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Multivariate meta-analysis with an increasing number of parameters

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Summary

Meta-analysis can average estimates of multiple parameters, such as a treatment's effect on multiple outcomes, across studies. Univariate meta-analysis (UVMA) considers each parameter individually, while multivariate meta-analysis (MVMA) considers the parameters jointly and accounts for the correlation between their estimates. The performance of MVMA and UVMA has been extensively compared in scenarios with two parameters. Our objective is to compare the performance of MVMA and UVMA as the number of parameters, p , increases. Specifically, we show that (i) for fixed-effect meta-analysis, the benefit from using MVMA can substantially increase as p increases; (ii) for random effects meta-analysis, the benefit from MVMA can increase as p increases, but the potential improvement is modest in the presence of high between-study variability and the actual improvement is further reduced by the need to estimate an increasingly large between study covariance matrix; and (iii) when there is little to no between study variability, the loss of efficiency due to choosing random effects MVMA over fixed-effect MVMA increases as p increases. We demonstrate these three features through theory, simulation, and a meta-analysis of risk factors for Non-Hodgkin Lymphoma.

Keywords

efficiency; fixed-effect models; multivariate meta-analysis; random effects models

1 Introduction

Multiple studies often target the same scientific question and aim to estimate the same set of parameters. Meta-analyses combine results across studies to obtain a single, more accurate estimate of the desired parameters (Higgins and Green, 2011). When estimating multiple parameters, such as the effect of one treatment on multiple outcomes (Gail *et al.*, 2000;

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Conflict of interest

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Gleser and Olkin, 2009), the association of multiple treatments or risk factors with a single outcome (Ritz *et al.*, 2008; Jackson *et al.*, 2009), or the parameters of a diagnostic test (Rutter and Gatsonis, 2001; Simel and Bossuyt, 2009), the two alternatives are to individually evaluate each parameter through univariate meta-analyses (UVMA) or to perform a single multivariate meta-analysis (MVMA) (Jackson *et al.*, 2011; Riley *et al.*, 2007b; Van Houwelingen *et al.*, 2002). By considering the correlations, MVMA can borrow information across parameters, thus increasing the precision of the summary estimates, as discussed by Riley (2009); Ritz *et al.* (2008); Riley *et al.* (2007b) and Riley *et al.* (2007a).

There are multiple factors that should be considered when deciding between MVMA and UVMA. For example, when the objective is to estimate a function of multiple parameters, MVMA is required for valid statistical inference. Consequently, MVMA should be used in studies comparing the sensitivity and specificity of a new diagnostic test. When studies only estimate subsets of the desired parameters, MVMA can significantly increase precision and reduce reporting bias. However, when studies do not publish within-study correlation matrices, MVMA may be impractical. In settings when both MVMA and UVMA are reasonable approaches, one factor to consider is that MVMA offers a potential gain in efficiency.

While methods for performing MVMA have been introduced and developed within both the fixed (FE) (Berkey *et al.*, 1995, 1996) and random effects (RE) frameworks (Berkey *et al.*, 1998; Jackson *et al.*, 2010; Chen *et al.*, 2012; Jackson *et al.*, 2013), the potential gain in efficiency has been repeatedly questioned (Riley *et al.*, 2007a; Bland, 2011; Trikalinos *et al.*, 2013). Much of the recent debate has focused on bivariate RE meta-analysis. Simulations, examples, and theory (Ishak *et al.*, 2007; Riley, 2009; Riley *et al.*, 2007b) all support that MVMA offers minimal benefit in most scenarios and even no benefit when the within-study covariance matrices are the same, as shown by Riley (2009). Comparisons of UVMA and MVMA in the presence of more than two parameters are limited (Berkey *et al.*, 1998; Jackson *et al.*, 2011), but in the available examples, the precision gained from MVMA appears to be slightly stronger. As the number of estimated parameters, p , increases, the potential for borrowing information across parameters increases, and gains from using MVMA should similarly increase. To our knowledge, however, there has been no focused discussion on how MVMA's gain in efficiency, in either the FE or RE frameworks, changes as the number of parameters, p , increases.

The impetus for this investigation is the growing popularity of meta-analyses in epidemiological studies (Blettner *et al.*, 2014). These studies often estimate a comparatively large number of parameters, such as the odds ratios for a set of related risk factors. Our objective is to provide guidance as to when MVMA may offer significantly more precise estimates of the targeted parameters. In the methods section, we define our metric of comparison to be the relative efficiency and describe the scenarios used to compare UVMA and MVMA. In the results section, we first derive the theoretical relationship between the relative efficiency and number of parameters for key instructive examples. We then use simulations to measure the relative efficiencies for many more complex examples. Finally, we apply these methods to studies from a consortium examining the association between lifestyle risk factors and the risk of Non-Hodgkin Lymphoma (Morton *et al.*, 2005a,b).

2 Methods

2.1 Notation

Assume that we have I studies. In study i , let $\boldsymbol{\mu}_i = (\mu_{1i}, \dots, \mu_{pi})'$ be a vector of p parameters and let $\mathbf{Y}_i = (Y_{1i}, \dots, Y_{pi})'$ be a study-specific estimate of those parameters. We assume that, conditional on $\boldsymbol{\mu}_i$, $\mathbf{Y}_i$ follows a multivariate normal distribution, $\mathbf{Y}_i | \boldsymbol{\mu}_i \sim MVN(\boldsymbol{\mu}_i, \mathbf{S}_i)$, where $\mathbf{S}_i$ is the within-study covariance matrix. We let $S_{kk,i}^2 = \text{Var}(Y_{ki} | \mu_{ki})$ and $\rho_{kl,i} = \text{Cor}(Y_{ki}, Y_{li} | \mu_{ki}, \mu_{li})$ for study i and parameters k and l . When there are only two parameters or when the correlation is the same for all parameters in the study, we drop the “kl” from the subscript and use ρ_i .

In the RE framework, we assume that study-specific parameters are random variables following a multivariate normal distribution, $\boldsymbol{\mu}_i \sim MVN(\boldsymbol{\mu}, \boldsymbol{\Sigma})$, where $\boldsymbol{\mu} = (\mu_1, \dots, \mu_p)'$ is the global mean and $\boldsymbol{\Sigma}$ is the between-study covariance matrix. We let $\sigma_k^2 = \text{Var}(\mu_k)$ and $\rho_{kl}^{\text{BS}} = \text{Cor}(\mu_k, \mu_l)$. In the FE framework, the study-specific parameters are all equal to the global mean, $\boldsymbol{\mu}_i \equiv \boldsymbol{\mu}$, or, equivalently, there is no between study heterogeneity, $\boldsymbol{\Sigma} = \mathbf{0}_{p \times p}$. The marginal model for study-specific estimates is therefore $\mathbf{Y}_i \sim MVN(\boldsymbol{\mu}, \mathbf{S}_i + \boldsymbol{\Sigma})$, with $\mathbf{S}_i + \boldsymbol{\Sigma}$ being the total covariance matrix for study i .

The MVMA estimate of $\boldsymbol{\mu}$ is (Raudenbush *et al.*, 1988; Berkey *et al.*, 1995, 1996):

$$\hat{\boldsymbol{\mu}}^M = \left[\sum_{i=1}^I (\hat{\mathbf{S}}_i + \hat{\boldsymbol{\Sigma}})^{-1} \right]^{-1} \sum_{i=1}^I (\hat{\mathbf{S}}_i + \hat{\boldsymbol{\Sigma}})^{-1} \mathbf{Y}_i, \quad (1)$$

where $\hat{\mathbf{S}}_i$ and $\hat{\boldsymbol{\Sigma}}$ estimate the within-study and between-study covariance matrices, respectively. For the RE framework, we estimate the between-study covariance matrix $\boldsymbol{\Sigma}$ by restricted maximum likelihood (REML), implemented in the *mvmeta* R package (Gasparrini *et al.*, 2012); other methods have also been proposed (Jackson *et al.*, 2011; Berkey *et al.*, 1998; Chen *et al.*, 2012; Jackson *et al.*, 2013; Jennrich and Schluchter, 1986; Arends *et al.*, 2003; Ma and Mazumdar, 2011; Mavridis and Salanti, 2013). We do not place any restrictions on the covariance structure in the REML estimation.

The UVMA estimate of $\boldsymbol{\mu}$ can be written similarly to Eq. (1), by setting all within-study and between-study correlations to equal 0,

$$\hat{\boldsymbol{\mu}}^U = \left[\sum_{i=1}^I (\hat{\mathbf{U}}_i + \hat{\mathbf{D}})^{-1} \right]^{-1} \sum_{i=1}^I (\hat{\mathbf{U}}_i + \hat{\mathbf{D}})^{-1} \mathbf{Y}_i, \quad (2)$$

where $\mathbf{U}_i = \text{diag}(\mathbf{S}_i)$ and $\mathbf{D} = \text{diag}(\boldsymbol{\Sigma})$. It is easy to see that asymptotically, as the number of subjects per study (FE framework) or as both the number of studies and number of subjects per study (RE framework) increase to infinity, $\hat{\boldsymbol{\mu}}^U$ and $\hat{\boldsymbol{\mu}}^M$ are unbiased estimates of $\boldsymbol{\mu}$ with variances

$$\text{Var}(\hat{\boldsymbol{\mu}}^U) \approx \left[\sum_{i=1}^I (\mathbf{U}_i + \mathbf{D})^{-1} \right]^{-1} \left[\sum_{i=1}^I (\mathbf{U}_i + \mathbf{D})^{-1} (\mathbf{S}_i + \sum) (\mathbf{U}_i + \mathbf{D})^{-1} \right] \left[\sum_{i=1}^I (\mathbf{U}_i + \mathbf{D})^{-1} \right]^{-1} \quad (3)$$

$$\text{Var}(\hat{\boldsymbol{\mu}}^M) \approx \left[\sum_{i=1}^I (\mathbf{S}_i + \sum)^{-1} \right]^{-1}. \quad (4)$$

We define the relative efficiency for $\hat{\mu}_k$, the k^{th} parameter of $\hat{\boldsymbol{\mu}}$, to be

$$\text{RelEff}_k := \frac{\text{Var}(\hat{\mu}_k^M)}{\text{Var}(\hat{\mu}_k^U)}$$

and use Eqs. (3) and (4) to calculate the asymptotic relative efficiency for any specified scenario. For evaluating $\hat{\boldsymbol{\mu}}^M$ and $\hat{\boldsymbol{\mu}}^U$ in RE models, we also discuss the estimates $\hat{\boldsymbol{\mu}}^{\text{MT}}$ and $\hat{\boldsymbol{\mu}}^{\text{UT}}$ that would be possible had the *true* values of $\boldsymbol{\Sigma}$ and $\mathbf{D}$ been known and used in Eqs. (1) and (2). We denote $\text{Var}(\hat{\mu}_k^{\text{MT}})/\text{Var}(\hat{\mu}_k^{\text{UT}})$ by RelEff_k^T . The main notation we use is summarized in Table 1.

We let $\hat{\boldsymbol{\mu}}^{\text{UB}}$ and $\hat{\boldsymbol{\mu}}^{\text{UT}}$ be, respectively, the UVMA and MVMA estimates produced by Bayesian methods (Wei and Higgins, 2013). For UVMA, we let the prior distributions for μ_j and σ_j^2 be normal (mean=0, variance=1000) and inverse gamma distributions (shape=1/2, scale drawn from inverse of a squared Unif(0,2)), respectively, where j indicates the parameter of interest. For MVMA, we let the prior distributions for $\boldsymbol{\mu}$ and $\boldsymbol{\Sigma}$ be multivariate normal (mean= $\mathbf{0}_p$, variance=1000 $\mathbf{I}_p$, where $\mathbf{I}_p$ is the $p \times p$ diagonal matrix) and inverse Wishart distributions (scale is a $p \times p$ identity matrix with entries drawn from the inverse of a squared Unif(0,2), p degrees of freedom), respectively. Bayesian analysis was performed by R and JAGS (Plummer, 2003) using the `rjags` package. For comparing efficiency, we estimated the variances of $\hat{\boldsymbol{\mu}}^{\text{UB}}$ and $\hat{\boldsymbol{\mu}}^{\text{MB}}$ by simulation.

2.2 Preface: two parameters (p=2) and two studies (I=2)

To understand when multivariate modeling has the potential to improve precision, we start by considering the scenario with two parameters (p=2) and two studies (I=2). The univariate and multivariate estimates for the first parameter, μ_1 , are

$$\hat{\mu}_1^U = \hat{v}_{11} Y_{11} + (1 - \hat{v}_{11}) Y_{12} \quad (5)$$

$$\hat{\mu}_1^M = \hat{w}_{11}Y_{11} + (1 - \hat{w}_{11})Y_{12} + \hat{w}_{21}(Y_{21} - Y_{22}), \quad (6)$$

where, for the FE case, the weights are estimates of:

$$v_{11} = \frac{S_{11,2}^2}{S_{11,1}^2 + S_{11,2}^2},$$

$$\frac{w_{11}}{1 - w_{11}} = \frac{S_{11,2}^2 - S_{12,2} \frac{S_{12,1} + S_{12,2}}{S_{22,1}^2 + S_{22,2}^2}}{S_{11,1}^2 - S_{12,1} \frac{S_{12,1} + S_{12,2}}{S_{22,1}^2 + S_{22,2}^2}},$$

$$w_{21} = \frac{S_{11,1}^2 S_{12,2} - S_{11,2}^2 S_{12,1}}{(S_{11,1}^2 + S_{11,2}^2)(S_{22,1}^2 + S_{22,2}^2) - (S_{12,1} + S_{12,2})^2},$$

where $S_{12,i}$ are the within-study covariances. Note that only MVMA estimates included multiples of estimates of the second parameter, namely Y_{21} and Y_{22} . The coefficients for Y_{21} and Y_{22} in Eq. (6), respectively w_{21} and $-w_{21}$, sum to zero. Therefore, including estimates of the second parameter does not influence $E[\hat{\mu}_1^M]$. The RE case is analogous, but $S_{kk,i}^2$ and $S_{12,i}$ are replaced by the sums of the within-study terms and the between-study terms.

For the FE case, for known within-study covariance matrices, the relative efficiency is a function of the correlations, ρ_1 and ρ_2 , and the within-study variances. We will also consider the fractions r_1 and r_2 , of the variances across studies,

$$r_k = \frac{S_{kk,1}^2}{S_{kk,1}^2 + S_{kk,2}^2}, \quad k=1, 2. \quad (7)$$

In particular, the relative efficiency only depends on the within-study variances through these fractions. In the results section, we study the relationship between the relative efficiency and the four parameters ρ_1 , ρ_2 , r_1 , r_2 . We emphasize that the subscripts for ρ refer to the study but those for r refer to the parameter.

2.3 Multiple parameters (p = 2)

We compare the efficiency of MVMA and UVMA across a variety of examples. In our first set of examples, we consider studies where the between-study and within-study covariance matrices follow simple patterns. Here, our objective is to understand the conditions that favor MVMA and lower the relative efficiency. In the second set of examples, we consider studies where the covariance matrices are more complex, such as those observed in the

InterLymph dataset, which is described in section 2.4. Here, our objective is to understand the potential gain in efficiency for more realistic settings.

We start by comparing MVMA and UVMA for FE meta-analysis. Our first example considers a meta-analysis of two studies, $I = 2$, where the within-study covariance matrices are exchangeable (compound symmetric). In this example, the asymptotic relative efficiency has a closed form expression, and this form shows how the relationship between the RelEff and the number of parameters depends on r , ρ_1 , and ρ_2 , where we can omit the ‘ k ’ subscript because of symmetry. Our second example, which still assumes within-study covariance matrices are exchangeable, increases the number of studies, letting $I = 20$, $S_i^2 = 1$, and $\rho_i = \rho(i - 1)/I$, $i = 1, \dots, I$. Again, a closed form expression can be used to describe the relationship between RelEff and p . Finally, we consider additional examples where $I=20$ and the covariance matrices are either AR(1) or block diagonal with blocks of size 5.

We next compare MVMA and UVMA for RE meta-analysis when Σ and D are known. Our first example considers a meta-analysis of twenty studies, $I = 20$, where both the within-study and between-study covariance matrices are exchangeable, $\rho^{BS} = 0.5$, $S_i^2 = 1$, and $\rho_i = (i - 1)/I$, $i = 1, \dots, I$. We use this example to evaluate how the relationship between RelEff^T and p depends on σ^2/S^2 . In our second example, where again the within-study covariance matrices are assumed exchangeable, we fix $\Sigma = 0$ and evaluate how the relationship depends on I . We note that this example is slightly redundant to the FE example, but will be a needed comparison for discussing the relative efficiency when Σ and D must be estimated. Finally, we consider additional examples where both the within-study and between-study covariance matrices are AR(1) or block diagonal with blocks of size 5. In our next set of examples, we compare MVMA and UVMA for RE meta-analysis when Σ and D are estimated. Values of $\text{Var}(\mu_k^M)$ and $\text{Var}(\mu_k^U)$ were calculated by simulation, described below, with 500 cases and 500 controls.

To understand how UVMA and MVMA are likely to compare in practice, we consider the relative efficiency for RE meta-analyses across a broad range of more complex scenarios. Our aim is to show that the patterns observed in the examples with exchangeable, AR(1), and block diagonal correlation matrices hold more generally. For this demonstration, we randomly generate, using the `clusterGeneration` R package (Qiu and Joe, 2015), covariance matrices Σ and S_i , $i \in \{1, \dots, I\}$ where each covariance matrix is constructed from eigenvalues randomly generated from $\text{Unif}(1,10)$ and eigenvectors corresponding to the columns of randomly generated orthogonal matrices. Therefore, we start by specifying a set of parameters: number of studies ($I \in \{10, 20\}$); studies either have unequal sample sizes (550, 650, ..., 1350, 1450 individuals for $I = 10$ and 430, 490, ..., 1510, 1570 individuals for $I = 20$) or equal sample sizes (1000 individuals); and $\sigma^2 \approx \overline{S^2}/5$, $\overline{S^2}$, or $5\overline{S^2}$, with $\overline{S^2}$ being the average of all within-study variances. Then for each of these 12 sets of parameters and a given p ($p \in \{5, 10, 15, 20\}$), we randomly generate 5 sets of covariance matrices (both within-study and between-study). For each set of covariance matrices, we then estimate the relative efficiency by the simulations described below. Results from these analyses are presented in the Figs. S6 and S7, with each of the 5 random scenarios corresponding to a different color.

For each example, we evaluated the variance of $\mu_k^M, \mu_k^{MT}, \mu_k^U, \mu_k^{UT}$, and, where applicable, μ_k^{MB} and μ_k^{UB} across 50,000 simulated case/control studies (10,000 for Figs. S6 and S7.) For each simulation, we generate $\mathbf{\mu}_i \sim MVN(0.2 \times \mathbf{1}_p, \mathbf{\Sigma})$, where $\mathbf{1}_p$ is a p -length vector with all entries equal to 1. $\mathbf{\Sigma}$ is either exchangeable, AR(1), block diagonal or a randomly generated positive definite matrix with equal diagonal entries. The vector of p covariates for individual m in populations i is generated as $\mathbf{X}_{im} \sim MVN(\mathbf{0}_p, 4/1000 \mathbf{S}_i^{-1})$, where $\mathbf{0}_p$ is a p -length vector with all entries equal to 0, with $\mathbf{S}_i$ chosen so that the within-study covariance matrices $\mathbf{S}_i$ have, for example, $S_{ii}^2 \approx 1$ and $\rho_i \approx (i-1)/I$ in the exchangeable scenario, or $\mathbf{X}_{im} \sim MVN(\mathbf{0}_p, 4/1000 \mathbf{S}_i^{*-1})$, where $\mathbf{S}^*$ is a randomly generated correlation matrix, based on an asymptotic approximation in (Agresti, 2014). Case-status is generated as $Y_{im} \sim \text{Bernoulli}(p_{im} = \text{logit}^{-1}(\mu_{0i} + \sum_{k=1}^p \mu_{ki} X_{imk}))$. We generated individuals until we had the number of desired cases and controls in each study.

2.4 Data Example: InterLymph consortium

The International Lymphoma Epidemiology Consortium (InterLymph) includes 17,471 individuals with Non-Hodgkin Lymphoma (NHL) and 23,096 controls from 20 case/control studies conducted in North America, Europe, and Australia and is described by Morton *et al.* (2005b,a). Their objective was to study the association between lifestyle and environmental factors with the risk of NHL. For purposes of exposition, we focus on the documented association between cigarette smoking and NHL, and between alcohol consumption and NHL (Morton *et al.*, 2005b,a), and use the following variables: the lifetime cigarette exposure in pack-years, the number of servings of wine per week, the number of servings of liquor per week, and the number of servings of beer per week. We used data from the 15 studies, ranging in size from 262 to 3,697 subjects, that contained all four variables and removed individuals with missing values. The study-specific results are presented in Table S1. Variables are highly correlated within studies and these correlations vary considerably across studies (Table S2 and Fig. S1, available as part of the Supporting Information). In each study we modeled the relationship between covariates and NHL using logistic regression. We report meta-analysis of the resulting $\log(OR)$ values.

2.5 InterLymph consortium: simulations

We also compare the performance of MVMA and UVMA on simulated datasets, where the underlying truth reflects our InterLymph results. These simulations, where the within- and between- study correlation matrices are similar to those observed in InterLymph, contrast the exchangeable, AR(1), and block diagonal matrices used in earlier examples. Let us denote the wine, liquor, beer, and smoking variables for individual m in study i by $X_{1,im}, X_{2,im}, X_{3,im}$, and $X_{4,im}$, with $\mathbf{X}_{im} = (X_{1,im}, X_{2,im}, X_{3,im}, X_{4,im})'$. Let $\mathbf{v}_i$ and $\mathbf{V}_i$ be the estimated mean and covariance for $\mathbf{X}_i$ among the controls. Let $\hat{\boldsymbol{\mu}}$ and $\hat{\boldsymbol{\Sigma}}$ be the MVMA estimates of the global mean and between study covariance matrix, respectively. For simulations, we start by defining a set of effects, $\boldsymbol{\mu}^{sim}$ for each study as either $\hat{\boldsymbol{\mu}}$ (FE framework) or as a random draw from a normal distribution, $N(\hat{\boldsymbol{\mu}}, \hat{\boldsymbol{\Sigma}})$ (RE framework). Then, for each study, we generate a vector $(Y_{im}, \mathbf{X}_{im})$ for each individual in a large population with $\mathbf{X}_{im} \sim N(\mathbf{v}_i, \mathbf{V}_i)$

and $Y_{im} \sim \text{Bernoulli}(p_{im} = \text{logit}^{-1}(\mu_0^{\text{sim}} + \sum_{k=1}^4 \mu_k^{\text{sim}} X_{imk}))$. We then select the same number of individuals for the case/control study as in the original study. We also generated datasets with $p = 8$ risk factors, with $\mathbf{X}_{im}$ following a normal distribution with mean $(\mathbf{v}_i, \mathbf{v}_i)'$ and covariance matrix:

$$\begin{pmatrix} \mathbf{V}_i & \rho_{\mathbf{X}} \mathbf{M}_i \\ \rho_{\mathbf{X}} \mathbf{M}_i & \mathbf{V}_i \end{pmatrix}, \quad (8)$$

where $\mathbf{M}_i = \mathbf{V}_i^0 \mathbf{V}_i^{0'}$, $\mathbf{V}_i^0 = (\sqrt{\text{Var}(X_{i1})}, \sqrt{\text{Var}(X_{i2})}, \sqrt{\text{Var}(X_{i3})}, \sqrt{\text{Var}(X_{i4})})'$, and $\rho_{\mathbf{X}} \in \{0, 0.5\}$. For the RE $p = 8$ scenarios, we considered the between-study covariance matrix:

$$\begin{pmatrix} \hat{\Sigma} & \mathbf{0} \\ \mathbf{0} & \hat{\Sigma} \end{pmatrix}, \quad (9)$$

where $\mathbf{0}$ is 4×4 matrix of zeros.

We considered six scenarios: RE or FE, $p = 4$ or 8 variables, and, with 8 variables, $\rho_{\mathbf{X}} = 0$ or $\rho_{\mathbf{X}} = 0.5$. For each scenario, we generated 50,000 simulations. For estimating asymptotic relative efficiencies, we needed the within-study covariance matrices, $\mathbf{S}_p$, and estimated them by the empirical covariances matrices of $\hat{\mu}_i$ across simulations, after subtracting Σ .

3 Results

3.1 Preface: two parameters, two studies ($p=2$, $I=2$)

For a FE meta-analysis, the relative efficiency of UVMA, compared to MVMA, of the first parameter can be described by Result 3.1:

Result 3.1

$$\text{RelEff}_1 = 1 - \frac{[\rho_1 \sqrt{(1-r_1)r_2} - \rho_2 \sqrt{r_1(1-r_2)}]^2}{1 - [\rho_1 \sqrt{r_1 r_2} + \rho_2 \sqrt{(1-r_1)(1-r_2)}]^2}. \quad (10)$$

The key observation, which similarly holds for $p > 2$ and $I > 2$, is that the UVMA becomes less efficient when there is a large difference in the within-study correlations. In our example (Fig. 1(a)), where $r_1 = r_2 = r$, the numerator in Eq. (10) simplifies to $r(1-r)(\rho_1 - \rho_2)^2$. The relative efficiency is 1 only when $\rho_1 - \rho_2 = 0$ and the relative efficiency decreases as $(\rho_1 - \rho_2)^2$ increases from 0. The exact gain in efficiency depends on r , with MVMA offering no benefit when $r \rightarrow 0$ or $r \rightarrow 1$ (Fig. S2(a)).

In practice, the relative variances, r_1 and r_2 , of the two parameters are often similar because they are both determined by the relative size of the two studies. However, we note that when

$r_1 = r_2$, the relative efficiency is no longer a strictly increasing function of $(\rho_1 - \rho_2)^2$ and will no longer equal 1 exactly when $\rho_1 - \rho_2 = 0$. Using $r_1 = 0.5$ (Fig. S2(b)) as an example, Eq. (10) shows

$$\text{RelEff}_1=1 \iff \rho_2=\rho_1 \sqrt{\frac{r_2}{1-r_2}},$$

$$\text{RelEff}_2=1 \iff \rho_2=\rho_1 \sqrt{\frac{1-r_2}{r_2}}.$$

Therefore, there are scenarios where MVMA can offer no gain beyond the commonly cited example of equal within-study covariance matrices (Riley *et al.*, 2007a; Riley, 2009).

3.2 Fixed-effect meta-analysis for multiple parameters ($p \geq 2$)

For a FE meta-analysis of multiple parameters ($p \geq 2$), we first consider the relative efficiency of UVMA, compared to MVMA, when the within-study covariance matrices are exchangeable. Result 3.2 shows that the relative efficiency decreases as p increases, but approaches a limit well above 0.

Result 3.2

$$\text{RelEff} = \frac{\sum_{i=1}^I \frac{1}{S_i^2} \sum_{i=1}^I \frac{1}{S_i^2(1-\rho_i)[1+(p-1)\rho_i]}}{\sum_{i=1}^I \frac{1}{S_i^2(1-\rho_i)} \sum_{i=1}^I \frac{1}{S_i^2[1+(p-1)\rho_i]}} \xrightarrow{p \rightarrow \infty} \frac{\sum_{i=1}^I \frac{1}{S_i^2}}{\sum_{i=1}^I \frac{1}{S_i^2(1-\rho_i)}} + \frac{\sum_{i=1}^I \frac{1}{S_i^2}}{\sum_{i=1}^I \frac{1}{S_i^2\rho_i}}.$$

When $I = 2$, this result simplifies:

$$\text{RelEff} = 1 - r(1-r) \frac{(\rho_1 - \rho_2)^2}{\{1 - [r\rho_1 + (1-r)\rho_2]\} \left\{ \frac{1}{p-1} + [r\rho_1 + (1-r)\rho_2] \right\}}. \quad (11)$$

We continue with the example where $I = 2$, $r = 0.5$, and $\rho_1 = 0$ (Fig. 1(b)). The relative efficiency decreases as p increases, and this decrease, per additional parameter, is larger when p is small. When $\rho_2 = 0.75$, the relative efficiency drops from 0.84 to 0.68 as p increases from 2 to 4, whereas it only drops from 0.52 to 0.50 as p increases from 12 to 14. In our example with $I = 20$ (Fig. 1(c)) the relative efficiency shows a similar trend as p increases. In both of these examples, the relative efficiency increases towards 1 as the range of correlations shrinks towards 0. Another feature is that the RelEff increases slightly as the number of studies decreases from $I = 20$ to $I = 5$ (Fig. 1(d)), suggesting the benefit of MVMA is greater in meta-analyses containing larger numbers of studies. We next consider the $I=20$ examples when the covariance matrices follow an AR(1) and block diagonal structure. In these examples (Fig. S3), which are more likely to represent real-world data, we find that relative efficiency does not decrease as strongly with the number of parameters. In

the example with the block diagonal covariance matrix, the relative efficiency clearly reaches its minimum when $p=5$, the size of the blocks.

3.3 Random effects meta-analysis for multiple parameters ($p = 2$)

The benefit of MVMA tends to be smaller, or the relative efficiency tends to be larger, when performing RE meta-analysis. We first present the scenario where Σ is known, thus looking at RelEff^T . We again start by considering an example where the covariance matrices are exchangeable, $I = 20$, $\rho_i \approx (i - 1)/I$, and $S_i^2 \approx 1$ (solid lines in Fig. 2(a)). We show that the relative efficiency increases as the ratio of the between-study and within-study variances increases. As a point of reference, we note that solid orange line (RelEff^T) in Fig. 2(a) is nearly identical to the solid orange line in Fig. 1(d), the slight difference being due to the data generation mechanism and the estimation of within-study covariance matrices. When comparing this FE scenario ($\sigma^2 = 0$) to the scenario where the within- and between- study variances are equal ($\sigma^2/S^2 = 1$), the RelEff^T increases from 0.73 to 0.95 for $p = 4$. Because all studies share a common between-study covariance matrix, the covariance matrices of $\mathbf{Y}_i$ become increasingly similar as σ^2 increases, thereby lowering the potential benefit of MVMA. Fig. 2(a) emphasizes that there is little to be gained by using MVMA when the between-study variance is comparatively large ($\sigma^2/S^2 = 5$).

We next considered the relative efficiency when the covariance matrices are AR(1) and block diagonal. Similar to our observations when using FE meta-analysis, the benefit from MVMA did not increase as rapidly with the number of parameters (Figs. S4 and S5). Moreover, the effects of changing either the number of studies or the ratio (σ^2/S^2) were similar to those observed in the comparable examples with an exchangeable correlation matrix. Finally, when we considered the examples where the covariance matrices were randomly generated (Figs. S6 and S7), we found the benefit of MVMA to be the smallest, with the $\text{RelEff}^T > 0.94$ when $\sigma^2/\overline{S^2} = 5$.

3.4 Estimating Σ for multiple parameters ($p = 2$)

In the previous examples, Σ and $\mathbf{D}$ were assumed known. Here, we consider the RelEff when using their estimates, $\hat{\Sigma}$ and $\hat{\mathbf{D}}$. We must estimate more parameters for MVMA, and therefore the relative efficiency of the UVMA is expected to increase. Figs. 2(a) and 2(b) show that despite estimating more parameters, estimates from MVMA still have lower variance than their counterparts from UVMA. We return to the example where the covariance matrices are exchangeable, $I = 20$, $\rho_i \approx (i - 1)/I$, and $S_i^2 \approx 1$. In Fig. 2(a), we see the loss of efficiency is relatively low when $I = 20$, regardless of the σ^2/S^2 ratio. We next consider the effect of decreasing the number of studies. Fig. 2(b) shows that as the number of studies decreases the loss in efficiency from having to estimate the covariance matrices increases. For completeness, we note that the loss in efficiency from having to estimate the covariance matrices in the $\Sigma = \mathbf{0}$ example (Fig. 2(b)) shows the cost from using a RE meta-analysis when the assumptions for a FE meta-analysis hold true. The potential cost from not using a FE meta-analysis, when applicable, therefore increases with p . When the correlation matrices are AR(1) and block diagonal (Figs. S4 and S5) and when the within-study covariance matrices are randomly generated (Figs. S6 and S7), similar trends are observed.

We next evaluated MVMA's gain in efficiency when using Bayesian methods. In general, the relative efficiencies, RelEff^B , observed for the Bayesian methods were similar to those observed when using RE meta-analysis with unknown covariance matrices. For the examples with the exchangeable, AR(1), and block diagonal covariance matrices, Figs. S4, S5, and S8 show the similarities between RelEff^B and RelEff . However, we note that when the number of studies is small ($I=5$), RelEff^B tends to be smaller than RelEff , indicating that MVMA may be slightly more important for Bayesian methods. For completeness, we also compared the performance of the Bayesian and frequentist MVMA estimates of μ . Across all examples (Figs. S4, S5, and S8), the two methods performed similarly, except we found that the variance of the Bayesian estimates tended to be slightly smaller when there were few studies ($I=5$).

3.5 InterLymph consortium: simulations

We simulated datasets similar to that collected by InterLymph as described in section 2.5. Comparisons between MVMA and UVMA are presented in Table 2. Each simulation included 18,091 individuals from 15 case/control studies, and focused on either $p = 4$ or 8 variables. We first considered the scenario where both the truth and chosen analysis are within the FE framework. Again, our theory-based estimates of relative efficiency predicted by Eqs. (3) and (4), are similar to those observed empirically. Therefore, when the number of parameters is large ($p=8$) and there is non-negligible correlation across multiple variables ($\rho_X = 0.5$), MVMA estimates may offer significant improvements in efficiency. When the true model is a FE model and the chosen analysis is RE, then the ratio of variances, $\text{Var}(\hat{\mu}_k^M)/\text{Var}(\hat{\mu}_k^U)$, is closer to 1 than either what is predicted by theory or obtainable when using a FE analysis. The loss of efficiency of the RE MVMA compared to FE MVMA when there was no between study heterogeneity was 25.6%, 19.5%, 9.6%, and 6.8% for $\hat{\mu}_1$, $\hat{\mu}_2$, $\hat{\mu}_3$, and $\hat{\mu}_4$ when $p = 4$, and 31.6%, 22.9%, 17.0%, and 10.2% when $p = 8$ and $\rho_X = 0.5$, respectively. When both the true model and chosen analysis are within the RE framework, then the theory suggests MVMA should offer significant improvement, reducing the variance of the estimates by 10% in most of the examples from Table 2. However, in practice, the gain in efficiency was not as large as predicted by theory.

3.6 InterLymph consortium: Data Analysis

We evaluated the associations between the risk of NHL and two behaviors, alcohol consumption and cigarette smoking, in the InterLymph consortium. Results are presented in Table 3. Similar to results from previous findings, we observed that alcohol consumption reduces the risk of NHL, while smoking increases the risk of NHL. Using the FE MVMA, an additional serving of wine, liquor, or beer per day equated to an *OR* of 0.98 (0.95–1.00), 0.98 (0.91–1.05), and 0.94 (0.91–0.98) respectively. For smoking, 60 pack-years equated to an *OR* of 1.21 (1.11–1.32) compared to never smokers. The results from all four analyses (MVMA or UVMA, FE or RE) are qualitatively similar. Wine, beer, and smoking showed statistically significant effects regardless of analysis, with the caveat that the p-value for wine in the FE meta-analysis was 0.056. For the FE framework, we observed tighter confidence intervals for the wine and liquor variables from the MVMA, compared to UVMA, as expected based on the lower relative efficiencies observed in our simulations.

(Table 2). For the RE framework, we also observed slightly tighter confidence intervals for MVMA, but as expected, the magnitude of the reduction is reduced. We also confirmed the well known observation that confidence intervals from RE meta-analysis are larger than those from FE meta-analysis, regardless of whether using MVMA or UVMA.

4 Discussion

Numerous studies, using simulation (Riley, 2009), theory (Riley *et al.*, 2007a; Riley, 2009), and examples (Jackson *et al.*, 2011; Ma and Mazumdar, 2011; Riley *et al.*, 2007a; Trikalinos *et al.*, 2013), have compared the efficiency of multivariate and univariate meta-analyses. Here, we expand the discussion by systematically exploring the relative efficiency of the two methods as the number of parameters p increases. For FE meta-analysis, we show that the benefit from using MVMA can significantly increase as p increases for diverse covariance structures among studies. For RE meta-analysis, we show that, theoretically, the benefit from MVMA can also significantly increase with p , but in practice, the benefits may be reduced by the need to estimate the between-study correlation matrix. Because the benefit of MVMA is far stronger in FE meta-analysis, choosing to use RE meta-analysis when p is large and there is no or little heterogeneity can come at a surprisingly large cost to efficiency.

Our conclusion is that there is likely to be only a minimal gain of efficiency, when substituting MVMA for UVMA, in many RE meta-analyses with $p > 2$. This conclusion agrees with the literature focused on the meta-analysis of two parameters (Riley *et al.*, 2007a; Riley, 2009) and a recent comparison of the two methods on 45 meta-analyses studying a categorical outcome (Trikalinos *et al.*, 2013). MVMA only offered significant gains in efficiency when using FE meta-analysis and when the estimates of all parameters were highly correlated. However, it is worth highlighting that those study characteristics that affect the relative efficiency of MVMA and UVMA estimates in the $p = 2$ scenario remain important for larger p . The improvement offered by MVMA is larger when the correlation structures vary greatly across studies and when the true study-specific parameters are similar across studies. In our data analysis, we focused on smoking and alcohol variables which do show a broad range of correlation structures. However, even in this targeted example, the gain in efficiency from using MVMA was minimal in RE meta-analysis.

This work is not meant to be a comprehensive comparison of MVMA and UVMA. We do not address issues such as when studies estimate different sets of parameters (Jackson *et al.*, 2011), publish only the most favorable results (Kirkham *et al.*, 2012), have covariates that can be modeled in a meta-regression (Berkey *et al.*, 1998; Jackson *et al.*, 2013), or are intended to estimate functions of multiple parameters (Riley *et al.*, 2007a). Furthermore, we assume that sample sizes are large enough so that estimated parameters follow an approximately normal distribution (Hamza *et al.*, 2008; Stijnen *et al.*, 2010; Trikalinos *et al.*, 2013; Böhning *et al.*, 2015) and that all within-study covariance matrices are available to the investigator (Ishak *et al.*, 2007; Riley *et al.*, 2008; Riley, 2009). Finally, we did not study other approaches such as methods that enforce structure on the between-study covariance matrix (Gasparrini and Armstrong, 2011).

In general, the choice of whether or not to use MVMA will depend on the specific objectives of the meta-analysis, the characteristics of the included studies, and the implicit cost of obtaining all within-study covariance matrices. In our discussed examples, we found that MVMA was most beneficial when using a FE meta-analysis and when the estimates of all parameters were highly correlated. When using RE meta-analysis, we found that the need to estimate the between-study covariance matrix limited the observed gain in efficiency. When only small groups of covariates were highly correlated, such as in our simulations where the within-study covariance matrices were either block-diagonal or AR(1), we found that the gain in efficiency was again limited. Similarly limited gains were observed in the InterLymph examples and when we randomly generated covariance matrices. In choosing the appropriate analysis, the potential gain in efficiency would be weighed against the various costs of the more complicated analysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

The relative efficiency (RelEff) compares the performance of MVMA and UVMA for FE meta-analysis when the covariance matrix is exchangeable. The RelEff (1) decreases as the difference between the within-study correlations increases (2) decreases as the number of parameters increases and (3) decreases as the number of studies increases. (a) A two-study, two parameter example illustrating (1). (b) A two-study, multi-parameter example illustrating (1) and (2). (c) A twenty-study, multi-parameter example illustrating (1) and (2). (d) A multi-study, multi-parameter example illustrating (1), (2), and (3). The notation includes I : number of studies, p : number of parameters, S_i^2 : within-study variance of an estimated parameter in study i , ρ_i : within-study correlation between two estimated parameters in study i , and $r = S_1^2 / (S_1^2 + S_2^2)$.

Fig. 2.

The relative efficiency when the between-study covariance matrices are known (RelEff^T) and when the between-study covariance matrices are unknown (RelEff) compares the performance of MVMA and UVMA for RE meta-analyses when the covariance matrices are exchangeable. Properties of RelEff^T and RelEff include (1) RelEff^T is less than RelEff (2) RelEff^T and RelEff both decrease as the number of parameters increases (3) RelEff^T and RelEff both decrease as the between-study variance decreases (4) the difference between RelEff^T and RelEff decreases as the number of studies increases. (a) A twenty-study, multi-parameter example illustrating (1), (2), and (3). (b) A multi-study, multi-parameter example illustrating (1), (2), and (4). The notation includes I : number of studies, p : number of parameters, S_i^2 : within-study variance of an estimated parameter in study i , σ^2 : between-study variance of a single parameter, Σ : between-study covariance matrix, ρ_i : within-study correlation between two estimated parameters in study i , ρ^{BS} : between-study correlation between two parameters.

Table 1

Notation used in the paper.

Type of quantity	Symbol	Description
Indices	$i = 1, \dots, I$	Index over studies
	$k = 1, \dots, p$	Index over parameters
Within-study parameters	$\boldsymbol{\mu}_i$	Parameters for study i
	$\mathbf{Y}_i$	Estimates of $\boldsymbol{\mu}_i$
	$\mathbf{S}_i$	Covariance matrix of $\mathbf{Y}_i$
	$\mathbf{U}_i$	$diag(\mathbf{S}_i)$
Between-study parameters	$\boldsymbol{\mu}$	Mean parameters across studies
	$\boldsymbol{\Sigma}$	Covariance matrix of $\boldsymbol{\mu}_i$
	$\mathbf{D}$	$diag(\boldsymbol{\Sigma})$
Meta-analysis parameters	$\hat{\boldsymbol{\mu}}^M$	MVMA estimate of $\boldsymbol{\mu}$
	$\hat{\boldsymbol{\mu}}^U$	UVMA estimate of $\boldsymbol{\mu}$
	$RelEff_k$	$Var(\hat{\mu}_k^M)/Var(\hat{\mu}_k^U)$

Table 2

The asymptotic and empirical relative efficiencies from the InterLymph simulations. Simulations either assumed μ_i was constant across studies (FE) or normally distributed (RE), included either 4 or 8 parameters, and let the two sets of four variables be independent ($\rho_X = 0$) or dependent ($\rho_X = 0.5$). Both the asymptotic/expected relative efficiencies and empirical/observed relative efficiencies are provided from FE and RE meta-analysis. Further details on the simulation framework are in Section 2.5.

Truth	Number of coefficients (p)	ρ_X	Parameter	FE analysis		RE analysis	
				Asymptotic RelEff	Empirical RelEff	Asymptotic RelEff	Empirical RelEff
FE	p = 4		μ_1	0.854	0.841	0.854	0.958
			μ_2	0.845	0.838	0.845	0.912
			μ_3	0.963	0.952	0.963	0.995
			μ_4	0.985	0.974	0.985	1.003
	p = 8	$\rho_X = 0$	μ_1	0.853	0.830	0.853	1.100
			μ_2	0.842	0.818	0.842	0.957
			μ_3	0.962	0.938	0.962	1.048
			μ_4	0.984	0.958	0.984	1.013
	p = 8	$\rho_X = 0.5$	μ_1	0.587	0.572	0.587	0.698
			μ_2	0.802	0.784	0.802	0.896
			μ_3	0.844	0.821	0.844	0.911
			μ_4	0.795	0.775	0.795	0.820
RE	p = 4		μ_1			0.889	1.045
			μ_2			0.897	0.926
			μ_3			0.911	0.954
			μ_4			0.977	0.977
	p = 8	$\rho_X = 0$	μ_1			0.890	1.152
			μ_2			0.898	0.951
			μ_3			0.911	0.972

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Truth	Number of coefficients (p)	ρ_X	Parameter	FE analysis		RE analysis	
				Asymptotic RelEff	Empirical RelEff	Asymptotic RelEff	Empirical RelEff
			μ_4			0.978	0.975
			μ_1			0.679	0.857
			μ_2			0.873	0.926
	$d = 8$	$\rho_X = 0.5$	μ_3			0.848	0.924
			μ_4			0.813	0.837

Table 3

Estimates of log ORs (95% confidence intervals) for lifestyle risk factors from the InterLymph consortium. Four estimates are provided for each log(OR). Multivariate (MVMA) and univariate (UVMA) estimates are provided for FE and RE effects meta-analysis. The wine, liquor, and beer variables are measured in servings per week/100, the smoking variable is measured in pack-years/100.

Variable	FE analysis		RE analysis	
	MVMA	UVMA	MVMA	UVMA
Wine	-0.33 (-0.67, 0.01)	-0.49 (-0.86, -0.12)	-0.59 (-1.01, -0.18)	-0.49 (-0.86, -0.12)
Liquor	-0.31 (-1.31, 0.69)	-0.18 (-1.26, 0.90)	0.06 (-1.56, 1.68)	0.26 (-1.39, 1.92)
Beer	-0.82 (-1.38, -0.27)	-0.96 (-1.53, -0.40)	-0.75 (-1.48, -0.01)	-0.92 (-1.75, -0.09)
Smoking	0.32 (0.17, 0.46)	0.32 (0.18, 0.47)	0.26 (0.06, 0.47)	0.26 (0.06, 0.46)