Addressing Outcome Reporting Bias in Meta-analysis: A Selection Model Perspective

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Abstract

Outcome Reporting Bias (ORB) poses significant threats to the validity of meta-analytic findings. It occurs when researchers selectively report outcomes based on the significance or direction of results, potentially leading to distorted treatment effect estimates. Despite its critical implications, ORB remains an under-recognized issue, with few comprehensive adjustment methods available. The goal of this research is investigate ORB-adjustment techniques through a selection model lenses, thereby extending some of the existing methodological approaches available in the literature. To gain a better insight into the effects of ORB in meta-analysis of clinical trials, specifically in the presence of heterogeneity, and to assess the effectiveness of ORB-adjustment techniques, we apply the methodology to real clinical data affected by ORB and conduct a simulation study focusing on treatment effect estimation with a secondary interest in heterogeneity quantification.

1 Introduction

Meta-analysis is a powerful statistical tool used to combine evidence from multiple studies investigating the same research question [12, 7]. It plays a crucial role in clinical research by providing a more comprehensive and robust analysis of treatment effects, especially when individual studies have limited statistical power. However, like any statistical method, meta-analysis is prone to biases that can affect its validity and reliability [7, 30, 13]. While publication bias (PB) is a well-known issue, with various statistical methods developed to address it, outcome reporting bias (ORB) is less explored but equally problematic [7, 30, 13, 22]. PB occurs when entire studies are not present in the literature due to the lack of significance or direction of results. On the other hand, ORB occurs when reporting decisions within published studies are influenced by results' significance or direction, leading to selective reporting of outcomes [20, 8, 10, 30, 21, 13, 33]. Therefore, unlike PB, studies affected by ORB may still be published, but certain outcomes, especially those unfavorable, may be omitted or reporting may be impartial, leading to inability to include the study outcome in a meta-analysis.

Studies have shown that ORB is prevalent in the meta-analysis literature, affecting reviews where both primary and secondary outcomes are often inadequately reported [5, 20, 28]. An investigation on a cohort of Cochrane systematic reviews by Kirkham *et al.* [20] found that more than half of the reviews did not include full data for the primary outcome of interest from eligible trials, and over a third contained at least one trial with high suspicion of ORB [20]. An investigation by Saini *et al.* [28], with a focus on meta-analyses where the primary outcome was a harmful one, found that 86% of Cochrane cohort reviews did not include full outcome data for the main adverse event of the trial, and ORB was suspected in nearly two thirds of the reviews [28]. A study by Chan *et al.* [5], inspecting 1402 outcomes from 48 trials with 68 publications, quantified the association between inadequate reporting of outcomes and statistical significance. They concluded that statistically significant beneficial outcomes have odds of being fully reported which are 2.7 times that of non-significant ones, with a 95% CI from 1.5 to 5.0 [5]. ORB poses a substantial threat to the integrity of meta-analyses, emphasizing the need for increased awareness and methods to mitigate its impact.

The current statistical methodologies to adjust for ORB, which differ in nature and underlying assumptions, can be summarized with the works of Kirkham *et al.* [21], Copas *et al.* [8, 10], Bay *et al.* [1], van Aert and Wicherts [33], including a bivariate meta-analysis adjustment of two correlated outcomes [21], a Bayesian extension of it [1], and a meta-regression approach [33]. The most established ORB-adjustment method, i.e., that of Copas *et al.* [10], relies on categorizing unreported outcomes into risk of bias categories - no risk (NR), low risk (LR), and high risk (HR) - based on the Outcome Reporting Bias in Trials (ORBIT) methodology. Given the classifi-

cation, assumed to be correct, Copas *et al.* [10] developed a likelihood-based ORB-adjustment method by adding a contribution from unreported study outcomes classified as HR of bias to the likelihood function, under the assumption that these were originally non-significant. In the Copas *et al.* [10] method, it is assumed that treatment effects, and possibly standard errors, are unreported, while sample sizes of the studies are known, and the adjustment is done separately for each outcome in the meta-analysis.

Our work can be seen as an extension of the Copas *et al.* [10] method by presenting ORB-adjustment through a selection model perspective, a framework typically used for PB adjustment [11, 15, 32]. The proposed approach for ORB adjustment offers a more flexible framework that does not require the ORBIT classification system, includes contribution from all unreported study outcomes, and allows for different assumptions on the missing data mechanism. We further consider the impact of heterogeneity between studies on ORB and ORB-adjustment, a novel aspect in the context of ORB, and conduct a simulation study investigating the impact of ORB and the effectiveness of ORB-adjustment, focusing on treatment effect estimation, with a secondary focus on heterogeneity, under different meta-analytic settings.

Throughout this work, we consider a random effects meta-analysis setting on a single beneficial outcome, i.e., an outcome for which a positive value indicates a beneficial direction of treatment. We assume normality and hence the following model:

$$y_i \sim \mathcal{N}(\theta_i, \sigma_i^2) \qquad \theta_i \sim \mathcal{N}(\mu, \tau^2), \tag{1}$$

where y_i and σ_i^2 are the observed treatment effect and standard error, respectively, for each study i, and the parameters of interest are μ, the treatment effect, and τ^2, the heterogeneity variance.

As a motivating example of ORB in meta-analysis, we consider the data used by Copas *et al.* [10], wherein a meta-analysis of 12 studies was conducted separately for 14 different outcomes, 2 considered beneficial and 12 harmful. The meta-analysis, originally by Bresnah *et al.* [3], includes studies investigating the effect of Topiramate, an antiepileptic drug first marketed in 1996, when used as an add-on treatment for drug-resistant focal epilepsy. Given that in this paper we focus on ORB and ORB correction for beneficial outcomes, we consider the 2 outcomes of the data assumed to have a positive effect, i.e., 50% seizure frequency reduction, and seizure freedom, illustrated in Table 1. We observe that all of the 12 studies in the meta-analysis report sizes; however, some studies do dot reporting the event frequencies, from which the log OR is computed and used as the normally distributed treatment effect, using a continuity correction in case of empty cell counts [10].

Table 1: Example meta-analysis data of beneficial outcomes affected by ORB [10, 3].

	Sample Size		50% Seizure Reduction		Seizure Freedom	
	T	C	T	C	T	C
Ben-Menachem 1996	28	28	12	0	Unrep	Unrep
Elterman 1999	41	45	16	9	4	2
Faught 1996	136	45	54	8	Unrep	Unrep
Guberman 2002	171	92	77	22	10	2
Korean 1999	91	86	45	11	7	1
Privitera 1996	143	47	58	4	Unrep	Unrep
Rosenfeld 1996	167	42	86	8	Unrep	Unrep
Sharief 1996	23	24	8	2	2	0
Tassinari 1996	30	30	14	3	0	0
Yen 2000	23	23	11	3	Unrep	Unrep
Zhang 2011	46	40	22	3	0	0
Coles 1999	52	51	Unrep	Unrep	Unrep	Unrep

This paper is organized as follows: Section 2 introduces the selection model framework typically used for PB and illustrates how this framework can be adapted to address ORB, considering various possible missing data mechanisms inspired by PB literature. Section 3 presents a simulation study investigating the impact of ORB and the effectiveness of the proposed ORB-adjustment method, with a focus on its application within a random effects meta-analysis model. Finally, Section 4 summarizes the proposed methodology and findings in a discussion, including limitations and conclusions.

2 Selection Models

Selection models have gained popularity in the PB adjustment literature [12, 15, 11, 32, 7], as they aim at correcting for the bias in treatment effect estimation by directly modelling the assumed missing data mechanism. Let y_i be the observed treatment effect estimate for study i in the meta-analysis, with distribution $f(y_i; \theta)$, assumed to be normal, where we denote θ as the unknown parameter of interest - in the context of the random effects meta-analysis of (1), θ is μ and τ^2.

The general form of a selection model in the PB literature involves the use of a weighted likelihood function which takes into account the observations y_i from published studies $i \in \{\text{Pub}\}$ by weighing them with a selection function $w(y_i)$ which describes the probability that study i is published/selected based on its significance [15, 11, 32]. By using the following relation:

$$f\left(y_i \mid i \in \{\text{Pub}\}\right) = \frac{f(y_i;\theta)\cdot w(y_i)}{\int_{-\infty}^{+\infty} f(y;\theta)\cdot w(y)dy,} \quad (2)$$

the PB-adjusted log-likelihood $\ell_{\text{Adj}}^{\text{PB}}(\theta)$ is derived [19, 16, 15, 11] as

$$\begin{aligned}\ell_{\text{Adj}}^{\text{PB}}(\theta) &= \sum_i \log f\left(y_i;\theta \mid i \in \{\text{Pub}\}\right) \\ &= \sum_{i\in\{\text{Pub}\}} \log f(y_i;\theta) \\ &\quad - \sum_{i\in\{\text{Pub}\}} \log\left[\int_{-\infty}^{\infty} f(y;\theta)\cdot w(y)dy\right].\end{aligned} \quad (3)$$

There are numerous forms which the selection function can take in the context of PB, with the general intuition being that in a meta-analysis of a beneficial outcome, for larger p-values, the probability of publication/selection decreases. Of note, in the case of a meta-analysis of a harmful outcome, we would expect the inverse, i.e., small, significant $p-$values to be likely not reported, as they would indicate harm [28, 10]. In the following sections we defined the selection functions assuming a beneficial outcomes and thus positive direction of treatment. The selection function $w(y_i)$ is thus often defined as a function of the p-value p_i, which constitutes an intuitive way of understanding the relationship between significance and probability of selection, [15, 11, 32]. Given that the p-value is simply a transformation of the observed treatment effect y_i and standard error σ_i, we use $w(y_i)$ for ease of notation.

2.1 Selection Models for ORB

In the PB selection model setting one takes into account only the non-missing studies $i \in \{\text{Pub}\}$ by defining the conditional log-likelihood, i.e., conditional on the studies being published. In the context of ORB adjustment methods, according to the framework developed by Copas *et al.* [10], the likelihood function takes into account studies for which we have both non-missing and missing outcome information. The studies have different log-likelihood contributions, depending on whether a study i reports the outcome, i.e., $i \in \{\text{Rep}\}$, or the study i does not report the outcome, i.e., $i \in \{\text{Unrep}\}$. The full ORB-adjusted log-likelihood, where $K = K_{\text{Rep}} + K_{\text{Unrep}}$ is the total number of studies, can be seen as

$$\begin{aligned}\ell_{\text{Adj}}^{\text{ORB}} &= \sum_{i=1}^{K} \ell(\theta) \\ &= \sum_{i\in\{\text{Rep}\}} \ell(\theta) + \sum_{i\in\{\text{Unrep}\}} \ell(\theta) \\ &= \sum_{i\in\{\text{Rep}\}} \log f\left(y_i;\theta\right) + \sum_{i\in\{\text{Unrep}\}} \log f\left(y_i;\theta\right).\end{aligned} \quad (4)$$

We can then adapt the formulation of equation (2) for ORB, by considering, for reported studies $\{i \in \text{Rep}\}$, the probability $w(y_i)$ of a study reporting an outcome, instead of the probability of a study being published. The following thus holds:

$$f\left(y_i \mid i \in \{\text{Rep}\}\right) = \frac{f\left(y_i;\theta\right)\cdot w(y_i)}{\int_{-\infty}^{\infty} f\left(y;\theta\right)\cdot w(y)dy}. \quad (5)$$

Similarly, for the unreported studies $i \in \{\text{Unrep}\}$, we can use the formulation (2) and consider the probability $1-w(y_i)$ of a study not reporting an outcome. We hence obtain

$$f\left(y_i \mid i \in \{\text{Unrep}\}\right) = \frac{f\left(y_i;\theta\right)\cdot\left(1-w(y_i)\right)}{\int_{-\infty}^{\infty} f\left(y\,;\theta\right)\cdot\left(1-w(y)\right)dy}. \quad (6)$$

Using (5) and (6), and solving for $f(y_i;\theta)$, we can re-write the ORB-adjusted log-likelihood (4) as

$$\begin{aligned}\ell_{\text{Adj}}^{\text{ORB}}(\theta) &= \sum_{i\in\{\text{Rep}\}} \log f(y_i;\theta) \\ &\quad - \sum_{i\in\{\text{Rep}\}} \log\left[\int_{-\infty}^{\infty} f\left(y;\theta\right)\cdot w(y)dy\right] \\ &\quad + \sum_{i\in\{\text{Unrep}\}} \log\left[\int_{-\infty}^{\infty} f(y;\theta)\cdot\left(1-w(y)\right)dy\right].\end{aligned} \quad (7)$$

The likelihood (7) is the generic setting using a weight function for the probability of reporting, i.e., for $i \in \{\text{Rep}\}$, and a weight function for the probability of not reporting, i.e, for $i \in \{\text{Unrep}\}$. In the Copas *et al.* [10] model formulation, specific assumptions were made regarding the missing data mechanism, which result in a simplification of (7). For the reported outcomes, Copas *et al.* [10] implicitly

do not assume any selection process, i.e., $w(y_i) = 1$ when $i \in \{\text{Rep}\}$. This means that no weight function representing the reporting probability based on the p-value is associated with the reported observations. In light of this assumption, (7) can be further simplified to

$$\ell_{\text{Adj}}^{\text{ORB}}(\theta) = \sum_{i\in\{\text{Rep}\}} \log f(y_i;\theta) + \sum_{i\in\{\text{Unrep}\}} \log\left[\int_{-\infty}^{\infty} f(y;\theta)\cdot(1-w(y))\,dy\right]. \tag{8}$$

The log-likelihood (8) is thus the generic form for ORB adjustment, which has different shapes depending on the selection function $w(y_i)$ used, representative of the missing data mechanism assumed for unreported study outcomes. Given the alignment of our ORB adjustment with the PB framework of selection models, one can use similar selection functions which are typically found in the PB literature.

2.1.1 Selection Functions

We present a series of selection functions, defined as functions of the one-sided p-value, $p_i = \Phi(-y_i/\sigma_i)$, where α is the threshold for significance, e.g., $\alpha = 0.05$. We use a one-sided p-value to model the probability of selection, in alignment with selection models of beneficial outcomes in PB [16, 32, 27]. One of the simplest selection functions used for PB is:

$$w_A(y_i) = \begin{cases} 1 & \text{if } p_i \le \alpha \\ 0 & \text{if } p_i > \alpha, \end{cases} \tag{9}$$

While this selection function can be found in the PB literature [19, 15, 32], we note that it is also the one implicitly used in the Copas *et al.* [10] adjustment, although the authors do not explicitly frame the ORB adjustment via a selection model framework. Of note, in Copas *et al.* [10], ORB-adjustment is applied by including only the unreported study outcomes classified at HR of bias by the ORBIT classification system. They thus omit the unreported study outcomes classified e.g., at LR of bias, and regard them as missing at random. Furthermore, the authors use the two-sided $p-$value $p_i = 2\cdot\Phi(y_i/\sigma_i)$ instead of the one-sided one proposed in this work. We deem a one-sided p-value to be more appropriate to model the underlying missing data mechanism for a beneficial effect of treatment, as it would be unlikely for significant outcomes, but in the wrong direction, to be reported [16, 32, 27].

Using the log-likelihood (8) and the selection function (9) for a subset of the unreported studies, i.e., those classified as HR of bias, along with a two-sided significance test, we can easily see how we obtain the simplified ORB-adjusted log-likelihood presented for the random effects model in Copas *et al.* [10], namely:

$$\begin{aligned}\ell_{\text{Adj}}^{\text{ORB}}(\theta) &= \sum_{i\in\{\text{Rep}\}} \log f(y_i;\theta) \\ &+ \sum_{i\in\{\text{HR}\}} \log\left[\int_{-\infty}^{+\infty} f(y;\theta)(1-w(y))dy\right] \\ &= -\frac{1}{2}\sum_{i\in\{\text{Rep}\}}\left[\log(\sigma_i^2+\tau^2) + \frac{(y_i-\mu)^2}{\sigma_i^2+\tau^2}\right] \\ &+ \sum_{i\in\{\text{HR}\}} \log\left[\Phi\left(\frac{z_\alpha\sigma_i-\mu}{\sqrt{\sigma_i^2+\tau^2}}\right) - \Phi\left(\frac{-z_\alpha\sigma_i-\mu}{\sqrt{\sigma_i^2+\tau^2}}\right)\right].\end{aligned} \tag{10}$$

The selection function (9) results in a simple shape of the ORB-adjusted log-likelihood; however, the underlying assumption regarding the missing data mechanism is somewhat strict, and extensions which relax its assumption are commonly found in the PB literature [15, 32]. One example is the function $w_B(y;\beta)$ with tuning parameter $\beta > 0$:

$$w_B(y;\beta) = \begin{cases} 1 & \text{if } p \le \alpha \\ \frac{p^{-\beta}}{\alpha^{-\beta}} & \text{if } p > \alpha \end{cases} \tag{11}$$

The idea of this selection function in the context of PB is that the associated probability of publishing which weights observations is greater than 0 for non-significant outcomes. Here, for the non-significant study outcomes, the associated probability of reporting is a decreasing function of the p-value, while significant study outcomes have an associated probability of reporting of 1.

In the context of ORB we further propose a different selection function, $w_C(y;\gamma)$ with tuning parameter $\gamma > 0$ in (12), for which the rationale is inverted compared to $w_B(y;\beta)$ in (11), as we assume that non-significant study outcomes have an associated probability of reporting 0, while significant study outcomes have an associated probability of reporting which is a decreasing function of the p-value. This can be motivated by scenarios where ORB results from prioritizing more impactful or clinically relevant findings in a published study [6, 31], leading to only highly significant outcomes being reported. This could be interpreted as a lower threshold for not reporting compared to PB, and thus a higher level of bias. At the

same time, given that the selection function allows for significant unreported outcomes, it can also account for settings in which outcomes are missing because they were deemed less relevant, resulting in a more random pattern of missing data and less bias [29]. Understanding the exact cause of unreporting can be challenging, and information on the strength of evidence for other outcomes in the meta-analysis could help clarify the likely cause of unreporting.

$$w_C(y;\gamma) = \begin{cases} 1 - \frac{p^\gamma}{\alpha^\gamma} & \text{if } p \leq \alpha \\ 0 & \text{if } p > \alpha \end{cases} \tag{12}$$

Based on the selection functions $w_B(y;\beta)$ in (11) and $w_C(y;\gamma)$ in (12) one could envisage a combination of these by using e.g., selection function $w_D(y;\beta,\gamma)$ in (13). In this case, one can flexibly specify both γ and β parameters, as well as the probability of reporting assumed for a study outcome at the significance threshold α, which we note ω_α. In the case of (11), ω_α was implicitly 1 and in case of (12) this was set to 0. Here, we set $\omega_\alpha = 0.5$, as a middle value between (11) and (12). The selection function $w_D(y;\beta,\gamma)$ has the potential of being used to conduct extensive sensitivity analyses when adjusting for ORB.

$$w_D(y;\beta,\gamma) = \begin{cases} 1 - (1 - w_\alpha)\left(\frac{p^\gamma}{\alpha^\gamma}\right) & \text{if } p \leq \alpha \\ w_\alpha \left(\frac{p^{-\beta}}{\alpha^{-\beta}}\right) & \text{if } p > \alpha \end{cases} \tag{13}$$

The selection functions proposed above, namely $w_A(y)$ in (9), $w_B(y;\beta,\gamma)$ in (11), $w_C(y;\gamma)$ in (12) and $w_D(y;\beta,\gamma)$ in (13) are plotted in Figure 1 for some example values of the $\gamma > 0$ and $\beta > 0$ parameters. Further rationale for the parameter choices are discussed in the simulation study protocol, available in the OSF project repository.

2.1.2 Imputation of Missing Variances

When utilizing any of the selection functions presented in the ORB-adjusted log-likelihood (8), we require knowledge of the standard error of the unreported study outcome, which is generally missing. This value hence needs to be imputed; we do so following the methodology of Copas *et al.* [10], used also in the ORB-adjustment approach of Bay *et al.* [1]

$$\sigma_i^2 \approx \frac{1}{\hat{k} n_i}, \tag{14}$$

where n_i is the sample size of each study i and $\hat{k}$ is:

$$\hat{k} = \frac{\sum_{i \in \{\text{Rep}\}} \sigma_i^{-2}}{\sum_{i \in \{\text{Rep}\}} n_i}. \tag{15}$$

With the selection model framework for ORB adjustment presented in this work, one is thus able to include a likelihood contribution from unreported study outcomes, by specifying the desired missing data assumption via a selection function, representative of the assumed probability of reporting. This framework enables the joint estimation, via maximum likelihood (ML), of the ORB-adjusted parameters of interest in the model, in our case treatment effect, as well the heterogeneity variance.

2.1.3 Application to Motivating Example

We applied the ORB-adjustment framework to the Epilepsy data from Bresnah *et al.* [3], Copas *et al.* [10], using the selection functions proposed in this study. These selection functions utilize a one-sided p-value for significance with a threshold of $\alpha = 0.05$, in contrast to Copas *et al.* [10], which used a two-sided p-value. While a one-sided threshold defines the underlying missing data mechanism, two-sided significance is used to construct profile likelihood (PL) confidence intervals (CIs) for the treatment effect estimate.

Figure 2 presents the point estimates and 95% CI for the log RR of the treatment effect for two beneficial outcomes in the meta-analysis: a 50% reduction in seizure frequency and seizure freedom. For both outcomes, the naive log RR estimate shows a significant positive treatment effect compared to the control.

For the 50% seizure frequency reduction, the ORB-adjusted estimates are slightly shifted towards the null value and are consistent across different selection functions. This minor shift is expected since only one study had unreported outcomes. However, for the seizure freedom outcome, with several unreported study outcomes, the ORB-adjusted estimates show a substantial shift towards the null, even negating the significance of the results. The differences between the ORB-adjusted estimates using various selection functions are more pronounced here.

The strictness of different ORB-adjustments, derived from the selection functions, is intuitive and stems from their underlying assumptions about unreported study outcomes. The estimate obtained using $w_B(\gamma = 3)$ is more conservative than that obtained with w_A. The selection function w_A assumes

Figure 1: Possible Selection Functions for ORB-adjustment. Function $w_A(y)$ from equation (9) in (a), function $w_B(y;\beta = 3)$ from equation (11) in (b), function $w_C(y;\gamma = 3)$ from equation (12) in (c), and functions $w_D(y;\beta = 1.5,\gamma = 7)$ and $w_D(y;\beta = 7,\gamma = 1.5)$ from equation(13) shown in (d).

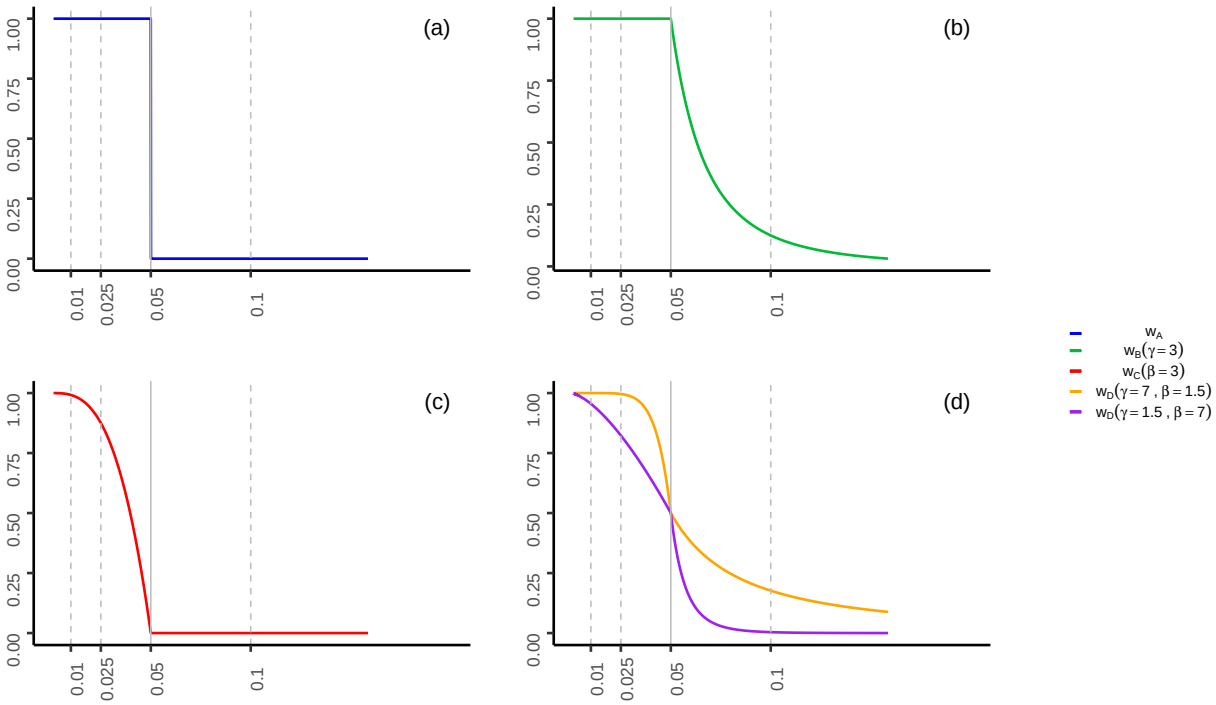
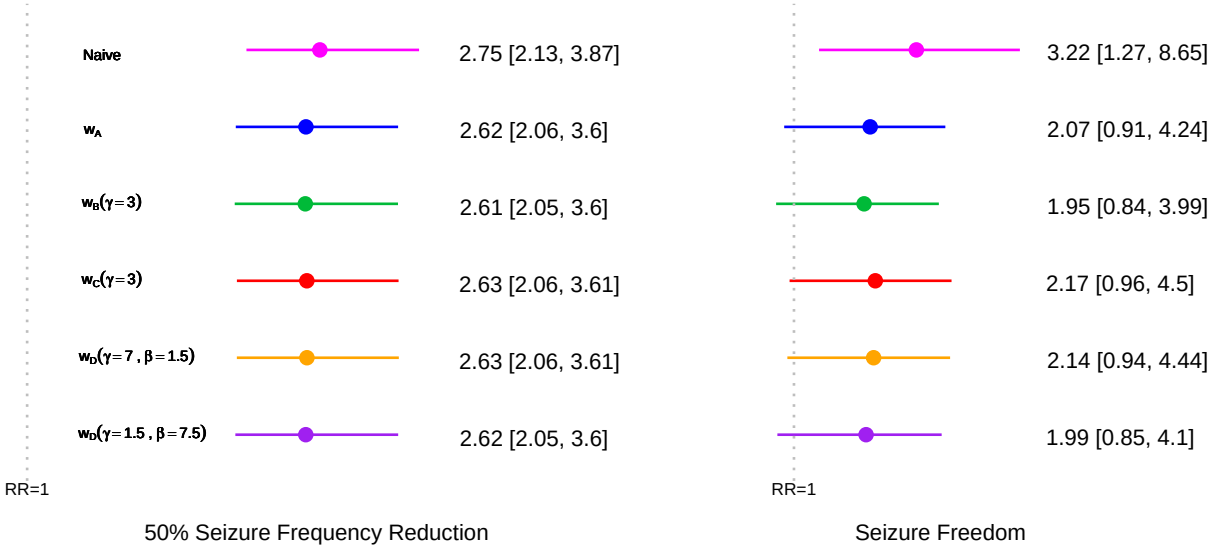


Figure 2: Application of ORB-adjustment to example data [10, 3], using the different selection functions showcased in Figure 1. In addition, the naive estimate, without ORB-adjustment, is shown for comparison.



a probability of unreporting of 1 for non-significant studies, regardless of the p-value magnitude, while $w_B(\gamma = 3)$ assumes a higher probability of unreporting for larger p-values, implying greater bias and thus stricter correction. Conversely, w_C is less conservative than w_A, as it assumes that some unreported outcomes may still be significant, indicating less bias and thus a less strict adjustment. Functions $w_D(\gamma = 1.5, \beta = 7)$ and $w_D(\gamma = 7, \beta = 1.5)$ align with $w_B(\gamma = 3)$ and $w_C(\beta = 3)$, respectively, suggesting that the larger parameter between γ and β drives the estimate. Since the true underlying data mechanism is unknown in this example, we further investigate the ORB-adjustment effect in a simulation study. This allows us to evaluate the ORB adjustment implementation using both correctly specified and misspecified models of the missing data mechanism.

3 Simulation Study

It is of interest to assess the extent to which ORB negatively impacts meta-analytic findings and the extent to which the ORB-adjustment methodology presented in the previous section is effective in reducing this bias. Our primary interest lies in the bias detection and mitigation for treatment effect estimation under different meta-analysis settings, e.g., varying levels of heterogeneity and meta-analysis study sizes. A secondary interest of the investigation is the possible impact of ORB on heterogeneity variance estimation. To achieve this, we conduct a simulation study wherein we first simulate a random effects meta-analysis of a single beneficial outcome and subsequently mimic selective reporting by removing the observed treatment effect and standard error from the meta-analysis dataset based on the strength and/or direction of the results, favoring the reporting of studies with small p-values. We then utilize different estimation methods for the parameters of interest and assess the performance of the methods using performance measures on a large number of simulations. The details of the simulation study can be found in the simulation study protocol (already available in the OSF project repository) and are summarized in the following setting description subsection.

3.1 Setting

The first step of the simulation process consists in simulating random-effects meta-analysis datasets in the presence of ORB. We first simulate a random effects meta-analysis study comprising K studies, each with treatment and control arms of equal sizes $n_i = n = 50$, and reported treatment effects y_i with standard errors σ_i. We first obtain the study-specific true treatment effects θ from

$$\theta_i \sim \mathcal{N}(\mu, \tau^2), \tag{16}$$

where μ is the overall treatment effect and τ^2 is the between-study heterogeneity variance. The observed treatment effects y_i are given by

$$y_i \sim \mathcal{N}(\theta_i, \sigma^2), \tag{17}$$

where $\sigma^2 = 2/n$, while the standard errors are generated from a scaled ^{2} distribution

$$\sigma_i^2 \sim \frac{\chi^2_{2n_i-2}}{(n_i-1)n_i}. \tag{18}$$

These values are generated independently for each study, assuming no correlation between studies. We then simulate ORB by selectively excluding certain studies from the meta-analysis based on the direction and significance of treatment effects. The ORB simulation process involves removing study outcomes with a probability of reporting determined by a decreasing function of the one-sided p-value, i.e., $p_i = \Phi(-y_i/\sigma_i)$. The function (19) used to simulate ORB is taken from simulation studies on PB, for consistency with our selection model approach, typical of PB settings. We simulate under two ORB settings, i.e., $\gamma = 1.5$ [11, 2, 23, 27] and $\gamma = 0.5$.

$$P(i \in \{\text{Rep}\}) = e^{-4 \cdot p_i^{\gamma}}. \tag{19}$$

Each meta-analysis dataset hence results in K or fewer of the original study outcomes. If for some meta-analysis datasets, less than two study outcomes are reported, the simulation is repeated until at least two reported study outcomes are obtained [11, 2, 23, 14]. The ORB-affected meta-analysis datasets are generated under different settings - we vary the number of studies in the meta-analysis, $K \in \{5, 15, 30\}$, the amount of between-study heterogeneity $I^2 \in \{0\%, 25\%, 50\%, 75\%, 90\%\}$ and the true underlying treatment effect $\mu \in \{0, ..., 0.8\}$ with increments of 0.1 [24, 18, 14].

After having simulated ORB, hence resulting in some treatment effects and standard errors unreported, we use maximum likelihood (ML) estimation to obtain point estimates of the treatment effect μ and the heterogeneity variance τ^2, along with profile likelihood (PL) confidence intervals (CI) [34, 10, 17]. The ML estimate and PL CI for μ and τ^2 are obtained using different log-likelihoods, depending on the information and/or missing data mechanism assumed, leading to i) naive, ii) complete data, and iii)

ORB-adjusted estimation methods. We further differentiate various ORB-adjusted estimates based on the selection function assumed for the probability of reporting.

The naive log-likelihood (i) includes the contribution only from reported study outcomes and disregards the unreported ones. The naive estimate serves as a baseline for comparison of the ORB-adjustment methodologies and quantifies the negative impact of ORB when the latter is not accounted for [32, 10]. The complete data log-likelihood (ii) uses all studies in the meta-analysis before ORB is simulated, and is a proxy for the true treatment effect if there were no ORB. The various ORB-adjusted estimates (iii) are obtained by maximizing the ORB-adjusted log-likelihood (8) using the different selection functions: $w_A(y)$ from (9), $w_B(y;\beta = 3)$ from (11), $w_C(y;\gamma = 3)$ from (12), and $w_D(y;\beta = 1.5,\gamma = 7)$, $w_D(y;\beta = 7,\gamma = 1.5)$ from (13), as well as the selection function (19) used to simulate ORB, so as to include the correct model specification in the adjustment. Since the latter can be indeed seen a selection function, we note as $w_{DGM}(y)$. The parameters of the selection functions, i.e., β or γ used in the adjustment correspond to those illustrated in Figure 1.

For each parameter setting, the simulation process is repeated $\mathrm{N_{sim}} = 3200$ times; the simulation size $\mathrm{N_{sim}}$ is calculated based on the expected variance of the unknown parameter estimate [18, 25] and a desired Monte Carlo Standard Error (MCSE) of 0.005 from IntHout *et al.* [18], Morris *et al.* [25]. The performance measures recorded for the unknown parameter are bias, empirical standard error (SE), mean squared error (MSE), coverage and power, along with the MCSEs of each, as per IntHout *et al.* [18], Morris *et al.* [25].

3.2 Results

Firstly, the results indicate a substantial bias in the estimation of the treatment effect when using naive estimation methods that do not account for ORB, as observable from Figures 3 and 4. This aligns with existing literature [10, 1, 33] and prior exploratory analysis [29]. As the true treatment effect size increases, the bias diminishes, reflecting the reduced likelihood of unreported studies, given the higher change of statistically significant results for large treatment effect sizes. Study size variations ($K = 5, 15, 30$) do not significantly affect the bias, while heterogeneity has a substantial impact. High heterogeneity settings, particularly with $I^2 = 90$, exhibit larger biases, reinforcing findings from previous exploratory work [29]. Incorporating heterogeneity effects into the ORB framework is thus important and offers novel insights compared to past investigations [10]. The observed patterns of naive estimation are consistent across both ORB simulation processes, regardless of the DGM parameter γ value, whether $\gamma = 1.5$ (which results in mostly non-significant unreported studies) or $\gamma = 0.5$ (where some significant unreported studies, with larger p-values, exist).

When applying the ORB-adjustment framework using selection functions, there is a difference to be noted depending on the study size. For $K = 15, 30$, the bias is eliminated when the selection function matches the ORB DGM, confirming the model's effectiveness when correctly specified. Different selection functions (w_A, w_B, w_C, w_D) show varying degrees of bias reduction. For the DGM with $\gamma = 1.5$, these ORB-adjusted estimates shift the bias towards the null but do not fully eliminate it unless the exact DGM function is used. w_B performs slightly better than w_A, and w_C performs the least well, with, however, overall minimal differences noted among the functions, particularly in low heterogeneity settings. In the $\gamma = 0.5$ setting, similar patterns are observed, with w_B being the least strict and w_C the most strict. The ORB-adjustment here tends to reduce the treatment effect size excessively, indicating potential overcorrection due to the steep p-value dependence. For the small meta-analysis size of $K = 5$, we observe that the ORB-adjustment is not very successful; the bias is reduced, but not eliminated, even with the correctly specified model, i.e., using the selection function w_{DGM}. We should thus use ORB-adjustment with caution when we have very few studies; we note that, $K = 5$ is the total number of studies, both reported and unreported; hence the number of reported studies is even smaller.

Beyond bias, the MSE of the naive estimate of treatment effect is substantially reduced in high heterogeneity settings, for all ORB-adjusted estimates, as can be seen from Figures 5 and 6. Similar to the results of the bias measures, we note better performance of the ORB-adjusted methods for $K = 15, 30$. Coverage, shown in Figures 7 and 8 can be substantially for naive estimation. Overall, the coverage of the naive estimates decreases as heterogeneity increases. For small treatment effect sizes, e.g., $\mu = 0$, the coverage is higher for small meta-analysis size, i.e., $K = 5$, and decreases as the meta-analysis size increases. This can be explained by larger CI for the $K = 5$ setting, which in turn cover the true underlying value. These observations hold for both ORB generating settings of $\gamma = 1.5$ and $\gamma = 0.5$. The coverage of the ORB-adjusted estimates is higher than the naive estimates, reflecting similar findings observed

for the bias. For the ORB DGM with $\gamma = 0.5$, there are no substantial difference between the various selection functions, including the correct model specification one, and overall the coverage is very high when adjusting for ORB. For the $\gamma = 1.5$ setting, the correct DGM selection function has highest coverage, while other estimates exhibit slightly lower coverage, especially when μ is small, similar to the performance observed for the bias. In Figure 8 we interestingly observe a dip in the coverage of the ORB-adjusted estimates around $\mu = 0.4$, which can be explained by the fact that, for smaller μ, with various unreported study outcomes, we expect higher widths of the CI [29] and thus higher coverage, while for larger μ, there are fewer unreported studies, so overall less bias and thus higher coverage. It is thus of key importance to have a holistic overview of various performance measures, given the confounding which can occur when only focusing on one.

Figures 9 and 10 show the power of the various estimates of the treatment effect. We observe that with naive estimation, for both ORB DGM processes $\gamma = 1.5$ and $\gamma = 0.5$, the power is severely inflated. This is aligned with expectations and results from other performance measures, as not accounting for ORB results in an overestimation of the beneficial effect of treatment and over-representation of significant findings. The power of the naive estimate is particularly high for high heterogeneity settings and for large meta-analysis study sizes. For the $\gamma = 1.5$ setting, we observe that the correct DGM selection function results in the lowest power among the various ORB-adjusted estimates, with other ORB-adjusted estimates in-between. For $\gamma = 0.5$, the opposite is observed, i.e., w_{DGM} results in highest power, with other ORB-adjusted estimates being lower. This is consistent with the bias findings, as most ORB-adjusted estimates were too conservative in the adjustment, shifting the estimate towards the null, with a thus increased likelihood of obtaining ORB-adjusted results which are not significant.

The last performance measure for the treatment effect estimate is the empirical standard error (ESE), shown in Figures 11 and 12. We first note that the ESE of the naive estimate, across the different study sizes and heterogeneity settings is overall consistent to the calculations done for the expected SE of $\hat{\mu}$ in the simulation study protocol. In this case, the naive estimate has overall slightly higher SE, given the presence of unreported study outcomes; furthermore, the naive ESE in some settings decreases slightly as μ increases, given the increasing amount of reported study outcomes. In most settings, there are no substantial differences in the ESE between the various ORB-adjusted estimates and the naive one. Some exceptions which can be notes are that for the small meta-analysis study size setting, i.e., $K = 1.5$, and high heterogeneity, e.g., $I^2 = 90$, the various ORB-adjusted estimates all have a similar ESE, which is lower than the naive one. On the other hand, for the same heterogeneity level but $K = 15, 30$, some ORB-adjusted estimates have high ESE than the naive one, in particular for the ORB DGM setting $\gamma = 0.5$. This could indicate a possible thresholding behavior, wherein adding contributions from a few unreported study outcomes can increase precision of the estimate, as we are using additional information which was not known with naive estimation, but, having many unreported outcomes contributing to the likelihood results in less precision due to uncertainty in the information added.

Our parameter of interest and the focus of our investigation was treatment effect, hence in the random effects model when carrying out MLE, the primary parameter was μ. However, we also had a secondary interest in the estimation of the heterogeneity variance τ^2 in the presence of ORB, and the effect of the ORB-adjustments on its estimation. The heterogeneity variance τ^2 is jointly estimated from the ML with the μ parameter, which constitutes an exploratory way of assessing its value. From Figures 13 and 14, we note some interesting differences between the two ORB DGM settings. For $\gamma = 1.5$, heterogeneity is underestimated for nearly all estimation methods, with the exception of the ORB-adjusted one according to the correctly specified model, i.e., using the selection function w_{DGM}. For $\gamma = 0.5$, for $K = 15, 30$, the heterogeneity is nearly always overestimated, while for $K = 5$ it is mostly underestimated - the correctly specified ORB-adjusted model estimates the lowest heterogeneity and is thus closes to the zero-bias line for $K = 15, 30$ and furthest from it for $K = 5$.

4 Discussion

This study addresses Outcome Reporting Bias (ORB), where the reporting of study outcomes is influenced by their significance, leading to overestimation of treatment effects in meta-analyses. We approached ORB adjustment through a selection model framework, a common method in publication bias (PB) literature, incorporating contributions from unreported study outcomes based on assumed missing data mechanisms. Our proposed selection functions expand on existing methods, including those from previous works like Copas *et al.* [10], by being more flexible in the missing data mechanisms and encom-

passing all unreported outcomes.

Applying ORB-adjustment to real-world meta-analyses on epilepsy Copas *et al.* [10], Bresnah *et al.* [3] showed substantial shifts towards null estimates, especially in cases with numerous unreported outcomes. The findings of our simulation study reveal several critical insights regarding the impact of Outcome Reporting Bias (ORB) on the estimation of treatment effects and the efficacy of ORB-adjustment techniques. Naive estimation methods that do not account for ORB show substantial bias, particularly in high heterogeneity settings, underscoring the importance of incorporating ORB adjustments. Our results demonstrate that ORB-adjustment frameworks using selection functions can significantly reduce bias, although their effectiveness varies with meta-analysis study size and the unrelying method used to simulate ORB. For larger meta-analyses ($K = 15, 30$), correctly specified ORB-adjustment models effectively eliminate bias, while different misspecifications are either not strict enough or slightly too strict, though they do not vary significantly in their performance. For smaller meta-analyses ($K = 5$), we must be cautious as bias reduction is limited even with correctly specified models. Other measures of performance confirm these findings, demonstrating, e.g., substantial improvements in the coverage and power of the treatment effect estimates with ORB-adjustment. These findings highlight the necessity of using ORB-adjustment methods to achieve more accurate treatment effect estimates and also suggest that heterogeneity estimation is impacted by ORB, warranting further attention to improve the robustness of meta-analyses in the presence of ORB.

The ORB-adjustment methodology proposed is flexible and broadly applicable, but several limitations exist. The framework operates on individual outcomes in meta-analyses, not accounting for correlations between outcomes. Future research could explore methods to incorporate such correlations. The current approach to imputing missing variances, as done in previous works [8, 10, 1, 29], might be extended through multiple imputation techniques. Adjustments were made for normally distributed outcomes, which might not be precise for binary data [8, 10]. Exploring a binomial likelihood for such cases could be a potential avenue [29]. In Saracini [29] we set-up the binomial likelihood contribution of reported study, which can be extended so as to include a term from unreported studies with a specified probability of reporting.

We established that heterogeneity variance estimation is affected by ORB, and conversely, the true underlying heterogeneity influences the treatment effect estimate bias due to ORB. Therefore, considering heterogeneity in ORB and ORB adjustments is of paramount importance. To address this, we focused on and conducted simulations using the random effects model, in contrast to Copas *et al.* [10], which concentrated on the fixed effects model. Maximum likelihood estimation (MLE) was used for estimating heterogeneity variance due to its connection to ORB-adjustment, i.e., the ORB adjustment itself is defined via a likelihood function contribution. More sophisticated methods in the likelihood framework, like restricted maximum likelihood (REML) could be considered [26, 34, 9, 29]. An exploratory REML approach was proposed in previous work [29], but a more robust derivation could be explored. Obtaining accurate estimates of τ^2 is crucial, and while challenging to intertwine it with ORB-adjustment outside the likelihood framework of joint estimation with μ, novel methods could be investigated [34, 26, 9]. Another potential area for future research is the effect of ORB on prediction intervals [**?**] and how ORB adjustments impact them, as mentioned in previous work [29].

Another possible avenue for future research is the multiple imputation (MI) of missing study outcomes, which has also been used in publication bias (PB). In the context of PB, Carpenter *et al.* [4] fit a model to the observed study data and impute missing studies using a missing at random assumption. However, they use a re-weighting scheme that follows similar selection function assumptions to those made in this work. Options to impute not at random by sampling from a different distribution that directly models the selection process could be considered. Additionally, in the PB context, Carpenter *et al.* [4] had to impute the study sizes, which, on the other hand, are known in the ORB setting proposed here. Hence, this could be a possible avenue for future research. In this sense, MI would benefit from modeling outcomes that are correlated to borrow strength in case of missing outcomes [4], as done in previous work on ORB [1, 21]. This could be of particular interest in cases, such as our motivating example from Copas *et al.* [10], Bresnah *et al.* [3], where numerous outcomes are considered in the meta-analysis. The challenge in this approach lies in the assumptions made on the correlations, which need to be estimated [29, 1, 21].

Our focus was on beneficial outcomes, but the methodology can be extended to harmful outcomes by adjusting the selection functions for a different missing data mechanism accordingly. This could mean changing the assumed selection mechanism for unreported outcomes to, for example, assuming that a positive value of the treatment effect for a harm-

ful outcome, or a significant one, results in a lower probability of reporting [10, 8, 28]. Future implementations of this ORB-adjustment framework could hence investigate which missing data assumptions are reasonable to make for harmful outcomes and, e.g., conduct a simulation study similar to the one done here for various, flexible, selection functions.

For future research on ORB, we encourage the refinement and further exploration of simulation studies and strongly recommend using a pre-defined protocol for transparency and reproducibility. The simulation study conducted in this work utilized a limited range of data-generating mechanism (DGM) parameters and ORB-adjustment selection functions. Future research could involve extensive sensitivity analyses and varying sample sizes to enhance the robustness of the findings, as well as comparisons with new potential approaches, such as the MI ones above-described.

Overall, this study highlights the significant impact of ORB on treatment effect estimation, as well as heterogeneity variance, and demonstrates the efficacy of a flexible ORB-adjustment framework. The methodology shows promise in mitigating ORB across various settings, with potential for further refinement and broader application.

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Figure 3: Bias in the estimation of the treatment effect for ORB simulated with $\gamma = 1.5$

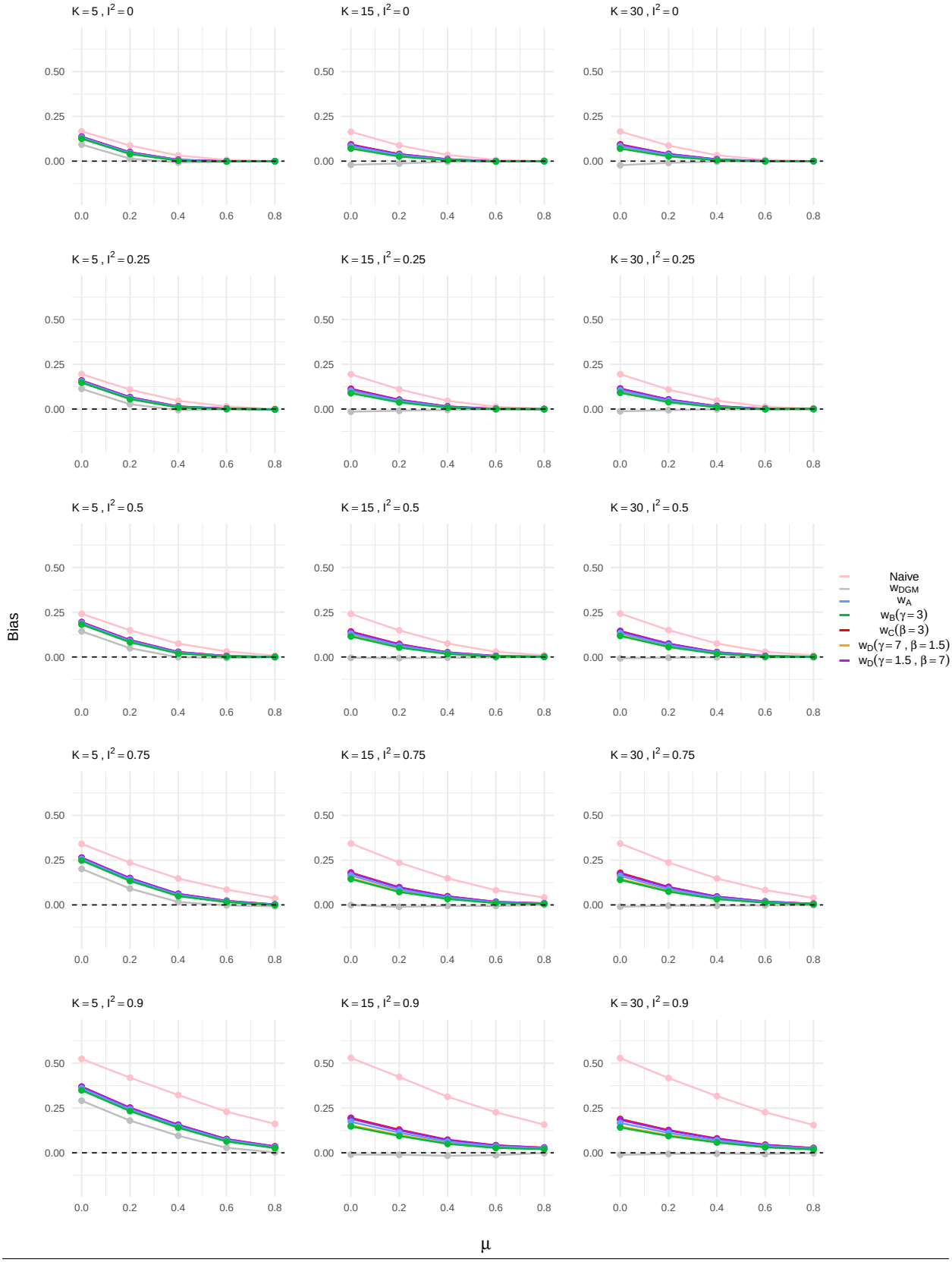

Figure 4: Bias in the estimation of the treatment effect for ORB simulated with $\gamma = 0.5$

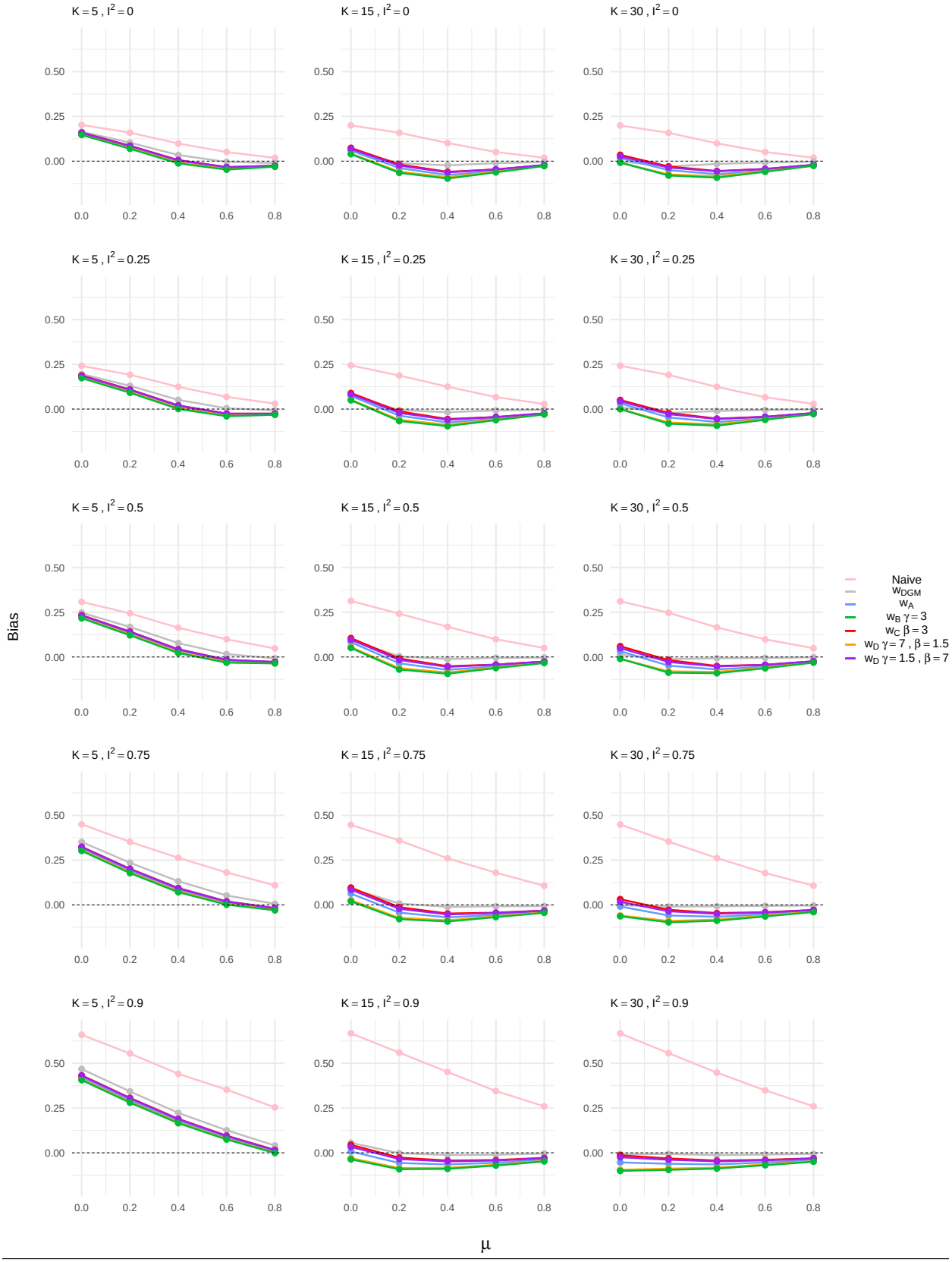

Figure 5: MSE in the estimation of the treatment effect for ORB simulated with $\gamma = 1.5$

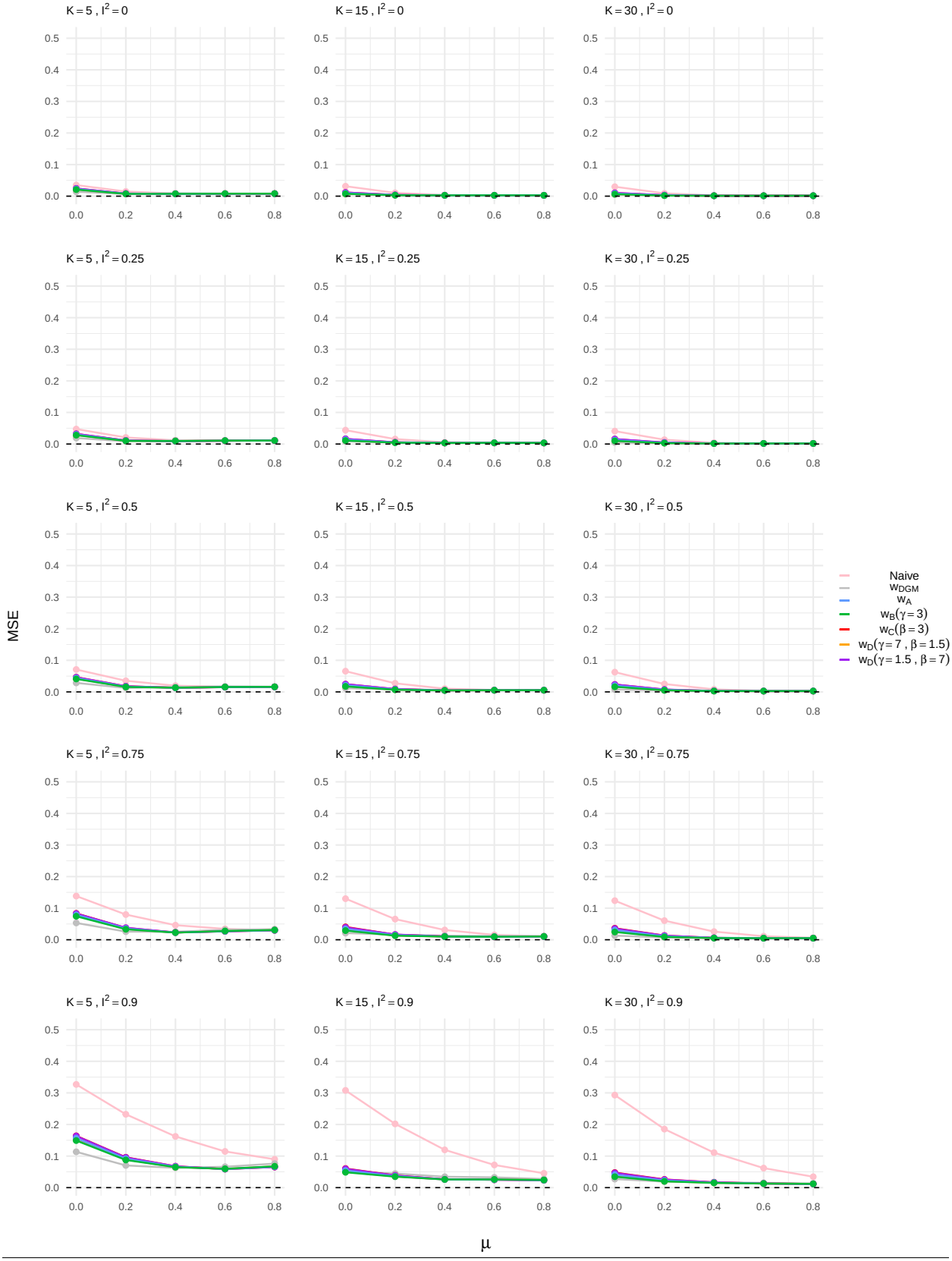

Figure 6: MSE in the estimation of the treatment effect for ORB simulated with $\gamma = 0.5$

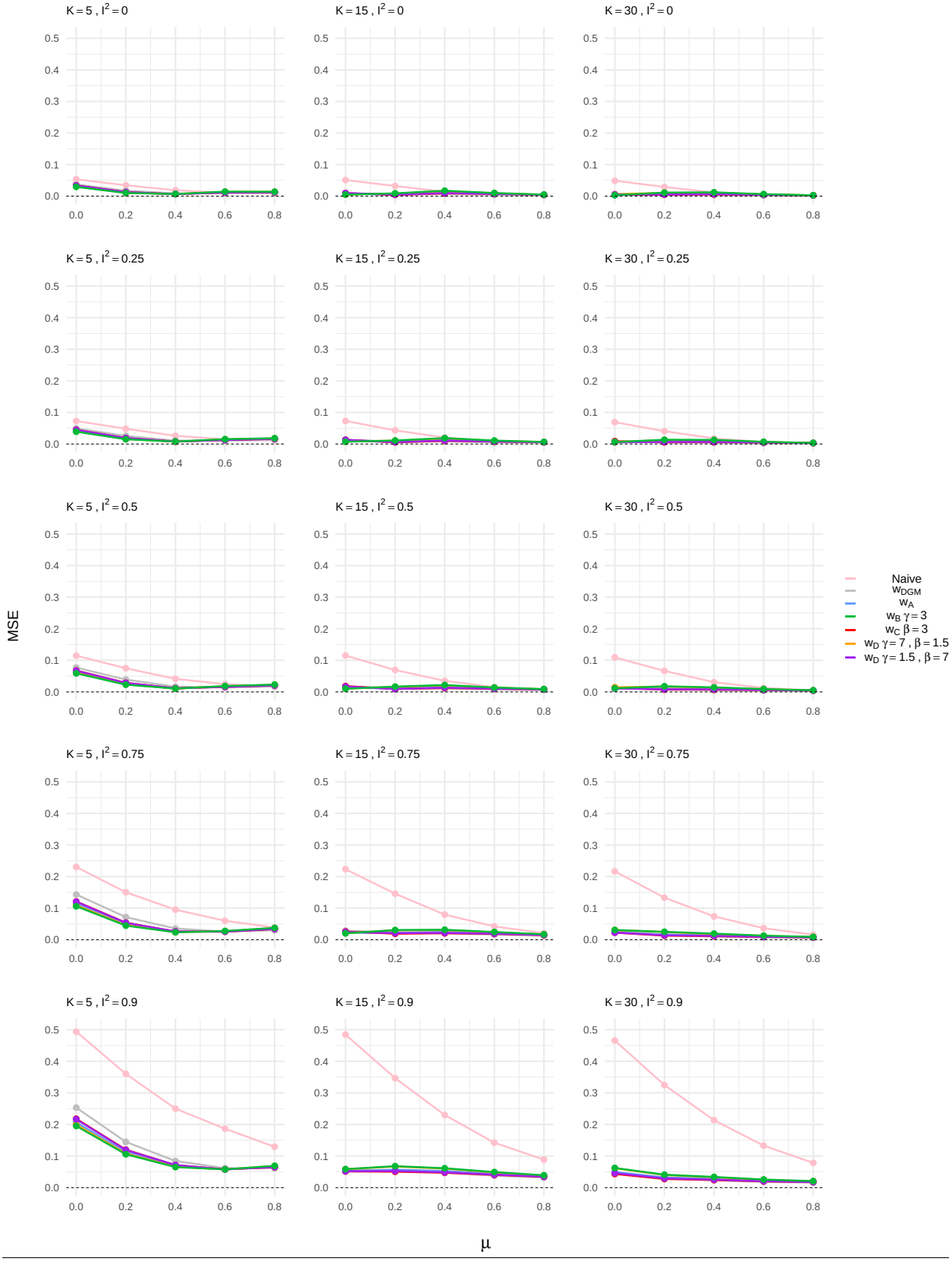

Figure 7: Coverage in the estimation of the treatment effect for ORB simulated with $\gamma = 1.5$

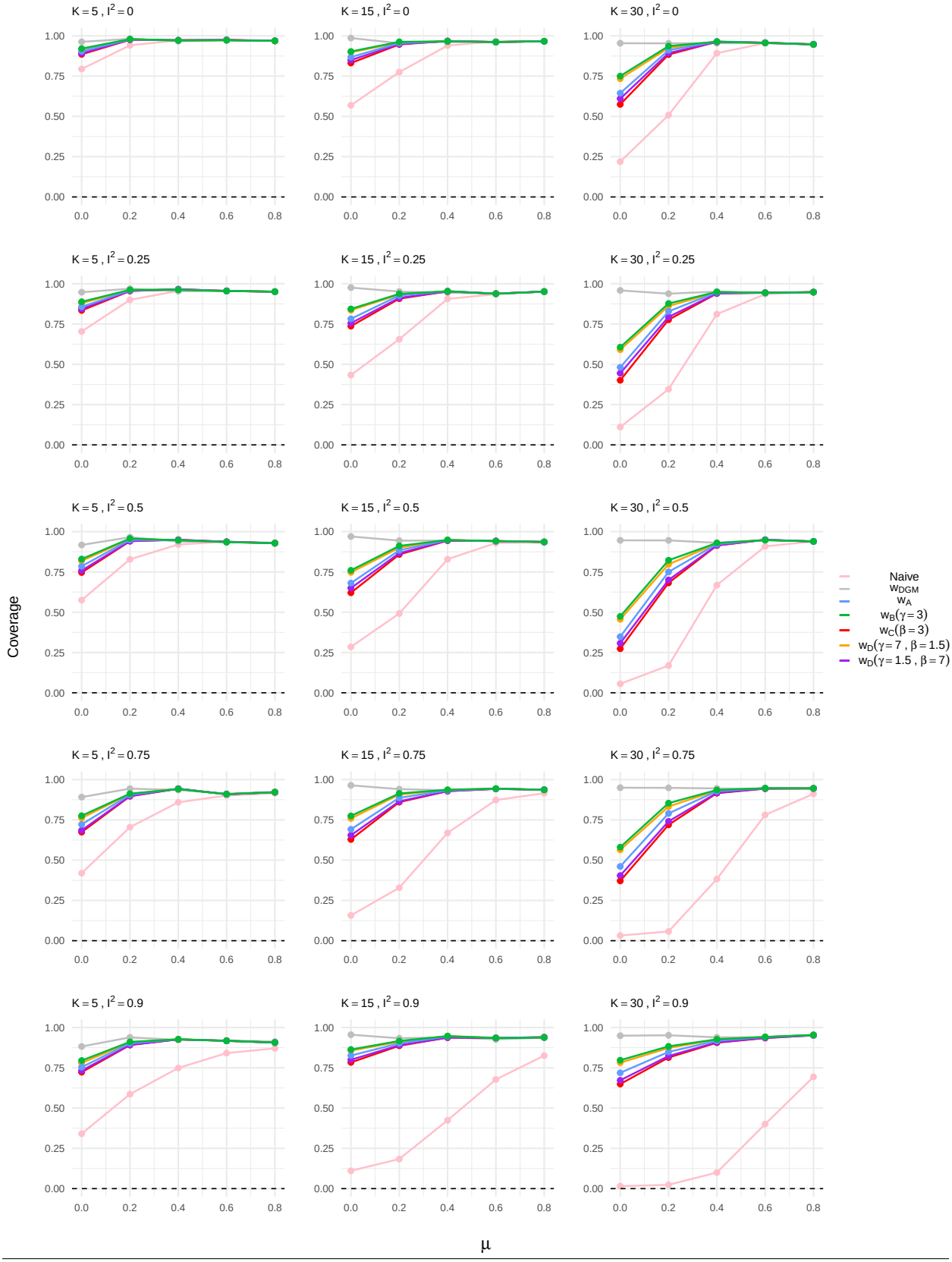

Figure 8: Coverage in the estimation of the treatment effect for ORB simulated with $\gamma = 0.5$

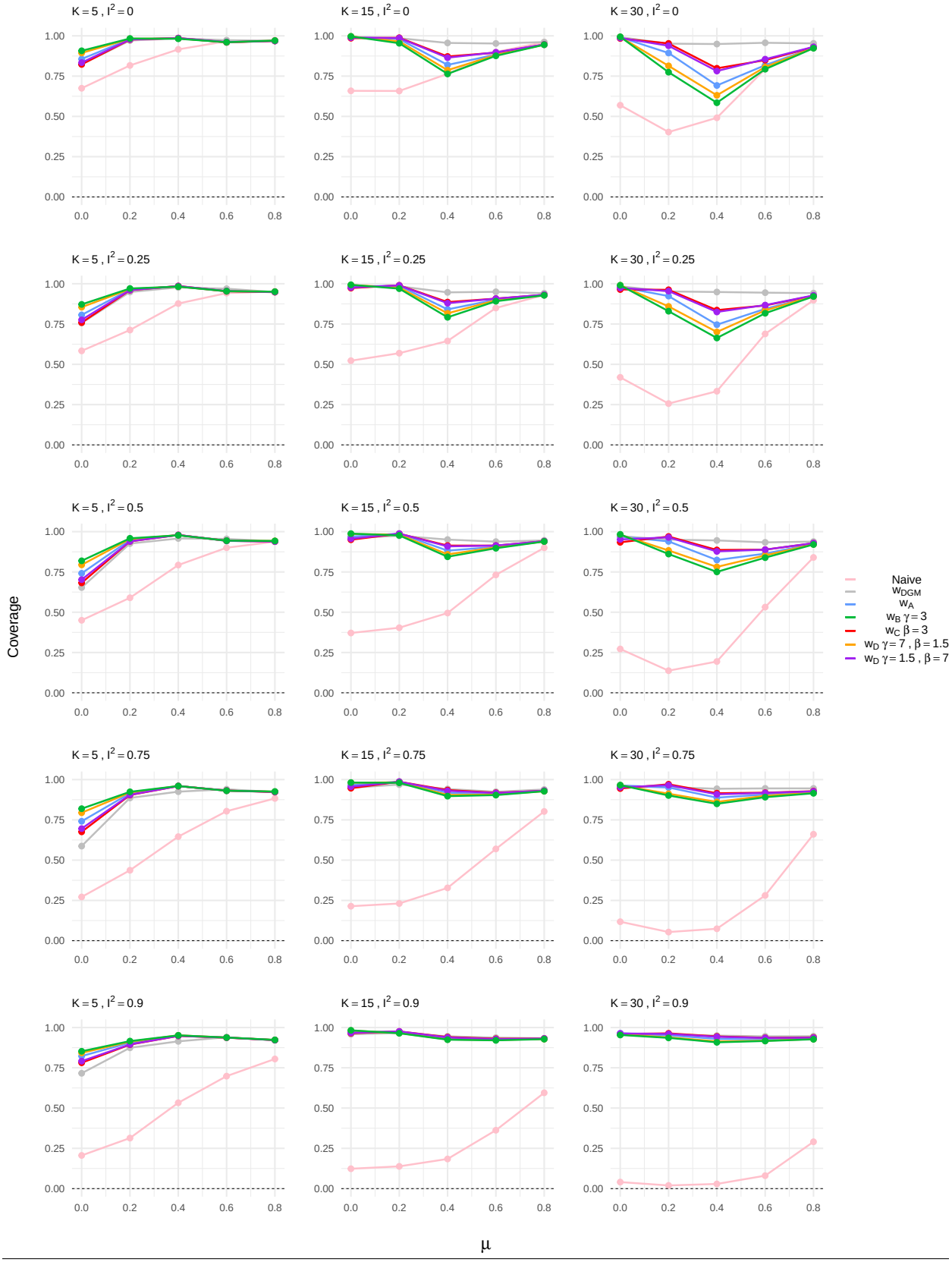

Figure 9: Power in the estimation of the treatment effect for ORB simulated with $\gamma = 1.5$

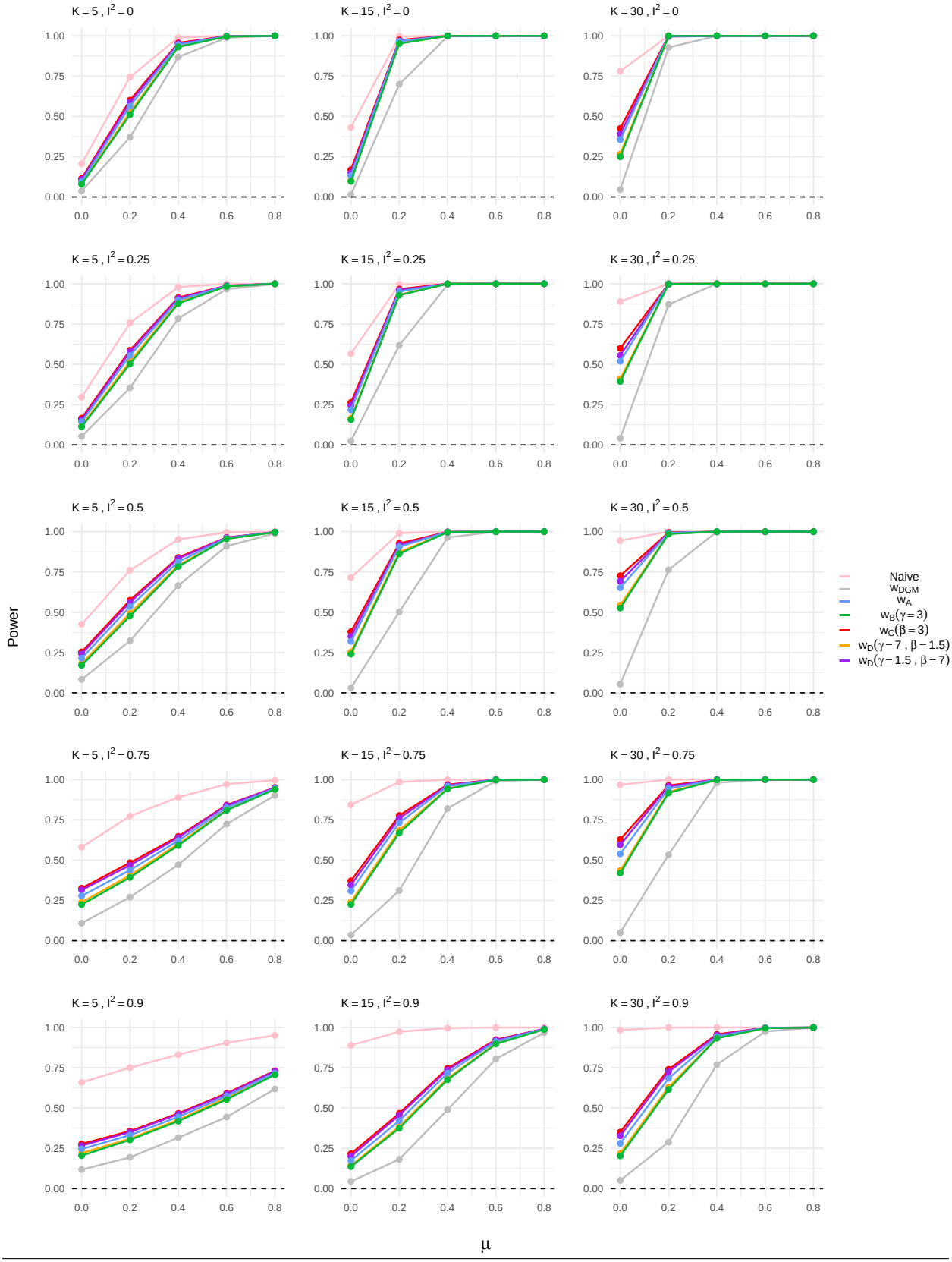

Figure 10: Power in the estimation of the treatment effect for ORB simulated with $\gamma = 0.5$

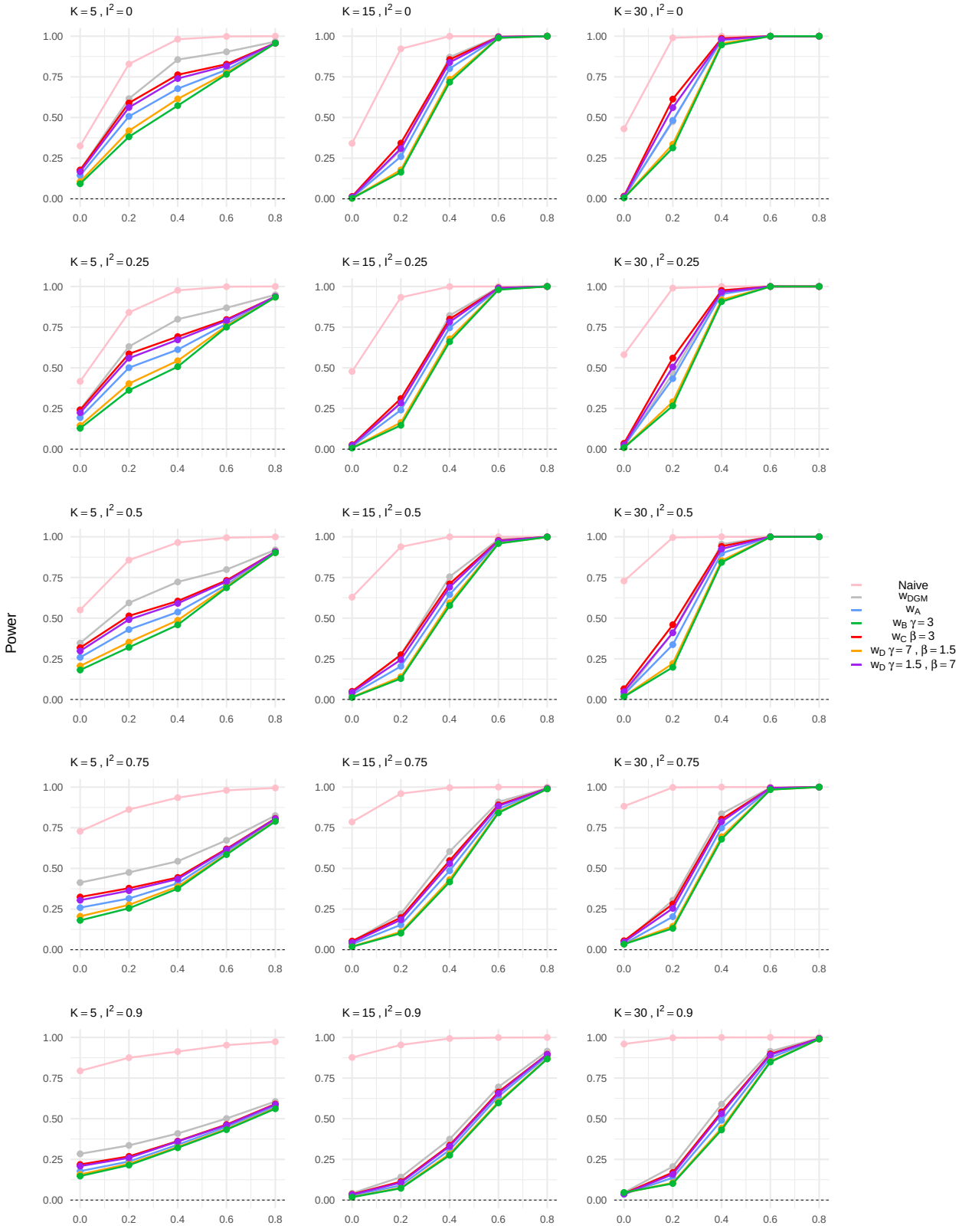

Figure 11: Empircal SE in the estimation of the treatment effect for ORB simulated with $\gamma = 1.5$

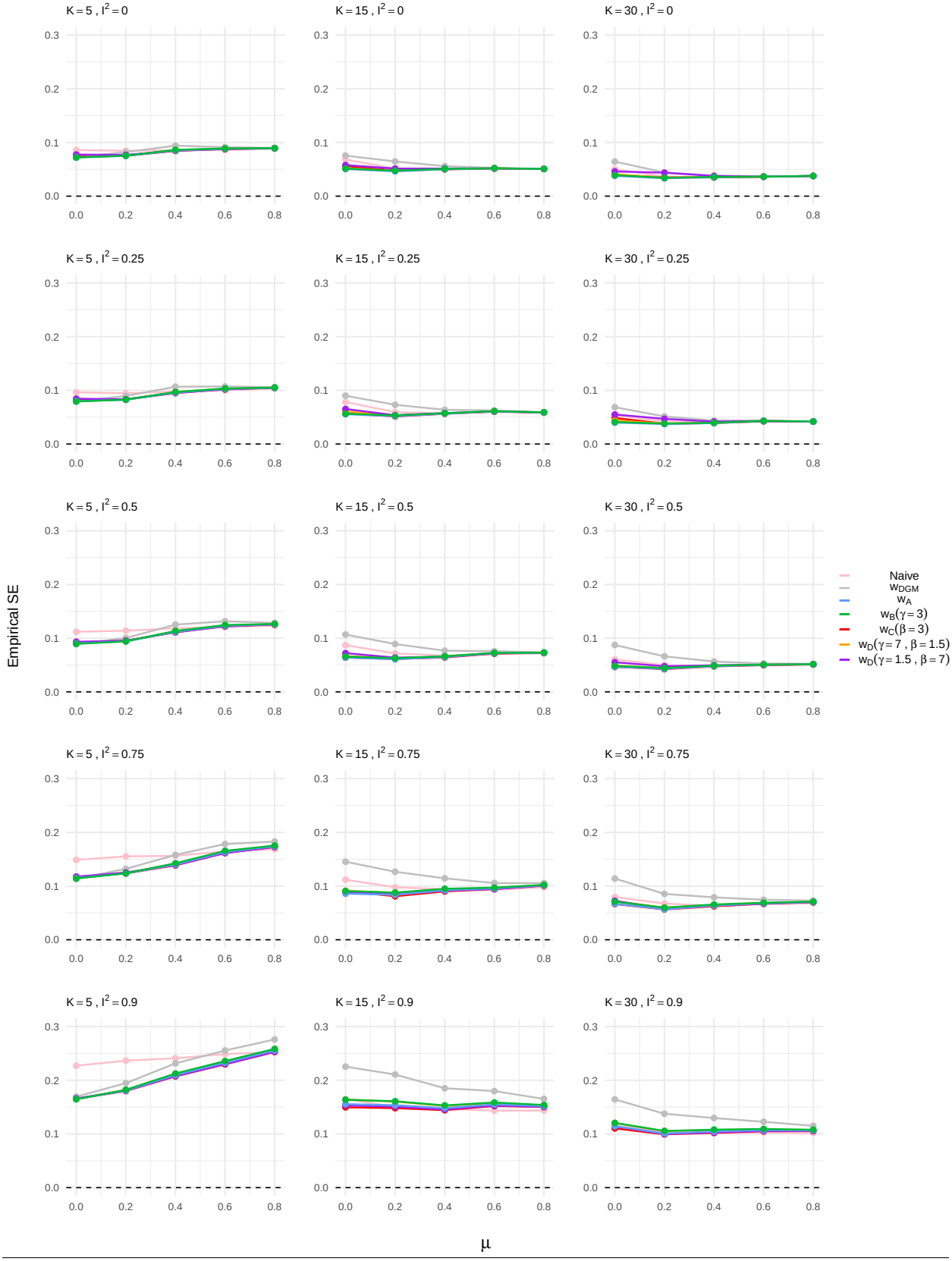

Figure 12: Empirical SE in the estimation of the treatment effect for ORB simulated with $\gamma = 0.5$

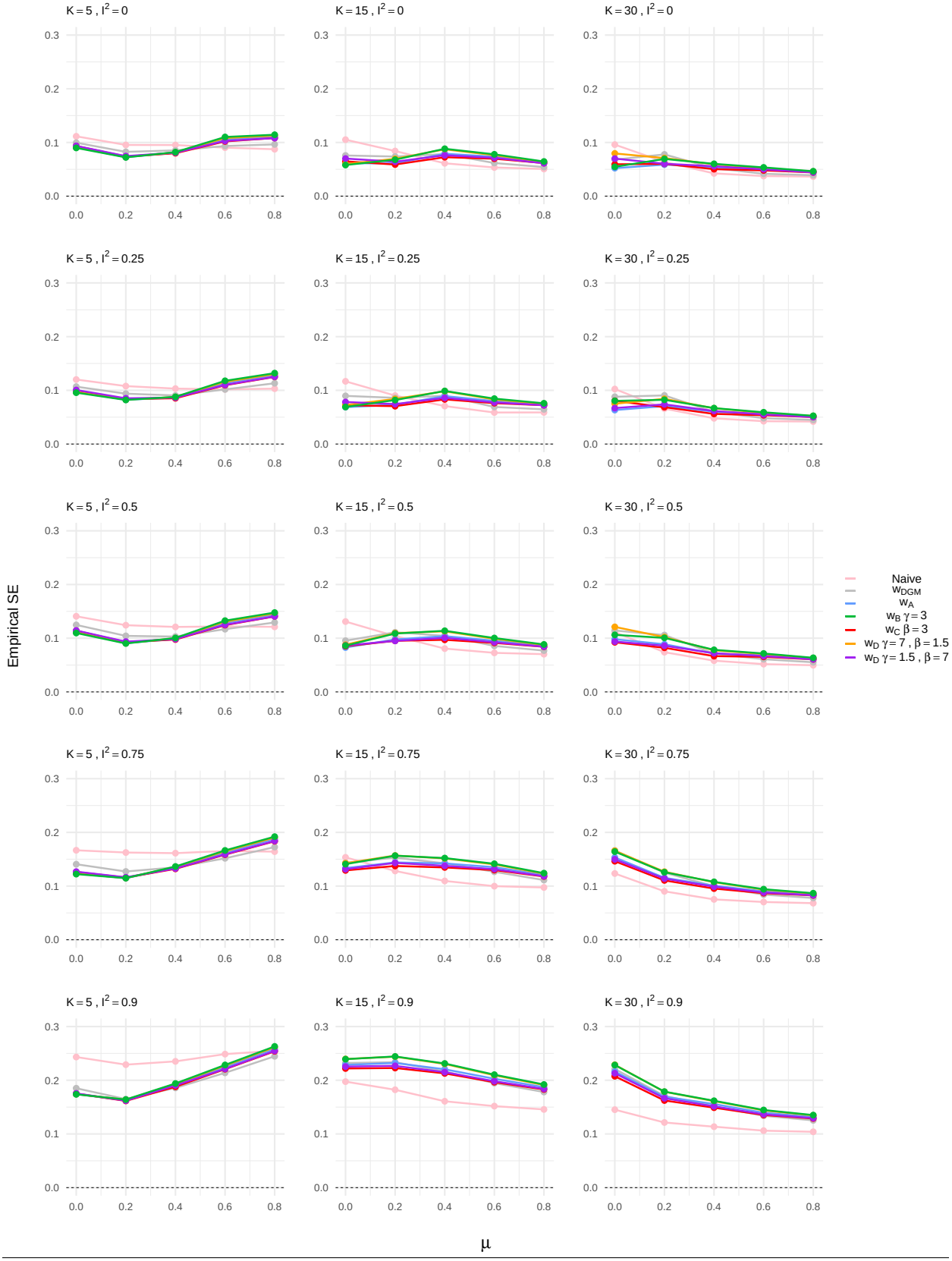

Figure 13: Bias in the estimation of the heterogeneity variance for ORB simulated with $\gamma = 1.5$

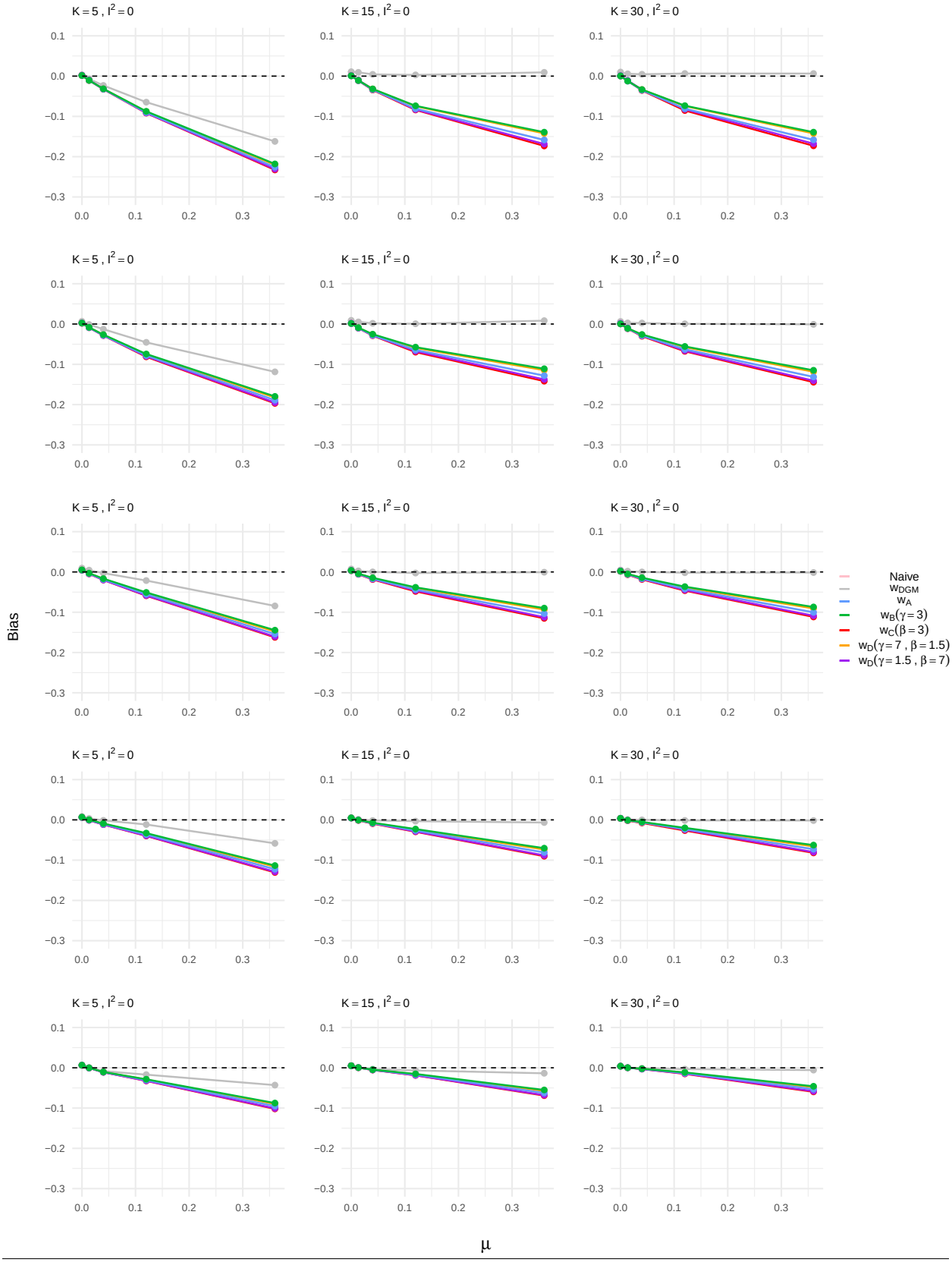

Figure 14: Bias in the estimation of the heterogeneity variance for ORB simulated with $\gamma = 0.5$