A bivariate likelihood approach for estimation of a pooled continuous effect size from a heteroscedastic meta-analysis study

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Abstract

The DerSimonian-Laird (DL) weighted average method has been widely used for estimation of a pooled effect size from an aggregated data meta-analysis study. It is mainly criticized for its underestimation of the standard error of the pooled effect size in the presence of heterogeneous study effect sizes. The uncertainty in the estimation of the between-study variance is not accounted for in the calculation of this standard error. Due to this negative property, many alternative estimation approaches have been proposed in literature. One approach was developed by Hardy and Thompson (HT), who implemented a profile likelihood approach instead of the moment-based approach of DL. Others have further extended the likelihood approach and proposed higher-order likelihood inferences (e.g., Bartlett-type corrections). Likelihood-based methods better address the uncertainty in estimating the between-study variance than the DL method, but all these methods assume that the within-study standard deviations are known and equal to the observed standard error of the study effect sizes. Here we treat the observed standard errors as estimators for the within-study variability and we propose a bivariate likelihood approach that jointly estimates the pooled effect size, the between-study variance, and the potentially heteroscedastic within-study variances. We study the performance of the proposed method by means of simulation, and compare it to DL, HT, and the higher-order likelihood methods. Our proposed approach appears to be less sensitive to the number of studies, and less biased in case of heteroscedasticity.

Key words: meta analysis, heterogeneity, heteroscedasticity, bivariate distribution, Likelihood estimation.

1 Introduction

The DerSimonian-Laird (DL) method (DerSimonian and Laird, 1986) has been and still is widely used to estimate a pooled effect size from aggregated data meta-analysis studies. The method is a weighted average of the study effect sizes, where the weights are the inverse study variances (including both the within and between study variability). The between-study variance component is estimated with a moment estimator. The DL method was shown to be negatively biased when the number of studies is small (Malzahn et al., 2000) and it does not account for the uncertainty in estimating the between study variability (Hardy and Thompson, 1996), potentially leading to liberal confidence intervals for the pooled effect size (Veroniki et al. 2019). Alternative methods have been proposed in literature to improve the DL method (Viechtbauer, 2005; Veroniki et al., 2019). The most familiar approach is the profile likelihood approach of Hardy and Thompson (HT) (1996), where the study effect sizes are assumed normally distributed and potentially heterogeneous, but with known within study variances. The pooled effect size
and the between-study variance component are then estimated jointly. The authors constructed a confidence interval for the pooled effect size that is based on the chi-square distribution of a likelihood ratio statistic (Hardy and Thompson, 1996). It has been shown that this profile likelihood approach has a closer to nominal coverage probability than the DL method (Veroniki et al., 2019; Tanizaki, 2004).

However, the likelihood ratio statistic is only asymptotically chi-squared distributed, and for small sample sizes the approximation might be poor (Barndorff-Nielsen and Hall, 1988). For this reason, Noma (2011) proposed a Bartlett-type correction for the likelihood ratio statistic (Norma, 2011). Additionally, the author proposed constructing confidence limits using the efficient score statistic and a Bartlett-corrected efficient score function (Cox and Hinkley, 1974; Guolo, 2012). These three methods for confidence intervals of the pooled effect size showed conservative coverage probabilities, especially when the number of studies is small, while the DL and the HT methods had liberal coverage probabilities (Cox and Hinkley, 1974).

The Bartlett-type correction of the likelihood ratio statistic is only appropriate for exponential families (Guolo, 2012). The commonly assumed random effects meta-analysis model is a member of the exponential family in the unlikely case of equal within-study variances (Guolo, 2012). Guolo (2012) therefore applied an approximation to the Bartlett-type correction introduced in Skovgaard (2001). This Guolo-Skovgaard (GS) approximation produced conservative coverage probabilities in case of a small number of studies, but its performance improved when the number of studies increases (Guolo, 2012). In one comparative study, the Bartlett-type correction method and the GS correction method were found to produce similar results (Veroniki, 2019).

All of the methods discussed so far, assume that the within-study standard deviation is given by the observed standard error of the study effect size, while the true within-study variability is unknown in practice. We will assume that the observed standard error is an estimator of the true within-study variability having a chi-square distribution function. We will introduce a bivariate likelihood approach for estimation of the pooled effect size, the between-study variance, and the within-study variances for heteroscedastic continuous outcomes. Using a case study and a simulation study, we compare our method to DL, HT, the Bartlett-type correction method, and the GS correction method.

In section 2 we describe the different approaches from literature and our proposed bivariate likelihood approach. The approaches are illustrated on a real case study that was published in literature before. Section 3 describes the simulation model we used. It simulates meta-analysis studies with both heterogeneous effect sizes and heteroscedastic standard errors. We believe that heteroscedastic errors are common in practice, but are seldom simulated (van den Heuvel et al., 2020). The results of the simulation study are provided in Section 4 and a discussion is provided in Section 5.

## 2 Statistical methods

An aggregated data meta-analysis usually consists of a set of \( m \) effect sizes (e.g., mean differences, odds ratios, correlation coefficients), accompanied with their standard errors and the degrees of freedom (Cochran, 1954), i.e., we observe triplet \((Y_i, S_i, df_i)\) for study \( i = 1, 2, ..., m \). It is typically assumed that the study effect size \( Y_i \) is distributed according to the meta-analysis model

\[
Y_i = \theta + U_i + \varepsilon_i, \tag{1}
\]

with \( \theta \) the true or pooled effect size, \( U_i \sim N(0, \tau^2) \) a random effect that is making the study effect sizes heterogeneous, \( \varepsilon_i \sim N(0, \sigma^2_i) \) a residual, and all random effects mutually independently distributed. The \( \tau^2 \) is the variance component for the between-study variability and \( \sigma^2_i \) is the variance component of the within-study variability. In literature it is commonly assumed that the within-study variability \( \sigma^2_i \) is known and given by \( S_i^2 \), but we believe that \( S_i^2 \) is at best an estimator of \( \sigma^2_i \). We will assume that \( Y_i \) follows model (1) and the distribution of \( df_i S_i^2 / \sigma^2_i \) is approximately chi-square with \( df_i \) degrees of freedom. These assumptions typically hold true when the study effect size is represented by a mean difference with underlying normally distributed data (van den Heuvel et al., 2020).
In sections 2.1, 2.2, and 2.3 we describe the DL method, existing likelihood-based methods, and our bivariate method for estimating the effect size \( \theta \) and constructing 95\% confidence intervals. Section 2.4 presents a case study from literature where all methods are being demonstrated.

### 2.1 The DerSimonian-Laird method

The DL method first estimates the between-study variance component \( \tau^2 \) with the moment estimator given by

\[
\hat{\tau}^2_{DL} = \max \left( 0, \frac{Q - (m - 1)}{\sum_{i=1}^{m} w_i - \sum_{i=1}^{m} w_i^2 / \sum_{i=1}^{m} w_i} \right),
\]

where \( w_i = 1/S_i^2 \), \( Q \) is Cochran’s Q-statistic given by \( Q = \sum_{i=1}^{m} [(Y_i - \bar{Y})^2 / S_i^2] \) (DerSimonian and Laird 1986), and \( \bar{Y} \) is the weighted average given by \( \bar{Y} = \sum_{i=1}^{m} (Y_i / S_i^2) / \sum_{i=1}^{m} (1 / S_i^2) \). Then the pooled estimator \( \hat{\theta}_{DL} \) of the effect size \( \theta \) is calculated using the estimator \( \hat{\tau}^2_{DL} \). The DL estimator is given by

\[
\hat{\theta}_{DL} = \left[ \sum_{i=1}^{m} Y_i (\hat{\tau}^2_{DL} + S_i^2)^{-1} \right] / \left[ \sum_{i=1}^{m} (\hat{\tau}^2_{DL} + S_i^2)^{-1} \right].
\]

A \((1 - \alpha) \times 100\) confidence interval on \( \theta \) may be determined by \( \hat{\theta}_{DL} \pm t_{\alpha/2, m-1} S_{DL} \), with \( t_{q,d}^{-1} \) the \( q^{th} \) upper quantile of the \( t \)-distribution with \( d \) degrees of freedom and \( S_{DL}^2 = [\sum_{i=1}^{m} 1 / (\hat{\tau}^2_{DL} + S_i^2)]^{-1} \) the estimated variance of the pooled estimator \( \hat{\theta}_{DL} \) having \( m - 1 \) degrees of freedom. Note that it has been more common in literature to use the normal quantile instead of the quantile of the \( t \)-distribution (Brockwell and Gordon, 2007; Thorlund et al., 2011; Jackson et al., 2010), but we believe that DerSimonian and Laird were not explicit on this topic (DerSimonian and Laird, 1986) and therefore did not rule out our preferred choice. We believe that our choice is in line with the work of Cochran (Cochran, 1954), who proposed to use the \( t \)-distribution with \( m - 1 \) degrees of freedom instead of the normal distribution, in particular in the presence of heterogeneity (see also Mzolo et al. (2013)). The use of this \( t \)-distribution is common when the standard error of Hartung-Knapp-Sidik-Jonkman is used (Sidik and Jonkman, 2005). The standard error \( S_{DL} \) is then multiplied with a data-driven scaling factor \( [\sum_{i=1}^{m} (Y_i - \hat{\theta}_{DL})^2 / ((\hat{\tau}^2_{DL} + S_i^2)(n - 1))]^{1/2} \) (see Sidik and Jonkman (2005). We will not study this corrected standard error, even though it is often proposed as the preferred method in ‘t Hout et al., 2014), because the use of this corrected standard error is not without criticism (Jackson et al., 2017; Partlett and Riley, 2017). Furthermore, comparisons between the use of this corrected standard error and the traditional DerSimonian-Laird method typically studied normal quantiles and never investigated the influence of the proposed \( t \)-distribution alone.

To obtain the estimates \( \hat{\tau}^2_{DL} \) and \( \hat{\theta}_{DL} \) and the confidence limits on \( \theta \) from data in our simulation study, we programmed the method in SAS, since most \( R \) packages seem to have incorporated a normal quantile or otherwise use the corrected standard error with the \( t \)-distribution (e.g., “meta” (Schwarzer, 2007) and “metafor” (Viechtbauer, 2010).

### 2.2 Existing likelihood-based methods

Three likelihood based approaches for parameter estimation and confidence intervals have been proposed in literature. They all make use of the same maximum likelihood estimators for the parameters \( \theta \) and \( \tau^2 \), which is based on the procedure of Hardy and Thompson (1996), but they differ in the construction of confidence intervals.

#### 2.2.1 The Hardy-Thompson method

The log-likelihood function that was proposed in Hardy and Thompson (1996) is given by

\[
l(\theta, \tau^2) = -\frac{1}{2} m \log(2\pi) - \frac{1}{2} \sum_{i=1}^{m} \log(\tau^2 + S_i^2) - \frac{1}{2} \sum_{i=1}^{m} (Y_i - \theta)^2 / (\tau^2 + S_i^2). \tag{2}
\]
It shows that the within-study variances $\sigma_i^2$ are assumed known and equal to $S_i^2$. Maximizing $\theta$ with respect to $\theta$ and $\tau^2$ results in solving the following two equations iteratively:

$$\theta = \frac{\sum_{i=1}^{m} Y_i (\tau^2 + S_i^2)^{-1}}{\sum_{i=1}^{m} (S_i^2)^{-1}},$$
$$\tau^2 = \frac{\sum_{i=1}^{m} (Y_i - \theta)^2 - S_i^2 (\tau^2 + S_i^2)^{-2}}{\sum_{i=1}^{m} (\tau^2 + S_i^2)^{-2}}. \tag{3}$$

The two solutions are Hardy and Thompson’s (HT) maximum likelihood estimators $\hat{\theta}_{HT}$ and $\hat{\tau}_{HT}^2$. For the construction of confidence regions on $(\theta, \tau^2)$ a kind of log-likelihood ratio statistic $T_{HT}(\theta, \tau^2)$ was proposed:

$$T_{HT}(\theta, \tau^2) = -2[l(\theta, \tau^2) - l(\hat{\theta}_{HT}, \hat{\tau}_{HT}^2)]. \tag{4}$$

It is assumed that $T_{HT}(\theta, \tau^2)$ is chi-square distributed with 2 degrees of freedom. All pairs of values $(\theta, \tau^2)$ that would satisfy $T_{HT}(\theta, \tau^2) < \chi^2_{1,1 - \alpha}$, with $\tau^2 \geq 0$ and $\chi^2_{1,1 - \alpha}$ the $\alpha$th upper quantile of the chi-square distribution with $d$ degrees of freedom, form the $100\% \times (1 - \alpha)$ confidence region on $(\theta, \tau^2)$ (Hardy and Thompson, 1996).

To obtain confidence intervals for $\theta$ and $\tau^2$ separately, a profile likelihood function was considered. Here we focus on the $100\% \times (1 - \alpha)$ confidence interval for $\theta$, but a similar approach can be applied to $\tau$. If we assume that $\theta$ is given, we could maximize the log-likelihood function in $T_{HT}$ for $\tau$ first, resulting in the constraint maximum likelihood estimator $\hat{\tau}(\theta)$.

Substituting this estimator in $T_{HT}$ results in the profile log-likelihood function $\tilde{l}(\theta) \equiv l(\theta, \hat{\tau}(\theta))^2$. The profile log-likelihood ratio statistic for $\theta$ is then defined as

$$\tilde{T}_{HT}(\theta) = -2[\tilde{l}(\theta) - l(\hat{\theta}_{HT})]. \tag{5}$$

All values of $\theta$ that would satisfy inequality $\tilde{T}_{HT}(\theta) < \chi^2_{1,1 - \alpha}$ would form the $100\% \times (1 - \alpha)$ confidence interval for $\theta$.

The [R] package “metaplus” (Beath, 2016) can determine the maximum likelihood estimators $\hat{\theta}_{HT}$ and $\hat{\tau}_{HT}^2$, the confidence region for $(\theta, \tau^2)$, and the two confidence intervals for $\theta$ and $\tau^2$ from real data. We have used this for the case study and simulation study.

### 2.2.2 The Noma-Bartlett method

The profile likelihood approach for $\theta$ mentioned in Section 2.2.1 is considered a first-order likelihood inference method (Guolo, 2012). Higher-order asymptotic methods for the proposed profile likelihood ratio statistic will provide more accurate inference (Barndorff-Nielsen and Hall, 1988; Cox and Hinkley, 1974), in particular for smaller values of $m$. Norma (2011) applied a Bartlett-type correction (Barndorff-Nielsen and Hall, 1988) to the profile likelihood ratio statistic $\tilde{T}_{HT}(\theta)$ in $\tilde{T}_{HT}$ by normalizing it with a constant that depends on the constraint maximum likelihood estimator $\hat{\tau}(\theta)$. The Noma-Bartlett (NB) method uses this corrected likelihood ratio statistic, which is given by $\tilde{T}_{NB}(\theta) = \tilde{T}_{HT}(\theta)/[1 + 2C(\hat{\tau}(\theta))]$, with

$$C(\tau^2) = \left[\frac{\sum_{i=1}^{m} (S_i^2 + \tau^2)^{-3}}{\sum_{i=1}^{m} (S_i^2 + \tau^2)^{-1} \sum_{i=1}^{m} (S_i^2 + \tau^2)^{-2}}\right].$$

The $100\% \times (1 - \alpha)$ confidence interval for $\theta$ is formed by all $\theta$’s satisfying $\tilde{T}_{NB}(\theta) < \chi^2_{1,1 - \alpha}$. For the case study and our simulation study we obtained the estimates of the pooled effect size $\theta$ and the NB confidence interval with the [R] package “pimeta” (Nagashima et al., 2019). Note that the NB method uses the estimators $\hat{\theta}_{HT}$ and $\hat{\tau}_{HT}^2$ of Hardy and Thompson, but provides only an alternative confidence interval for $\theta$.

### 2.2.3 The Guolo-Skovgaard method

Instead of using the profile likelihood ratio statistic $\tilde{T}_{HT}(\theta)$ in $\tilde{T}_{HT}$, a signed profile likelihood ratio statistic can be used:

$$\tilde{r}_G(\theta) = \text{sign}(\hat{\theta}_{HT} - \theta) \sqrt{l(\hat{\theta}_{HT}, \hat{\tau}_{HT}^2) - l(\theta, \hat{\tau}(\theta))}. \tag{6}$$
The statistic $\hat{r}_{GS}(\theta)$ is approximately normally distributed (Guolo, 2012). Thus the set of values $\theta$ for which inequalities $z_{\alpha/2} \leq \hat{r}_{GS}(\theta) \leq z_{1-\alpha/2}$ hold true, with $z_q$ the $q^{th}$ quantile of a standard normal distribution, provides a $100\% \times (1 - \alpha)$ confidence interval for $\theta$.

Alternatively, a Skovgaard correction to the signed profile likelihood ratio statistic in (6) can be applied in a random-effects meta-analysis. This Guolo-Skovgaard corrected statistic is given by

$$\tilde{r}_{GS}(\theta) = \hat{r}_G(\theta) + [\hat{r}_G(\theta)]^{-1} \log(\tilde{u}(\theta)/\hat{r}_G(\theta)),$$

with $\tilde{u}(\theta) = \left[ S^{-1}(\theta)q(\theta) \right]_1 | I(\hat{\theta}_{HT}, \hat{\tau}^2_{HT}) |^{1/2} | J(\hat{\theta}_{HT}, \hat{\tau}^2_{HT}) |^{-1} | S(\theta) | | I_{22}(\theta, \hat{\tau}^2(\theta)) |^{-1/2}$, $S(\theta)$ the $2 \times 2$ matrix given by

$$S(\theta) = \left( \begin{array}{cc} \sum_{i=1}^m (S^2_i + \hat{\tau}^2(\theta))^{-1} & \sum_{i=1}^m (\hat{\theta}_{HT} - \theta)(S^2_i + \hat{\tau}^2(\theta))^{-1} \\ 0 & \sum_{i=1}^m (S^2_i + \hat{\tau}^2(\theta))^{-2} \end{array} \right),$$

$q(\theta)$ the vector given by

$$q(\theta) = \left( -\sum_{i=1}^m \frac{(\hat{\theta}_{HT} - \theta)(S^2_i + \hat{\tau}^2(\theta))^{-1}}{(S^2_i + \hat{\tau}^2(\theta))^{-1} - (S^2_i + \hat{\tau}^2(\theta))^{-1}} \right),$$

$I(\theta, \tau^2)$ the $2 \times 2$ Fisher information matrix, $I_{22}(\theta, \hat{\tau}^2)$ the second diagonal element of $I(\theta, \tau^2)$, $J(\theta, \tau^2)$ the Hessian matrix (i.e., $J(\theta, \tau^2) = -EJ(\theta, \tau^2)$), and $S^{-1}(\theta)q(\theta)$ the first element of the vector $S^{-1}(\theta)q(\theta)$. The Guolo-Skovgaard (GS) $100\% \times (1 - \alpha)$ confidence interval for $\theta$ is obtained by the set of values of $\theta$ that satisfies $z_{\alpha/2} \leq \tilde{r}_{GS}(\theta) \leq z_{1-\alpha/2}$. These confidence limits will be calculated from data using [R] package “metaLik” (Guolo and Varin, 2012). Also the GS method uses the estimators $\hat{\theta}_{HT}$ and $\hat{\tau}^2_{HT}$ of Hardy and Thompson, and constructs only an alternative confidence interval for $\theta$.

### 2.3 A bivariate distribution method

The methods discussed in Sections 2.1 and 2.2 provide estimators and confidence intervals for the parameters $\theta$ and $\tau^2$ conditionally on $\sigma^2_i = S^2_i$. We believe that $S^2_i$ should be viewed as an estimator for $\sigma^2_i$. In this view it will not be likely equal to $\sigma^2_i$. Treating $S^2_i$ as an estimator for $\sigma^2_i$, instead of conducting a conditional analysis, has been acknowledged in literature (Hardy and Thompson, 1996), but it has also been refuted, since it would not or marginally affect the calculation of confidence intervals for $\theta$ compared to the conditional analysis (Hardy and Thompson, 1996). It is clear that the estimator for the between-study variance plays a more dominant role in the calculation of confidence intervals on $\theta$ than the within-study variances. Nevertheless, we propose a bivariate distribution method in which both $Y_i$ and $S^2_i$ are jointly modelled.

We assume that $Y_i$ follows model (1) and $S^2_i$ has approximately a chi-square distribution, i.e., $df_i S^2_i / \sigma^2_i \sim \chi^2_{df_i}$, with $df_i$ the degrees of freedom for $S^2_i$. We assume that $df_i$ is either observed or can be calculated from the aggregated information. Furthermore, we assume that $\sigma^2_i \approx \sigma^2 \eta_i$, with $\eta_i > 0$ a known value that would typically depend on the sample size of study $i$. Thus we assume that the residual variances in (1) are considered heteroscedastic across studies as a consequence of different study sizes, but they share a common within-study variance parameter $\sigma^2$. The assumption $\sigma^2_i \approx \sigma^2 \eta_i$ is in line with literature on pooling estimates from biological assays (Cochran, 1954) and helps us maintain a parsimonious model. Estimating $m$ variance parameters $\sigma^2_i$ may result in an overfit and will lead to numerical complexities.

One example is $\eta_i = [n_i - 3]^{-1}$, with $n_i$ the total sample size for study $i$. This choice fits with pooling Fisher’s $z$ transformed correlation coefficients. Estimation of the variance parameter $\sigma^2$ is then expected to be close to one. An other example is $\eta_i = [n^{-1}_{ij} + n^{-1}_{ij}]$, with $n_{ij}$ the sample size for the binary exposure $j \in \{0, 1\}$. This choice fits with pooling mean differences. The variance parameter $\sigma^2$ represents the between-participant variation within studies (van den Heuvel et al., 2020). More generally, we may always consider $\eta_i = [df_i]^{-1}$, where $df_i$ is then viewed as the effective sample size of study $i$. The variance parameter $\sigma^2$ would then become a nuisance parameter as a measure of within-study variability without having a direct meaning to
the underlying individual data from the studies. Note that our simulation model will be more heteroscedastic than what we assume in this estimation approach to verify the robustness of our approach.

The log-likelihood function for the bivariate distribution of \((Y_i, S^2_i)\) is given by

\[
l(\theta, \tau^2, \sigma^2) \approx -\frac{1}{2} \left[ m \log(2\pi) + \sum_{i=1}^{m} \left( \log(\tau^2 + \sigma^2_i) + (Y_i - \theta)^2 / (\tau^2 + \sigma^2_i) \right) \right.
\]

\[+ \left. d f \log(2) + \sum \left( 2 \log \Gamma(\frac{d f_i}{2}) + (d f_i - 2) \log (\chi^2_i + \tau^2) \right) \right],
\]

with \(\chi_i^2 = d f_i S^2_i / \sigma^2_i\) the chi-square statistic, \(d f = \sum_{i=1}^{m} d f_i\) the total number of degrees of freedom, and \(\Gamma\) the gamma function. Note that the sum \(\sum_{i=1}^{m} \chi_i^2\) in the likelihood (7) is also chi-square distributed with \(d f\) degrees of freedom (Moschopoulos, 1985). Calculating the likelihood equations for the estimation of the parameters \(\theta, \tau^2, \) and \(\sigma^2\), leads to the two equations in (3) with \(S^2_i\) replaced by \(\sigma^2_i = \sigma^2 / d f_i\), and additionally to a third equation

\[
\sum_{i=1}^{m} \frac{(Y_i - \theta)^2 - (\tau^2 + \sigma^2_i)}{d f_i (\tau^2 + \sigma^2_i)^2} = \sum_{i=1}^{m} \frac{(d f_i - 2) \sigma^2_i - d f_i S^2_i}{d f_i \sigma^2_i}.
\]

Here \(\sigma^2\) can be obtained by applying the Newton-Raphson method (Choi and Wette, 1969) if \(\theta\) and \(\tau^2\) would be given. Estimation of all three parameters \(\theta, \tau^2, \) and \(\sigma^2\) can be obtained with the procedure NLMMIXED of SAS software. The ML estimators of our bivariate distribution method are referred to as \(\hat{\theta}_{BD}, \hat{\tau}^2_{BD},\) and \(\hat{\sigma}^2_{BD}\). The programming codes for procedure NLMMIXED are provided in the appendix.

An asymptotic 100% \(\times (1-\alpha)\) confidence interval on \(\theta\) can also be provided by the SAS procedure NLMMIXED and it is given by \(\hat{\theta}_{BD} \pm t_{m-1,\alpha/2} SE(\hat{\theta}_{BD})\), with \(t_{m-1,\alpha/2}\) the \(\alpha^{th}\) upper quantile of the \(t\)-distribution with \(d\) degrees of freedom, and \(SE(\hat{\theta}_{BD})\) the estimated asymptotic standard error of the estimator \(\hat{\theta}_{BD}\) (SAS Institute, 1996). SAS uses the number of random effects minus one \((m - 1)\) as the default number of degrees of freedom.

We do realize that the proposed bivariate method requires more input than the other described methods, since the number of degrees of freedom \(d f_i\) associated with the within-study variance estimate \(S^2_i\) is required in our approach. However, in practice we expect that meta-analysts may have access to this information or otherwise can calculate or create the appropriate degrees of freedom for \(S^2_i\).

### 2.4 Case study from literature

To illustrate the approaches, we applied them to a meta-analysis on mean platelet volume (MPV) and coronary artery disease (CAD) (Sansanayudh et al., 2014). One of their aims was to conduct a systematic review and meta-analysis comparing mean differences in MPV between patients (CAD) and controls. Forty studies were included in this meta-analysis based on the authors eligibility criteria, but 36 studies reported a mean difference and only 31 studies compared the mean MPV between CAD patients and controls. We used the data of these 31 studies (see Figure 2 in Sansanayudh et al. (2014) ). For these studies we extracted the means, standard deviations, and sample sizes for patients and controls and calculated the mean difference, an estimate of the standard error, and an accompanied degrees of freedom (see Section 3).

The pooled mean difference with their 95% confidence intervals and the estimate for the between study variance \(\tau^2\) for our five approaches are presented in Table 1. The estimates from HT, NB, and GS are all equal, since they are the maximum likelihood estimates for likelihood function (2). They only differ in the calculation of confidence intervals. DL has the smallest pooled estimate, the smallest estimate for \(\tau^2\), and the narrowest 95% confidence interval. The 95% confidence intervals for NB and GS are slightly wider than the 95% confidence interval of HT, which is the intention of these two methods. The pooled estimate of BD is very close to the estimate of HT, but the 95% confidence interval is slightly wider than the 95% confidence interval of NB and GS. The estimate of the between-study variance of BD is also slightly larger than the estimate of HT. The reported pooled estimate in (Sansanayudh et al., 2014) based on DL was 0.70 (0.55; 0.85). The 95% confidence interval is smaller than ours, since we used a \(t\)-distribution instead of the normal distribution.

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**Figure 2:** Pooled estimate of mean difference in MPV between CAD patients and controls. For these studies we extracted the means, standard deviations, and sample sizes for patients and controls and calculated the mean difference, an estimate of the standard error, and an accompanied degrees of freedom (see Section 3).

**Table 1:** The estimates from HT, NB, and GS are all equal, since they are the maximum likelihood estimates for likelihood function (2). They only differ in the calculation of confidence intervals. DL has the smallest pooled estimate, the smallest estimate for \(\tau^2\), and the narrowest 95% confidence interval. The 95% confidence intervals for NB and GS are slightly wider than the 95% confidence interval of HT, which is the intention of these two methods. The pooled estimate of BD is very close to the estimate of HT, but the 95% confidence interval is slightly wider than the 95% confidence interval of NB and GS. The estimate of the between-study variance of BD is also slightly larger than the estimate of HT. The reported pooled estimate in (Sansanayudh et al., 2014) based on DL was 0.70 (0.55; 0.85). The 95% confidence interval is smaller than ours, since we used a \(t\)-distribution instead of the normal distribution.
Table 1: Combined estimate of mean difference of MPV, along with 95% confidence limits and the between-study variance estimate

| Method | $\theta$ with 95% confidence limits | $\hat{\tau}^2$ |
|--------|------------------------------------|-------------|
| DL     | 0.6990 (0.5437; 0.8542)            | 0.1532      |
| HT     | 0.7031 (0.5259; 0.8835)            | 0.2137      |
| NB     | 0.7031 (0.5198; 0.8898)            | 0.2137      |
| GS     | 0.7031 (0.5216; 0.8901)            | 0.2137      |
| BD     | 0.7033 (0.5004; 0.9064)            | 0.2284      |

3 Simulation model

We use a simulation model to generate data from an individual participant data (IPD) meta-analysis. The IPD is used to calculate a study effect size $Y_i$, an accompanied standard error $S_i$, and its associated degrees of freedom $df_i$. The aggregated data is then pooled using the methods described in Section 2. Different settings for the IPD model parameters were selected. A number of 1000 simulation runs were generated for each setting. For each simulation run, the parameter $\theta$ is estimated and accompanied with a 95% confidence interval using the methods described in Section 2. We present the bias, mean squared error (MSE), and the coverage probability for the main parameter $\theta$.

3.1 Simulation model

We simulated an IPD meta-analysis with $m$ studies. The sample size $n_i$ for study $i = 1, \cdots, m$ varied from study to study. This sample size was drawn from an overdispersed Poisson distribution, i.e., $n_i | \gamma_i \sim \text{Poi}(\lambda \exp\{0.5\gamma_i\})$, with $\gamma_i \sim \Gamma(a_0, b_0)$ drawn from a gamma distribution. Then within each study the participants are randomly allocated to two groups (e.g., treatments) with probabilities $p$ and $1 - p$, resulting in $n_{i0}$ participants in the control group (i.e., $n_{i0} | n_i \sim \text{Bin}(n_i, p)$) and $n_{i1} = n_i - n_{i0}$ participants in the exposed group. A continuous response $Y_{ijk}$ for individual $k (= 1, \cdots, n_{ij})$, in group $j (= 0, 1)$, of study $i$ is then simulated according to a heteroscedastic linear mixed effects model (Quintero and Lesaffre, 2017; Davidian and Carroll, 1987):

$$Y_{ijk} = \mu_j + U_{ij} + \xi_j \exp(V_i) \epsilon_{ijk},$$

with $\mu_j$ the mean of group $j$, $U_{ij}$ a study-specific random effect for group $j$, $\xi_j$ a group-specific residual variance parameter, $V_i$ a random effect for residual heteroscedasticity across studies, and $\epsilon_{ijk} \sim N(0, 1)$ standard normally distributed and independent of random effects $U_{i0}, U_{i1}$, and $V_i$. It is assumed that $(U_{i0}, U_{i1}, V_i)^T$ has a multivariate normal distribution with means 0 and variance-covariance matrix $\Sigma$ given by

$$\Sigma = \begin{pmatrix}
\sigma_0^2 & \rho_M \sigma_0 \sigma_1 & \rho_V \sigma_0 \sigma_2 \\
\rho_M \sigma_0 \sigma_1 & \sigma_1^2 & \rho_V \sigma_1 \sigma_2 \\
\rho_V \sigma_0 \sigma_2 & \rho_V \sigma_1 \sigma_2 & \sigma_2^2
\end{pmatrix}.$$

The value of $\rho_M$ represents the correlation between the study-specific random effects $U_{i0}$ and $U_{i1}$ for the exposed and the control group, respectively. The value $\rho_V$ represents the correlation between the study mean and the logarithm of the random heteroscedastic residual variance.

There are two forms of residual heteroscedasticity in IPD model 2. One is at the level of the participant and introduced via parameter $\xi_j^2$ and the other one is at the level of the study introduced via the random term $\exp(V_i)$. The variance $\xi_j^2$ indicates a fixed heteroscedasticity in variability between individuals for the two groups (i.e., the group affects both the level and the variability) and is consistent across studies, while $\exp(V_i)$ indicates a random heteroscedasticity.
The observed study effect measure aggregated at the study level is given by the raw mean difference \( Y_i = \bar{Y}_{ij0} - \bar{Y}_{ij1} \), for study \( i \), where \( \bar{Y}_{ij} = \sum_{k=1}^{n_{ij}} Y_{ijk}/n_{ij} \) is the average value for group \( j \) in study \( i \). Based on model (3), the observed study effect can be written into the well-known random effects model\(^4\) for meta-analysis studies (Brockwell and Gordon, 2007)

\[
Y_i = \theta + U_i + \varepsilon_i, \tag{9}
\]

with \( \theta = \mu_0 - \mu_1 \) the overall mean difference, \( U_i \equiv U_{i0} - U_{i1} \) represents the study effect size heterogeneity, \( \varepsilon_i = \exp(V_i)(\xi_0\varepsilon_{i0} - \xi_1\varepsilon_{i1}) \) is the within-study residual with \( \bar{\varepsilon}_{ij} = \sum_{k=1}^{n_{ij}} \varepsilon_{ijk}/n_{ij} \). If \( \rho_M = 1 \) and \( \sigma_0 = \sigma_1 \), \( U_{i0} - U_{i1} \) is degenerate in zero or non-existent, while for all other settings of \( \rho_M < 1 \), \( \sigma_0 > 0 \), and \( \sigma_1 > 0 \) it will lead to heterogeneous study effect sizes. Without the existence of \( V_i \), the residuals \( \varepsilon_i \) in (9) are still heteroscedastic across studies \( \text{VAR}(\varepsilon_i) = \xi_0^2/n_{i0} + \xi_1^2/n_{i1} \), unless sample sizes are consistent across studies.

The estimated standard error \( S_i \) for the study effect size \( Y_i \) is given by \( S_i^2 = S_{i0}^2/n_{i0} + S_{i1}^2/n_{i1} \), where \( S_{ij}^2 = \sum_{k=1}^{n_{ij}} (Y_{ijk} - \bar{Y}_{ij})^2/(n_{ij} - 1) \) is the sample variance for group \( j \) in study \( i \). Here we allow that the variability between individuals within treatments could be different. The variance \( S_i^2 \) can be rewritten into

\[
S_i^2 = \exp(2V_i)(\xi_0^2s_{i0}^2/n_{i0} + \xi_1^2s_{i1}^2/n_{i1}), \tag{10}
\]

with \( (n_{ij} - 1)s_{ij}^2 = \sum_{k=1}^{n_{ij}} (\varepsilon_{ijk} - \bar{\varepsilon}_{ij})^2 \) chi-square distributed with \( n_{ij} - 1 \) degrees of freedom. The corresponding degrees of freedom \( df_i \) for \( S_i^2 \) can be determined by Satterthwaite approach (Satterthwaite, 1946):

\[
df_i = S_i^4/[S_{i0}^4/(n_{i0}^2(n_{i0} - 1)) + S_{i1}^4/(n_{i1}^2(n_{i1} - 1))]. \tag{11}
\]

The simulation model deviates from the model assumptions described in Section 2 due to the introduction of the random variable \( V_i \). First of all, the marginal distribution of \( Y_i \) is no longer normal, although the conditional distribution of \( Y_i \) given \( V_i \) is normally distributed with mean \( \theta \) and variance \( \exp(2V_i)(\xi_0^2/n_{i0} + \xi_1^2/n_{i1}) \). Secondly, the variance of \( Y_i \) given \( S_i^2 \) is unequal to \( S_i^2 \), since the conditional distributions of \( Y_i \) and \( S_i^2 \) given \( V_i \) are independent (see van den Heuvel et al. (2020)). Finally, the marginal distribution of \( S_i^2 \) is not directly related to a chi-square distribution. Only the conditional distribution of \( S_i^2 \) given \( V_i \) is approximately chi-square distributed using Satterthwaite approach (Satterthwaite, 1946), i.e., \( df_iS_i^2/[\exp(V_i)(\xi_0^2/n_{i0} + \xi_1^2/n_{i1})] \) is approximately chi-square distributed with \( df_i \) degrees of freedom conditioned on \( V_i \). And it becomes exactly chi-square distributed with \( n_{i0} + n_{i1} - 2 \) degrees of freedom conditioned on \( V_i \), when both \( \xi_0 = \xi_1 \) and \( n_{i0} = n_{i1} \) hold. The marginal distribution of \( S_i^2 \) is less traceable. Thus all proposed estimation methods with their accompanied confidence intervals for \( \theta \) in Section 2 are at best approximate methods for the data of our simulated meta-analysis. We believe that none of the approaches has an obvious direct advantage over any of the other methods.

The settings of the parameters are chosen such that the simulation corresponds approximately with a meta-analysis of clinical trials on for instance hypertension treatment (for systolic blood pressure). Parameter settings used to generate the aggregated data \( (Y_i, S_i, df_i) \) from the individual participant data are \( m \in \{10, 20, 30\} \), \( \lambda = 100 \), \( a_0 = b_0 = 1 \), \( p = 0.5 \), \( \mu = 160 \), \( \theta = -2 \), \( \xi_0^2 = \xi_1^2 = 100 \). We will run several combinations of the remaining parameters \( \sigma_0^2, \sigma_1^2, \sigma_2^2, \rho_M \) and \( \rho_V \) of the IPD model:

1. **Setting 1**: Homogeneous study effects and no random heteroscedastic residuals: \( \sigma_0^2 = 0, \sigma_1^2 = 0, \sigma_2^2 = 0, \rho_M = 0 \) and \( \rho_V = 0 \),

2. **Setting 2**: Heterogeneous study effects and no random heteroscedastic residuals: \( \sigma_0^2 = 2, \sigma_1^2 = 3, \sigma_2^2 = 0, \rho_M = 0.7 \), and \( \rho_V = 0 \).

\( ^4 \)In the random effects model it is often assumed that the random variables \( U_i \) and \( \varepsilon_i \) are independent and normally distributed, but due to our random heteroscedastic variable \( \exp(V_i) \) both assumptions will be violated.
3. **Setting 3:** Heterogeneous study effects and random heteroscedastic residuals without correlation: $\sigma_0^2 = 2$, $\sigma_1^2 = 3$, $\sigma_2^2 = 1$, $\rho_M = 0.7$, and $\rho_V = 0$.

4. **Setting 4:** Heterogeneous study effects and random heteroscedastic residuals with low correlation: $\sigma_0^2 = 2$, $\sigma_1^2 = 3$, $\sigma_2^2 = 1$, $\rho_M = 0.7$, and $\rho_V = 0.3$.

5. **Setting 5:** Heterogeneous study effects and random heteroscedastic residuals with medium correlation: $\sigma_0^2 = 2$, $\sigma_1^2 = 3$, $\sigma_2^2 = 1$, $\rho_M = 0.7$, and $\rho_V = 0.5$.

6. **Setting 6:** Heterogeneous study effects and random heteroscedastic residuals with high correlation: $\sigma_0^2 = 2$, $\sigma_1^2 = 3$, $\sigma_2^2 = 1$, $\rho_M = 0.7$, and $\rho_V = 0.7$.

4 Results

Tables 2 and 3 present the bias and the MSE of the three different estimation methods (DL, HT, and BD), respectively. Note that the Noma-Bartlett and Guolo-Skovgaard confidence intervals make use of the maximum likelihood estimators of Hardy and Thompson.

For the settings without heteroscedasticity (settings 1 and 2) the biases of DL, HT, and BD are all similar, irrespective of sample size biases remain within 1.2% of the true effect size ($\theta = -2$) for the homogeneous study effect sizes. In the presence of uncorrelated heterogeneous study effect sizes and random heteroscedasticity (setting 3), again all biases are very close to zero for all three sample sizes. However, in case of correlated heterogeneous study effect sizes and random heteroscedasticity (settings 4 through 6), only BD seems to have small biases for all sample sizes and it is never larger than 0.9% of the true effect size. The biases of DL and HT are away from zero, in particular when the correlation between the heterogeneous study effect sizes are strongly correlated to the random heteroscedasticity. The sample size does not seem to affect this. The bias can then reach a level of 5% of the true effect size. For $m = 10$, BD and DL are similar and very close to zero. The performance of DL seems to be the worst for $m = 20$, with a bias that could reach 1.5%. Unfortunately, HT seem to provide a small negative bias for all three study sizes that can reach more than 5%.

Table 2: Bias of the estimation methods under different simulation settings and for $\theta = -2$.

| Setting | $m = 10$ |         |         |         | $m = 20$ |         |         |         | $m = 30$ |         |         |
|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|         | DL      | HT      | BD      |         |         |         |         |         |         |         |         |
| 1       | -0.024  | -0.024  | -0.024  | -0.021  | -0.021  | -0.020  |         |         | -0.010  | -0.010  | -0.011  |
| 2       | -0.006  | -0.008  | -0.007  | -0.013  | -0.015  | -0.012  | -0.004  | -0.004  | -0.004  |         |         |
| 3       | 0.007   | 0.010   | -0.010  | -0.001  | 0.001   | -0.018  | -0.001  | -0.001  | -0.006  |         |         |
| 4       | -0.034  | -0.036  | -0.007  | -0.043  | -0.044  | -0.017  | -0.045  | -0.046  | -0.007  |         |         |
| 5       | -0.062  | -0.068  | -0.006  | -0.073  | -0.075  | -0.016  | -0.075  | -0.077  | -0.007  |         |         |
| 6       | -0.091  | -0.098  | -0.005  | -0.103  | -0.107  | -0.015  | -0.106  | -0.108  | -0.006  |         |         |

The performance of MSE for the three estimation methods is very consistent across all settings. For all methods, the MSE increases with settings, which is expected due to the increased variability. Setting 1 has no study heterogeneity and no random heteroscedasticity, and thus the smallest variability across meta-analysis studies. Setting 2 has heterogeneous study effect sizes but no heteroscedasticity yet. Then for settings three to six, the residual variance increases due to the random heteroscedasticity and an increased positive correlation $\rho_V$, while the heterogeneity in study effect sizes remains constant (although the correlation seem to have little effect). When no random heteroscedasticity is present, the MSE of the three estimation approaches DL, HT, and BD are almost identical. However, when heteroscedasticity is present, the MSE of BD is larger than the MSE of DL and HT. The MSE of DL and HT seem to be identical across all settings and sample sizes. It seems that the random heteroscedasticity does hardly affect the MSE of DL and HT, since it is at the same level as setting 2 which had no random heteroscedasticity, but BD is strongly affected.
Table 3: MSE of the estimation methods under different simulation settings and for $\theta = -2$.

| Setting | $m = 10$ | $m = 20$ | $m = 30$ |
|---------|----------|----------|----------|
|         | DL | HT | BD | DL | HT | BD | DL | HT | BD |
| 1       | 0.239 | 0.238 | 0.232 | 0.105 | 0.104 | 0.102 | 0.069 | 0.069 | 0.068 |
| 2       | 0.435 | 0.435 | 0.429 | 0.197 | 0.197 | 0.196 | 0.128 | 0.128 | 0.127 |
| 3       | 0.434 | 0.438 | 0.588 | 0.202 | 0.203 | 0.280 | 0.127 | 0.127 | 0.181 |
| 4       | 0.431 | 0.435 | 0.605 | 0.202 | 0.204 | 0.276 | 0.126 | 0.127 | 0.182 |
| 5       | 0.432 | 0.436 | 0.610 | 0.204 | 0.206 | 0.271 | 0.128 | 0.129 | 0.182 |
| 6       | 0.436 | 0.441 | 0.617 | 0.208 | 0.210 | 0.265 | 0.132 | 0.132 | 0.183 |

Figure 1 presents the coverage probabilities for the five methods on calculation of 95% confidence intervals on the main parameter $\theta$ for the six different simulation settings. For the (unrealistic) case of homogeneous effect sizes without random heteroscedasticity (setting 1) the methods show above nominal coverage probabilities, although the HT method seems closer to nominal than the others. When the number of studies is $m = 30$ all coverages are very close to 97%. The DL, BD, NB, and GS method seem to decrease to this coverage when study sizes increase from $m = 10$ to $m = 30$, while HT show a small increase to this coverage. In case random heteroscedasticity is introduced, the DL and HT method seem to underperform and provide liberal coverage probabilities, while DB, NB, and GS seem to provide coverages (very) close to the nominal 95% coverage, although the GS method seem to be slightly, but consistently, conservative at $m = 10$ studies. For the heterogeneous effect sizes with no random heteroscedasticity (setting 2), all methods seem close to the nominal coverage of 95%, in particular when the number of studies is $m = 20$ or larger.
(e) Heterogeneous and heteroscedastic effect sizes with $\rho_{02} = \rho_{12} = 0.5$ (setting 5).

(f) Heterogeneous and heteroscedastic effect sizes with $\rho_{02} = \rho_{12} = 0.7$ (setting 6).

Figure 1: Empirical coverage percentages of 95% confidence intervals of five methods for the overall effect size under different settings and study sizes.

To complete the comparison, we also compared the estimates of the between study variance $\tau^2$ for the three estimation methods DL, HT, and BD. For the first setting the variance $\text{VAR}(U_i) = \text{VAR}(U_{i0} - U_{i1})$ is $\tau^2 = 0$ and in the remaining settings this variance is $\tau^2 = \sigma_0^2 + \sigma_1^2 - 2\rho_M \sigma_0 \sigma_1 = 2 + 3 - 2 \times 0.7 \times \sqrt{2} \times \sqrt{3} \approx 1.5707$. However, in case of heteroscedasticity, the correlation between the heterogeneous study effect sizes $U_i$ and the random heteroscedasticity $V_i$ may affect the estimation of the between study variance, but we expect it to be still close to 1.5707. The results of the estimates are presented in the following table.

Table 4: Between study variances of the three estimation methods under different simulation settings.

| Setting | $m = 10$ | $m = 20$ | $m = 30$ |
|---------|----------|----------|----------|
|         | DL       | HT       | BD       | DL       | HT       | BD       | DL       | HT       | BD       |
| 1       | 0.436    | 0.281    | 0.238    | 0.296    | 0.207    | 0.172    | 0.240    | 0.177    | 0.146    |
| 2       | 1.779    | 1.404    | 1.306    | 1.601    | 1.410    | 1.330    | 1.589    | 1.468    | 1.393    |
| 3       | 1.728    | 1.320    | 1.661    | 1.560    | 1.380    | 1.629    | 1.569    | 1.449    | 1.615    |
| 4       | 1.725    | 1.325    | 1.683    | 1.564    | 1.379    | 1.625    | 1.575    | 1.445    | 1.581    |
| 5       | 1.723    | 1.332    | 1.674    | 1.565    | 1.380    | 1.629    | 1.576    | 1.441    | 1.556    |
| 6       | 1.722    | 1.333    | 1.675    | 1.563    | 1.376    | 1.614    | 1.563    | 1.439    | 1.549    |

Without heterogeneity and random heteroscedasticity, all methods are biased, but the BD method is closest to the truth and the bias reduces with sample size. In case of heterogeneity, but without random heteroscedasticity, the DL approach is closest to the true value when sample sizes $m$ are 20 or larger. DL seems to overestimate the variance, while HT and BD underestimates the variance. This latter observation is well known characteristic of maximum likelihood estimation for variance components. In case of heterogeneity and random heteroscedasticity, the BD and DL method are closer to the truth than the HT method. The BD method is better than DL when sample sizes are small, while DL is slightly better than BD when sample sizes are larger. The HT method seems to be biased in all settings.

5 Discussion

The purpose of this article was to introduce a joint analysis of the study effect sizes and its estimated standard error for aggregated data meta-analyses. A combination of a normal and chi-square distribution was used to describe the distribution of the observed bivariate statistics. The performance of this bivariate distribution was compared to that of the DerSimonian-Laird method and three likelihood-based methods. The likelihood-based methods assumed that the
residual variance of the study effect size is equal to the squared standard error. We studied the profile likelihood approach of Hardy and Thompson, the Bartlett-corrected likelihood ratio, and the Skovgaard corrected likelihood ratio. A simulation study with different scenarios was carried out using different numbers of studies and different correlation structures between the study effect sizes and its standard error. The simulation settings explicitly studied (random) heteroscedasticity of the true residual variance of the study effect sizes, because we believe that heteroscedasticity is common in practice. None of the five studied approaches are equipped to deal with this heteroscedasticity explicitly.

Differences between the methods for estimation of the pooled effect size with its accompanied confidence interval were relatively small, but some differences were observed. When heteroscedasticity is introduced, the DerSimonian-Laird and Hardy-Thompson approach show a small bias in the pooled effect size. This bias most likely caused a liberal coverage probability, a conclusion already established in literature (Norma, 2011; Guolo, 2012). In case we apply the Hartung-Knapp-Sidak-Jonkman standard error estimate for the DerSimonian-Laird method, the coverage improves for the homogeneous and homoscedastic setting, but it remains similar to the DL results for all other settings (data not shown). Since the corrected likelihood approaches use a finite sample approximation of the distribution of the Hardy-Thompson estimator, these corrected approaches provide the same bias as the Hardy-Thompson method, but they do improve the coverage probability. The Bartlett-type and the Skovgaard corrected likelihood ratio methods have comparable results, and are slightly conservative when the number of studies is small, but for larger study sizes they provide nominal coverage probabilities. These conclusions have been established earlier too (Norma, 2011; Veroniki et al., 2019). More generally, all methods provide nominal coverages as the number of studies increases. Our bivariate approach provided similar and consistent results in all performance measures under heterogeneity and random heteroscedasticity, with coverage probabilities close to nominal for all sample sizes. The coverage is very similar or better than the two finite sample size corrected likelihood approaches and outperforms DerSimonian-Laird and Hardy-Thompson approaches. The disadvantage of our approach is the need for a degrees of freedom, but the analysis is straightforward and based on first-order asymptotics that do not need a finite sample correction. It also performs well when studies are heterogeneous in both the study effect sizes and their standard errors.

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Conflict of interest

The authors have declared no conflict of interest.
Appendix: code used for implementing the Bivariate distribution method

The following programming codes in proc NLMIXED assume that there exists a data set “Effect_Sizes” with different columns and rows. The rows represent studies which are listed in column “Study”. For each study we have two separate rows: one row for the effect size $Y_i$ and a second row for the variance $S^2_i$. The effect size $Y_i$ and variance $S^2_i$ are below each other in the same column called “Outcome” and to identify these different responses we have a column “Response” with levels “effect size” and “variance”. Finally, there is a column with the degrees of freedom for each study. Table 5 shows schematically how the data is organized.

Table 5: Schematic overview of how the data of a meta-analysis should be organized to execute our bivariate distribution approach.

| Study | Response   | Outcome | Degrees |
|-------|------------|---------|---------|
| 1     | effect size| $Y_1$   | $df_1$  |
| 1     | variance   | $S^2_1$ | $df_1$  |
| 2     | effect size| $Y_2$   | $df_2$  |
| 2     | variance   | $S^2_2$ | $df_2$  |
| ...   | ...        | ...     | ...     |
| $m$   | effect size| $Y_m$   | $df_m$  |
| $m$   | variance   | $S^2_m$ | $df_m$  |

PROC NLMIXED DATA = Effect_Sizes QPOINTS=10 MAXITER=100 TECH=NEWRAP;
PARMS THETA = 0 LNSTAU = 0 SD = 10;
MU = THETA + U;
TAU2 = EXP(2*LNSTAU);
VAR_I = (SD**2)/Degrees;
IF Response = “effect size” THEN DENS = -0.5*LOG(2*3.14159)-0.5*LOG(VAR_I)-0.5*((Outcome - MU)**2)/VAR_I;
ELSEIF Response = “variance” THEN DENS = -(Degrees/2)*LOG(2)-LGAMMA(Degrees/2)+((Degrees/2)-1)*LOG(Degrees*Outcome/VAR_I)-0.5*Degrees*Outcome/VAR_I;
MODEL Outcome~GENERAL(DENS);
RANDOM U ~ NORMAL (0, TAU2) SUBJECT = Study;
RUN;QUIT;
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