	0.3	0.3	0.3	-0.0035	0.6326	-0.0067	1.6734	-0.0032	2.3689	-37.26%	65.97%
4	3	3	6	6	0.3	0.3	0.3	0.3	-0.0037	0.5142	-0.0068	1.2594	-0.0031	2.0844	-49.00%	24.91%
5	3	3	6	6	0.3	0.3	0.3	0.3	-0.0029	0.8439	-0.0043	3.1977	-0.0013	2.7228	-16.30%	217.16%
2	3	3	9	9	0.3	0.3	0.3	0.3	-0.0016	0.4792	0.0013	1.0592	0.0029	1.9707	-26.07%	63.42%
3	3	3	9	9	0.3	0.3	0.3	0.3	-0.0017	0.4719	0.0013	1.0449	0.0030	1.9729	-27.19%	61.21%
4	3	3	9	9	0.3	0.3	0.3	0.3	-0.0023	0.3769	0.0001	0.7479	0.0024	1.7566	-41.85%	15.39%
5	3	3	9	9	0.3	0.3	0.3	0.3	-0.0036	0.5576	-0.0012	1.5505	0.0024	2.0636	-13.97%	139.22%
2	3	3	15	15	0.3	0.3	0.3	0.3	-0.0051	0.3097	-0.0062	0.5300	-0.0011	1.5742	-15.46%	44.67%
3	3	3	15	15	0.3	0.3	0.3	0.3	-0.0046	0.3070	-0.0059	0.5259	-0.0012	1.5757	-16.20%	43.55%
4	3	3	15	15	0.3	0.3	0.3	0.3	-0.0039	0.2573	-0.0050	0.4045	-0.0011	1.4772	-29.77%	10.42%
5	3	3	15	15	0.3	0.3	0.3	0.3	-0.0048	0.3275	-0.0057	0.6014	-0.0010	1.5745	-10.60%	64.16%
2	5	5	10	10	0.3	0.3	0.3	0.3	-0.0308	0.4121	-0.0354	0.8357	-0.0046	1.8314	-15.86%	70.63%
3	5	5	10	10	0.3	0.3	0.3	0.3	-0.0297	0.4089	-0.0349	0.8301	-0.0053	1.8357	-16.51%	69.49%
4	5	5	10	10	0.3	0.3	0.3	0.3	-0.0256	0.3169	-0.0302	0.5626	-0.0046	1.6353	-35.30%	14.87%
5	5	5	10	10	0.3	0.3	0.3	0.3	-0.0393	0.4686	-0.0487	1.2116	-0.0094	1.8778	-4.32%	147.38%
2	5	5	15	15	0.3	0.3	0.3	0.3	0.0038	0.2910	0.0026	0.4886	-0.0012	1.5573	-11.64%	48.36%
3	5	5	15	15	0.3	0.3	0.3	0.3	0.0042	0.2899	0.0027	0.4872	-0.0015	1.5593	-11.97%	47.94%
4	5	5	15	15	0.3	0.3	0.3	0.3	0.0049	0.2377	0.0033	0.3675	-0.0017	1.4609	-27.82%	11.59%
5	5	5	15	15	0.3	0.3	0.3	0.3	0.0062	0.3145	0.0063	0.6383	0.0001	1.5654	-4.50%	93.82%
2	5	5	20	20	0.3	0.3	0.3	0.3	-0.0168	0.2241	-0.0169	0.3296	-0.0001	1.4084	-8.96%	33.90%
3	5	5	20	20	0.3	0.3	0.3	0.3	-0.0168	0.2235	-0.0172	0.3292	-0.0004	1.4101	-9.20%	33.74%
4	5	5	20	20	0.3	0.3	0.3	0.3	-0.0141	0.1908	-0.0145	0.2661	-0.0004	1.3564	-22.49%	8.10%
5	5	5	20	20	0.3	0.3	0.3	0.3	-0.0170	0.2312	-0.0168	0.3374	0.0002	1.3951	-6.08%	37.07%
2	10	10	20	20	0.3	0.3	0.3	0.3	0.0138	0.1877	0.0131	0.2660	-0.0008	1.3667	-6.59%	32.37%
3	10	10	20	20	0.3	0.3	0.3	0.3	0.0137	0.1877	0.0130	0.2660	-0.0007	1.3670	-6.59%	32.37%
4	10	10	20	20	0.3	0.3	0.3	0.3	0.0131	0.1606	0.0131	0.2168	-0.0001	1.3192	-20.08%	7.89%
5	10	10	20	20	0.3	0.3	0.3	0.3	0.0157	0.1898	0.0144	0.2679	-0.0013	1.3621	-5.55%	33.32%

Table B.7: estimated summary effects and variances of summary effects for log odds ratio

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	3	3	0.3	0.3	0.3	0.3	-0.0172	1.7797	-0.0138	4.3804	0.0034	2.4211	-45.24%	34.77%
3	3	3	3	3	0.3	0.3	0.3	0.3	-0.0253	1.6672	-0.0219	4.1472	0.0034	2.4583	-48.70%	27.60%
4	3	3	3	3	0.3	0.3	0.3	0.3	-0.0245	1.4525	-0.0208	3.3984	0.0037	2.2370	-55.31%	4.56%
5	3	3	3	3	0.3	0.3	0.3	0.3	-0.0290	2.0004	-0.0227	6.2246	0.0062	2.9500	-38.45%	91.52%
2	5	5	5	5	0.3	0.3	0.3	0.3	0.0545	1.1808	0.0549	2.4644	0.0005	2.0171	-23.87%	58.89%
3	5	5	5	5	0.3	0.3	0.3	0.3	0.0566	1.1547	0.0575	2.4217	0.0009	2.0340	-25.55%	56.14%
4	5	5	5	5	0.3	0.3	0.3	0.3	0.0481	0.9531	0.0487	1.7958	0.0006	1.7861	-38.55%	15.78%
5	5	5	5	5	0.3	0.3	0.3	0.3	0.0645	1.4344	0.0646	4.2891	0.0001	2.3960	-7.52%	176.53%
2	10	10	10	10	0.3	0.3	0.3	0.3	-0.0127	0.5780	-0.0119	0.8865	0.0008	1.4863	-7.65%	41.65%
3	10	10	10	10	0.3	0.3	0.3	0.3	-0.0130	0.5769	-0.0120	0.8855	0.0010	1.4878	-7.82%	41.49%
4	10	10	10	10	0.3	0.3	0.3	0.3	-0.0107	0.4888	-0.0098	0.6879	0.0009	1.3775	-21.90%	9.91%
5	10	10	10	10	0.3	0.3	0.3	0.3	-0.0106	0.6092	-0.0101	1.0649	0.0005	1.4939	-2.66%	70.15%
2	20	20	20	20	0.3	0.3	0.3	0.3	-0.0246	0.2615	-0.0243	0.3162	0.0003	1.2000	-5.09%	14.77%
3	20	20	20	20	0.3	0.3	0.3	0.3	-0.0246	0.2615	-0.0243	0.3162	0.0003	1.2000	-5.09%	14.77%
4	20	20	20	20	0.3	0.3	0.3	0.3	-0.0227	0.2409	-0.0225	0.2849	0.0002	1.1767	-12.56%	3.41%
5	20	20	20	20	0.3	0.3	0.3	0.3	-0.0250	0.2619	-0.0245	0.3163	0.0005	1.1994	-4.94%	14.81%
2	3	6	3	6	0.3	0.3	0.3	0.3	0.1977	1.3980	0.2175	3.2014	0.0199	2.2337	-37.30%	43.57%
3	3	6	3	6	0.3	0.3	0.3	0.3	0.1201	1.3483	0.1500	3.1131	0.0299	2.2623	-39.53%	39.61%
4	3	6	3	6	0.3	0.3	0.3	0.3	0.1182	1.1377	0.1561	2.4115	0.0379	2.0084	-48.98%	8.15%
5	3	6	3	6	0.3	0.3	0.3	0.3	0.0569	1.9006	0.2163	7.6600	0.1594	3.1413	-14.76%	243.53%
2	5	10	5	10	0.3	0.3	0.3	0.3	0.0625	0.8852	0.1092	1.6778	0.0468	1.8231	-18.67%	54.15%
3	5	10	5	10	0.3	0.3	0.3	0.3	0.0361	0.8774	0.0898	1.6683	0.0537	1.8315	-19.39%	53.28%
4	5	10	5	10	0.3	0.3	0.3	0.3	0.0745	0.7267	0.1274	1.2378	0.0529	1.6223	-33.23%	13.72%
5	5	10	5	10	0.3	0.3	0.3	0.3	0.0725	1.1359	0.1733	4.1317	0.1008	2.1430	4.36%	279.60%
2	10	20	10	20	0.3	0.3	0.3	0.3	0.0181	0.4123	0.0530	0.5753	0.0349	1.3606	-8.52%	27.65%
3	10	20	10	20	0.3	0.3	0.3	0.3	0.0165	0.4122	0.0521	0.5753	0.0356	1.3608	-8.54%	27.65%
4	10	20	10	20	0.3	0.3	0.3	0.3	0.0524	0.3596	0.0755	0.4707	0.0231	1.2903	-20.21%	4.44%
5	10	20	10	20	0.3	0.3	0.3	0.3	0.0348	0.4220	0.0667	0.5845	0.0318	1.3506	-6.36%	29.69%

Table B.8: estimated summary effects and variances of summary effects for log odds ratio

Zero modification method	n_{11}	n_{12}	n_{21}	n_{22}	π_{11}	π_{12}	π_{21}	π_{22}	Mean of sTE_{IVW}	Mean of $Var(sTE_{IVW})$	Mean of sTE_{BC}	Mean of $Var(sTE_{BC})$	Mean of D	Mean of VR	Relative bias of $Var(sTE_{IVW})$	Relative bias of $Var(sTE_{BC})$
2	3	3	5	5	0.3	0.3	0.3	0.3	-0.0374	1.4262	-0.0359	3.2313	0.0015	2.1863	-32.08%	53.88%
3	3	3	5	5	0.3	0.3	0.3	0.3	-0.0417	1.3679	-0.0396	3.1200	0.0020	2.2127	-34.86%	48.58%
4	3	3	5	5	0.3	0.3	0.3	0.3	-0.0364	1.1613	-0.0343	2.4509	0.0021	1.9795	-44.70%	16.71%
5	3	3	5	5	0.3	0.3	0.3	0.3	-0.0490	1.6997	-0.0515	5.2452	-0.0024	2.6586	-19.06%	149.78%
2	3	3	6	6	0.3	0.3	0.3	0.3	0.0015	1.2990	-0.0019	2.8461	-0.0033	2.0971	-26.31%	61.45%
3	3	3	6	6	0.3	0.3	0.3	0.3	0.0005	1.2511	-0.0027	2.7582	-0.0032	2.1213	-29.03%	56.47%
4	3	3	6	6	0.3	0.3	0.3	0.3	-0.0011	1.0636	-0.0049	2.1585	-0.0038	1.8979	-39.66%	22.45%
5	3	3	6	6	0.3	0.3	0.3	0.3	0.0020	1.5630	0.0018	4.7121	-0.0002	2.5054	-11.33%	167.31%
2	3	3	9	9	0.3	0.3	0.3	0.3	-0.0051	0.9566	-0.0029	1.7767	0.0023	1.7572	-18.28%	51.77%
3	3	3	9	9	0.3	0.3	0.3	0.3	-0.0069	0.9364	-0.0041	1.7491	0.0028	1.7727	-20.01%	49.42%
4	3	3	9	9	0.3	0.3	0.3	0.3	-0.0066	0.7919	-0.0044	1.3389	0.0022	1.6010	-32.35%	14.38%
5	3	3	9	9	0.3	0.3	0.3	0.3	-0.0112	1.0693	-0.0111	2.4021	0.0001	1.8713	-8.66%	105.20%
2	3	3	15	15	0.3	0.3	0.3	0.3	-0.0066	0.6109	-0.0082	0.9142	-0.0015	1.4321	-11.05%	33.11%
3	3	3	15	15	0.3	0.3	0.3	0.3	-0.0058	0.6036	-0.0075	0.9079	-0.0017	1.4415	-12.12%	32.19%
4	3	3	15	15	0.3	0.3	0.3	0.3	-0.0053	0.5325	-0.0070	0.7496	-0.0017	1.3653	-22.47%	9.14%
5	3	3	15	15	0.3	0.3	0.3	0.3	-0.0072	0.6374	-0.0089	1.0192	-0.0017	1.4489	-7.19%	48.40%
2	5	5	10	10	0.3	0.3	0.3	0.3	-0.0394	0.7865	-0.0450	1.3656	-0.0056	1.6594	-11.81%	53.12%
3	5	5	10	10	0.3	0.3	0.3	0.3	-0.0369	0.7789	-0.0435	1.3560	-0.0066	1.6665	-12.66%	52.05%
4	5	5	10	10	0.3	0.3	0.3	0.3	-0.0324	0.6494	-0.0386	1.0104	-0.0062	1.5012	-27.18%	13.29%
5	5	5	10	10	0.3	0.3	0.3	0.3	-0.0471	0.8676	-0.0608	1.7907	-0.0137	1.7144	-2.72%	100.79%
2	5	5	15	15	0.3	0.3	0.3	0.3	0.0054	0.5604	0.0046	0.8310	-0.0008	1.4311	-8.96%	35.00%
3	5	5	15	15	0.3	0.3	0.3	0.3	0.0061	0.5575	0.0051	0.8288	-0.0010	1.4353	-9.43%	34.64%
4	5	5	15	15	0.3	0.3	0.3	0.3	0.0070	0.4847	0.0056	0.6727	-0.0015	1.3526	-21.26%	9.28%
5	5	5	15	15	0.3	0.3	0.3	0.3	0.0092	0.5938	0.0099	0.9976	0.0007	1.4441	-3.54%	62.06%
2	5	5	20	20	0.3	0.3	0.3	0.3	-0.0235	0.4358	-0.0239	0.5840	-0.0003	1.3132	-6.86%	24.81%
3	5	5	20	20	0.3	0.3	0.3	0.3	-0.0230	0.4341	-0.0236	0.5832	-0.0006	1.3166	-7.22%	24.64%
4	5	5	20	20	0.3	0.3	0.3	0.3	-0.0197	0.3886	-0.0204	0.4996	-0.0007	1.2698	-16.95%	6.77%
5	5	5	20	20	0.3	0.3	0.3	0.3	-0.0229	0.4481	-0.0234	0.5979	-0.0004	1.3040	-4.23%	27.78%
2	10	10	20	20	0.3	0.3	0.3	0.3	0.0194	0.3636	0.0191	0.4742	-0.0004	1.2825	-4.96%	23.94%
3	10	10	20	20	0.3	0.3	0.3	0.3	0.0191	0.3635	0.0189	0.4741	-0.0002	1.2829	-4.99%	23.92%
4	10	10	20	20	0.3	0.3	0.3	0.3	0.0181	0.3251	0.0188	0.4072	0.0007	1.2398	-15.03%	6.43%
5	10	10	20	20	0.3	0.3	0.3	0.3	0.0222	0.3682	0.0214	0.4777	-0.0009	1.2767	-3.76%	24.86%