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Multivariate meta-analysis for data consortia, individual patient meta-analysis, and pooling projects

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Abstract

We discuss maximum likelihood and estimating equations methods for combining results from multiple studies in pooling projects and data consortia using a meta-analysis model, when the multivariate estimates with their covariance matrices are available. The estimates to be combined are typically regression slopes, often from relative risk models in biomedical and epidemiologic applications. We generalize the existing univariate meta-analysis model and investigate the efficiency advantages of the multivariate methods, relative to the univariate ones. We generalize a popular univariate test for between-studies homogeneity to a multivariate test. The methods are applied to a pooled analysis of type of carotenoids in relation to lung cancer incidence from seven prospective studies. In these data, the expected gain in efficiency was evident, sometimes to a large extent. Finally, we study the finite sample properties of the estimators and compare the multivariate ones to their univariate counterparts.

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1. Introduction

In meta-analysis, estimates of parameters of treatment or exposure effects from different studies are extracted from the literature and combined to obtain a single summary estimate. Standard meta-analysis is quick and inexpensive and allows combining estimates based on different methods of estimation, models, and study designs. The univariate meta-analysis model is a form of a random effects model

$$y_s = \beta + b_s + e_s, \quad s = 1, \ldots, S, \tag{1}$$

where y_s is the estimate of β from the sth study, b_s is the random between-studies effect with variance σ_b^2 and e_s represents the within-studies sampling variability with variance σ_s^2 (DerSimmonian and Laird, 1984). In addition, it is reasonably assumed that b_s and e_s are mutually independent within- and between-studies.

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When $\sigma^2 = 0$, the studies are homogeneous and β can be estimated by a fixed effects model, using weighted least squares with the weights taken to be the reciprocal of the variances σ_s^2 (Greenland, 1994, p. 687). Otherwise, a random effects model is used to estimate β as the weighted mean with the weights for each study given by the reciprocal of $\widehat{\sigma}_b^2 + \sigma_s^2$. DerSimmonian and Laird suggested the popular Q-statistic for testing the hypothesis that there is no between-studies variation, i.e. $H_0 : \sigma_b^2 = 0$. The statistical properties of the univariate meta-analysis model are discussed in a number of papers, including Whitehead and Whitehead (1991), Berkey et al. (1995), Hardy and Thompson (1998), Aitken (1999), Brockwell and Gordon (2001), and Demidenko (2004).

In pooling projects, data consortia, and individual patient (IDP) meta-analysis, the estimates of the effects of all model covariates, including that corresponding to the covariate of principal interest, and their estimated variance–covariance matrix are available. There are many examples of such studies in epidemiology, including the Harvard School of Public Health's long-standing Pooling Project of Prospective Studies on Diet and Cancer in Men and Women (Hunter et al., 1996; Smith-Warner et al., 1998, 2001), which motivated this research, Harvard School of Public Health's Pooling Project of Prospective Studies of Diet and Cardiovascular Disease in Men and Women (Pereira et al., 2004), the Collaborative Group on Hormonal Factors in Breast Cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2004), the Collaborative Ovarian Cancer Group (Whittemore et al., 1992), a pooling project of hormones and ovarian cancer (Arslan et al., 2003), the Melanoma Genetics Consortium (Bishop et al., 2002), the Breast and Prostate Cancer and Hormone-related Gene Variants Cohort Consortium (http://epi.grants.cancer.gov/BPC3/), a pooling project of sinonasal cancer among wood workers (Gordon et al., 1998), a pooling project of the gene glutathione S-transferase M1 and bladder cancer (Engel et al., 2002), a pooling project of the effects of glutathione S-transferase M1 polymorphisms and smoking on lung cancer risk (Benhamou et al., 2002), a pooling project of 53 epidemiological studies on alcohol, tobacco and breast cancer (Beral et al., 2002), a pooling project of case-control studies of thyroid cancer (Bosetti et al., 2001), the International Lymphoma Epidemiology Consortium (Interlymph) (Morton et al., 2005), and many others. In the clinical literature, similar designs are becoming more common, typically under the name *IDP meta-analysis* (Clarke and Stewart, 2001; Berlin et al., 2002; Kelley and Kelley, 2004; Kelley et al., 2002; Steinberg et al., 1997; Jeng et al., 1995; Olkin and Sampson, 1998; Szczech et al., 1998; Adachi et al., 2005; Clarke and Stewart, 2001).

In this paper, we first ask the question "Can more efficient estimates of the parameter of interest be obtained by taking the multivariate nature of the models from which these estimates are obtained into account more directly?" Once finding that efficiency can indeed be gained, we introduce a family of multivariate pooling estimators which include the maximum likelihood estimates (MLE) under multivariate normality, as well as several estimators derived from within a generalized estimating equations (GEE) framework. In Section 4, we generalize the univariate Q-test of homogeneity to the multivariate setting, assuming multivariate normality and with this assumption relaxed. We then apply the methods to a pooled analysis of type of carotenoid intake in relation to lung cancer incidence among the seven prospective studies (Männistö et al., 2004) in Section 5. Section 6 gives results from a simulation study investigating the finite sample properties of the estimators and significance tests as a function of several realistic number of participating studies, S. In the final section, we discuss some alternative approaches and limitations of the methods.

2. Asymptotic relative efficiency of the multivariate estimator

The impetus of this paper is the idea that by combining information obtained in pooling projects, data consortia, and IDP using a multivariate meta-analysis model, we will improve efficiency. In this section we investigate this idea analytically. We assume a multivariate meta-analysis model analogous to (1) above,

$$\mathbf{y}_s = \boldsymbol{\beta} + \mathbf{b}_s + \mathbf{e}_s, \quad s = 1, \ldots, S, \tag{2}$$

where now $\boldsymbol{\beta}$ is a p-vector, and $\mathbf{b}_s$ and $\mathbf{e}_s$ have zero means with covariance matrices $\boldsymbol{\Sigma}_b$ and $\boldsymbol{\Sigma}_s$. We may or may not assume that $\mathbf{b}_s$ and $\mathbf{e}_s$ are normally distributed; in the latter case we write $\mathbf{b}_s \sim \mathrm{MVN}(\mathbf{0}, \boldsymbol{\Sigma}_b)$ and $\mathbf{e}_s \sim \mathrm{MVN}(\mathbf{0}, \boldsymbol{\Sigma}_s)$. The two random terms, $\mathbf{b}_s$ and $\mathbf{e}_s$ have the same interpretation as in the univariate model, and are reasonably assumed independent within- and between-studies. The combined $((p+3)p/2)$-dimensional vector of unknown parameter is $\boldsymbol{\theta} = (\boldsymbol{\beta}, \mathrm{vech}(\boldsymbol{\Sigma}_b))$.

Without loss of generality we can assume that the first component of vector $\boldsymbol{\beta}$ is of interest. If only data on the first component of $\mathbf{y}_s$ is taken into account and matrix $\boldsymbol{\Sigma}_b$ is known, we arrive at the univariate meta-analysis model with

the variance of the estimate

$$var(\widetilde{\beta}_1) = \frac{1}{\sum_{s=1}^{S}(\Sigma_{s11} + \Sigma_{b11})^{-1}}, \tag{3}$$

where Σ_{s11} and Σ_{b11} are the (1, 1)th elements of matrices $\mathbf{\Sigma}_s$ and $\mathbf{\Sigma}_b$. If all data were used the multivariate meta-analysis model (2) is applied with the variance

$$var(\widehat{\beta}_1) = \left[\left(\sum_{s=1}^{S}(\mathbf{\Sigma}_b + \mathbf{\Sigma}_s)^{-1}\right)^{-1}\right]_{11}, \tag{4}$$

as the (1, 1)th element of the inverse matrix. The proof that $var(\widehat{\beta}_1) \leqslant var(\widetilde{\beta}_1)$ for any S is found in Appendix A.2. Although this result is not surprising, we obtain conditions under which there is no gain in using the multivariate model: (1) if the correlation between the first component of $\mathbf{y}_s$ and the rest is zero, or (2) if all within-covariance matrices of $\mathbf{e}_s$ are the same ($\mathbf{\Sigma}_s = \mathbf{\Sigma}$ for all s, $s = 1, \ldots, S$). Neither of these conditions are likely to occur in practice because (1) neither matrix $\mathbf{\Sigma}_b$ nor matrices $\{\mathbf{\Sigma}_s, s = 1, \ldots, S\}$ are restricted to be block-diagonal, and (2) typically, studies have different sample sizes and therefore $\mathbf{\Sigma}_s \neq \mathbf{\Sigma}$ for all s, $s = 1, \ldots, S$. In our example of the effect of carotenoids on lung cancer (Section 5), the correlation between the within-study estimates of y_{s1} with $\{y_{sj}, j = 2, \ldots, 10\}$ ranges between 0.1 and 0.6. So we expect, in general, to see at least some efficiency gain through multivariate pooling.

3. A family of multivariate pooling estimators

All of the methods we consider for obtaining estimates of $\boldsymbol{\beta}$ and $\mathbf{\Sigma}_b$ in model (2) can be cast in an unbiased estimating equations (EE) format (Huber, 1967; Carroll et al., 1995, p. 261). This makes it possible to define a number of possible multivariate estimators concisely as given in Table 1 and to use standard asymptotic results for unbiased EE to deduce their asymptotic properties. The general form of the EE for $\boldsymbol{\beta}$ and $\mathbf{\Sigma}_b$ considered here are given by

$$\mathbf{U}(\boldsymbol{\theta}) = \sum_{s=1}^{S} \mathbf{W}_s(\mathbf{y}_s - \boldsymbol{\beta}) = \mathbf{0}, \tag{5}$$

$$\mathbf{T}(\boldsymbol{\theta}) = \sum_{s=1}^{S} f(\mathbf{y}_s, \mathbf{W}_s; \boldsymbol{\theta}) = \mathbf{0}. \tag{6}$$

Table 1
Estimating functions for $\boldsymbol{\beta}$ and $\mathbf{\Sigma}_b$

Method	Score for $\boldsymbol{\beta}$, $\mathbf{U}(\boldsymbol{\theta})$[a]	Score for $\mathbf{\Sigma}_b = \{\sigma_{ijb}\}$, $\mathbf{T}(\boldsymbol{\theta})$	Computational options
MVML	$\sum_{s=1}^{S} \mathbf{W}_s(\mathbf{y}_s - \boldsymbol{\beta})$	$\sum_{s=1}^{S}[(\mathbf{y}_s - \boldsymbol{\beta})'\mathbf{V}_{ijs}(\mathbf{y}_s - \boldsymbol{\beta}) - v_{ijs}]$[b]	FSQP[c], EM[d]
MVEE1	$\sum_{s=1}^{S} \mathbf{W}_s(\mathbf{y}_s - \boldsymbol{\beta})$	$\sum_{s=1}^{S}[(y_{si} - \beta_i)(y_{sj} - \beta_j) - (\sigma_{bi}^2 + \sigma_{bj}^2)]$	Minimize SS[e] via FSQP
MVEE2[f]	$\sum_{s=1}^{S}(\widehat{\mathbf{\Sigma}}_b + \mathbf{\Sigma}_s)^{-1}(\mathbf{y}_s - \boldsymbol{\beta})$	N/A	Direct solution
MVEE3[g]	$\sum_{s=1}^{S}(\widehat{\mathbf{\Sigma}}_b^* + \mathbf{\Sigma}_s)^{-1}(\mathbf{y}_s - \boldsymbol{\beta})$	N/A	Direct solution

[a] $\mathbf{W}_s = (\mathbf{\Sigma}_b + \mathbf{\Sigma}_s)^{-1}$.
[b] $\mathbf{V}_{ijs} = \{v_{ijs}\} = -\mathbf{W}_s\mathbf{F}_{ij}\mathbf{W}_s$, where the entries of the $p \times p$ index matrix $\mathbf{F}_{ij}$ are zero except the (i, j) and the (j, i) which are 1.
[c] FSQP: Forward Sequential Quadratic Programming by Panier and Tits.
[d] EM: EM algorithm by Laird and Ware (1982).
[e] $SS = \|\mathbf{U}(\boldsymbol{\theta})\|^2 + \|\mathbf{T}(\boldsymbol{\theta})\|^2$.
[f] $\widehat{\mathbf{\Sigma}}_b = \left[\sum_{s=1}^{S}(\mathbf{y}_s - \widehat{\boldsymbol{\beta}}_0)(\mathbf{y}_s - \widehat{\boldsymbol{\beta}}_0)' - \mathbf{\Sigma}_s\right] \Big/ S$.
[g] $\widehat{\mathbf{\Sigma}}_b^* = \sum_{s=1}^{S}[(\mathbf{y}_s - \widehat{\boldsymbol{\beta}}_0)(\mathbf{y}_s - \widehat{\boldsymbol{\beta}}_0)'/(S-1) - \mathbf{\Sigma}_s/S]$, where $\widehat{\boldsymbol{\beta}}_0$ is a fixed effects unbiased estimator ($\mathbf{\Sigma}_b = \mathbf{0}$).

The weight matrix $\mathbf{W}_s = \mathbf{W}_s(\boldsymbol{\sigma})$ and the functions f are listed in Table 1 for each method, where $\boldsymbol{\theta} = (\beta, \sigma)$ and $\boldsymbol{\sigma} = \text{vech}(\boldsymbol{\Sigma}_b)$. For most estimators considered, the function used to estimate the elements of $\boldsymbol{\Sigma}_b$, $f(\mathbf{y}_s, \mathbf{W}_s; \boldsymbol{\theta})$, provides a method-of-moments estimator for the second central moment, perhaps weighted. Since

$$E[\mathbf{U}(\boldsymbol{\theta})] = E\left[\sum_{s=1}^{S} \mathbf{W}_s(\mathbf{y}_s - \boldsymbol{\beta})\right] = \mathbf{0},$$

the solution to equations of this form is consistent when $S \to \infty$ with asymptotic covariance matrix given later in this section. Also, it can be shown for the estimators given in Table 1 that for finite S we have ($E\mathbf{T}(\boldsymbol{\theta}) = 0$) or, at least asymptotically, $E(\mathbf{T}(\boldsymbol{\theta})) \to \mathbf{0}$, when $S \to \infty$. The first estimator in Table 1, MVML, is the multivariate maximum likelihood estimator for $\boldsymbol{\beta}$ and $\boldsymbol{\Sigma}_b$ under the multivariate normality assumptions for $\mathbf{b}_s$ and $\mathbf{e}_s$ given in the previous section. In epidemiology and other biomedical applications, the within-study sample size is substantially larger than the number of studies, and it is assumed that the estimates of the within-studies variances are close to the true ones—that is, the within-study variance–covariance matrices, $\{\boldsymbol{\Sigma}_s\}$, are treated as known. To relax the assumption of multivariate normality, several possible unbiased EE arise, all of which will yield consistent estimators, and are given in Table 1. Like the MVML, MVEE1 simultaneously estimates $\boldsymbol{\beta}$ and $\boldsymbol{\Sigma}_b$ by jointly solving unbiased EE for all parameters, using the methods of moments estimator for $\boldsymbol{\Sigma}_b$ (the estimator for $\boldsymbol{\beta}$, as follows from (5), is then expressed in closed form). To simplify numerical calculations, MVEE2 and MVEE3 plug in closed-form estimates for $\boldsymbol{\Sigma}_b$ and then solve the (asymptotically) unbiased EE for $\boldsymbol{\beta}$ alone, as the closed-form weighted least squares estimator. These methods use a multivariate methods-of-moment estimator for $\boldsymbol{\Sigma}_b$.

Under the theory of estimators, which are solutions to asymptotically unbiased EE, as laid out originally by Godambe (1960) and Huber (1967) and nicely summarized in Carroll et al. (1995), under certain regularity conditions the solution $\widehat{\boldsymbol{\theta}}$ to $\mathbf{H}(\boldsymbol{\theta}) = \sum_{i=1}^{n} \mathbf{H}_i(\boldsymbol{\theta}) = \mathbf{0}$ is consistent for $\boldsymbol{\theta}$ and has the asymptotic covariance matrix given by the sandwich formula, $Cov(\widehat{\boldsymbol{\theta}}) = (\mathbf{A}^{-1})\mathbf{B}(\mathbf{A}^{-1})'$, where

$$\mathbf{A} = \frac{1}{n}\sum_{i=1}^{n} E\left\{\frac{\partial \mathbf{H}_i(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}}\right\}, \quad \mathbf{B} = \frac{1}{n}\sum_{i=1}^{n} Cov(\mathbf{H}_i(\boldsymbol{\theta})). \tag{7}$$

In the case of our EE (5) and (6), we have $\mathbf{H}(\theta) = (\mathbf{U}(\boldsymbol{\theta}), \mathbf{T}(\boldsymbol{\theta}))$. If the distribution of $\mathbf{y}_s$ is symmetric, or less restrictively, if the third moment is zero, matrix $\mathbf{B}$ becomes block-diagonal and the asymptotic distribution of $\widehat{\boldsymbol{\beta}}$ does not depend on the method of estimation of $\boldsymbol{\Sigma}_b$. In Appendix A.3, we prove that the asymptotic covariance matrix of $\widehat{\boldsymbol{\beta}}$ from the EE presented in Table 1 coincides with the MLE covariance matrix $(\sum_{s=1}^{S}(\boldsymbol{\Sigma}_b + \boldsymbol{\Sigma}_s)^{-1})^{-1}$ when $\mathbf{y}_s$ has zero third moment. This observation matches with previous results given by Demidenko and Stukel (2002) and Demidenko (2004) for general linear mixed effect models: under symmetry, any consistent estimator of the random effect covariance matrix in a linear mixed effects model leads to an asymptotically efficient estimator of $\boldsymbol{\beta}$. Consequently, if the distribution of $\mathbf{y}_s$ is symmetric, the efficiency proof in Appendix A.2 applies to MVEE1–MVEE3, and the variance of each component of vector $\widehat{\boldsymbol{\beta}}$, obtained from the multivariate EE, will also be less or equal than the respective univariate analog, for large number of studies.

3.1. Computational issues

The feasible sequential quadratic programming (FSQP) algorithm of Panier and Tits (1993) was used to obtain MVML by direct maximization of the likelihood function. The FSQP is a non-linear optimization method which restricts the search within the range of the parameter space, required here because all possible values of $\boldsymbol{\Sigma}_b$ must be positive definite. Further efficiency in applying this algorithm is gained by supplying code for the gradient and Hessian of the log likelihood through the automatic differentiation software ADIFOR (Bischof et al., 1992), thereby avoiding algebraic derivations and coding.

We have had success using as initial values for $\widehat{\boldsymbol{\beta}}^{(0)}$ the univariate estimator given by the estimators of Cochran (1954) and DerSimmonian and Laird (1986). These values are recommended as starting points for the FSQP or other algorithms for likelihood maximization. For initial values of $\widehat{\boldsymbol{\Sigma}}_b^{(0)}$, we have had success using a diagonal matrix with diagonal elements given by the univariate DerSimmonian and Laird's estimates of the between-studies variance σ_{bi}^2, $i = 1, \ldots, p$. Model (2) can also be fit in SAS (1999), using PROC MIXED (the sample code for this can be obtained

by writing to the third author). To enhance numerical stability, it helps to scale $\mathbf{y}_s$ by a vector $\mathbf{c}$, so that the components of $\mathbf{y}_s$ are not too small and fall within a similar order of magnitude. After convergence is obtained, the estimates needs to be rescaled back to the original using the vector $\mathbf{c}$.

The estimates of $\boldsymbol{\beta}$ and $\boldsymbol{\Sigma}_b$ from MVEE1 are obtained by using FSQP to minimize the sum of squares given by $\mathrm{SS} = \|\mathbf{H}(\boldsymbol{\theta})\|^2$, where $\mathbf{H}(\boldsymbol{\theta}) = (\mathbf{U}(\boldsymbol{\theta}), \mathbf{T}(\boldsymbol{\theta}))$ is the combined $(p(p+3)/2)$-dimensional estimating equation (EE) (Ryan and Contreras, 2000). The Jacobian of SS was computed by automatic differentiation with ADIFOR (Bischof et al., 1992); the minimum of SS should be zero. MVEE2–3 have a direct non-iterative solution trading computational convenience for some loss of efficiency. Sometimes a negative definite covariance matrix was obtained for MVEE2 and MVEE3 for $\hat{\boldsymbol{\Sigma}}_b$. This was more likely to occur when the variance components are on or near the boundary of the parameter space, i.e. when the determinant is zero.

4. Two tests for between-studies homogeneity

The test for between-studies homogeneity, with the alternative heterogeneity hypothesis, is an important aspect of meta-analysis. If the between-studies covariance matrix is zero, the random effects model reduces to a fixed effects model with $\boldsymbol{\beta}$ estimated by multivariate weighted least squares. Two tests are suggested in this section. We first develop a test under the assumption that $\mathbf{b}_s$ and $\mathbf{e}_s$ in model (2) are multivariate normal (MVN). We then relax the MVN assumption assuming that the number of studies, S, goes to infinity.

4.1. Test for between-studies homogeneity under MVN

In model (2), we now additionally assume that $\mathbf{b}_s$ and $\mathbf{e}_s$ have MVN distribution and $\{\boldsymbol{\Sigma}_s, s = 1, \ldots, S\}$ are known positive definite $p \times p$ matrices. It can be shown (Rao, 1973, Section 3.b) that under the null hypothesis

$$\mathrm{H}_0 : \boldsymbol{\Sigma}_b = \mathbf{0}, \tag{8}$$

a test statistic can be constructed that has the χ^2-distribution, namely,

$$\sum_{s=1}^{S} (\mathbf{y}_s - \widehat{\boldsymbol{\beta}})' \boldsymbol{\Sigma}_s^{-1} (\mathbf{y}_s - \widehat{\boldsymbol{\beta}}) \sim \chi^2((S-1)p). \tag{9}$$

This test may be viewed as a multivariate generalization of a popular univariate Q-test of DerSimmonian and Laird (1984). If random effects are present in model (2), the weighted sum of squares in (9) will have values larger than in the absence of random effects and will exceed the critical value for the $1-\alpha$ quantile of χ^2-distribution with $(S-1)p$ degrees of freedom. We can further generalize test (9) as follows. Let $\mathbf{Z}$ be a $p \times r$ matrix of rank $r \leqslant p$. Then it is easy to see that under the null hypothesis

$$\mathrm{H}_0 : \mathbf{Z}'\boldsymbol{\Sigma}_b\mathbf{Z} = \mathbf{0} \tag{10}$$

we have

$$\sum_{s=1}^{S} (\mathbf{Z}'\mathbf{y}_s - \widehat{\boldsymbol{\beta}})' (\mathbf{Z}'\boldsymbol{\Sigma}_s\mathbf{Z})^{-1} (\mathbf{Z}'\mathbf{y}_s - \widehat{\boldsymbol{\beta}}) \sim \chi^2((S-1)r), \tag{11}$$

where

$$\widehat{\boldsymbol{\beta}} = \left(\sum_{s=1}^{S} (\mathbf{Z}'\boldsymbol{\Sigma}_s\mathbf{Z})^{-1} \right)^{-1} \left(\sum_{s=1}^{S} (\mathbf{Z}'\boldsymbol{\Sigma}_s\mathbf{Z})^{-1} \mathbf{Z}'\mathbf{y}_s \right).$$

The hypothesis specified by (10) is very flexible and can be used to test whether between-studies heterogeneity exists in some subsets of $\boldsymbol{\beta}$, for example, with respect to the element corresponding to the exposure of interest, or a group of exposures of interest. For these reasons, in practice, the hypothesis given by (10) is more relevant than that given by (8).

4.2. Asymptotic test for between-studies homogeneity

In this section, we derive an asymptotic test statistic for $H_0 : \mathbf{\Sigma}_b = \mathbf{0}$, which does not assume that $\mathbf{b}_s$ and $\mathbf{e}_s$ are MVN. Asymptotics are as the number of studies gets large, $S \to \infty$. We assume that the jth component of the vector $\mathbf{v}_s = \mathbf{\Sigma}_s^{-1/2}\mathbf{e}_s$ has kurtosis κ_j and that there exist positive scalars a and A such that $a\mathbf{I} \leqslant \mathbf{\Sigma}_s \leqslant A\mathbf{I}$ for all s. Then under (9) we have

$$Z_S = \sum_{s=1}^{S} (\mathbf{y}_s - \widehat{\boldsymbol{\beta}})' \mathbf{\Sigma}_s^{-1} (\mathbf{y}_s - \widehat{\boldsymbol{\beta}}) \simeq \mathrm{N}\left(Sp, S\sum_{j=1}^{p} (\kappa_j - 1) \right), \tag{12}$$

as $S \to \infty$. The proof of (12) is given in Appendix A.1. Thus, in order to test the hypothesis (8), we compute the left-hand side (12). If it is greater than the $(1-\alpha)$-quantile of the normal distribution $\mathrm{N}(pS, S\sum_{j=1}^{p}(\kappa_j - 1))$, we reject (8). In practice, we need to estimate κ_j. A consistent estimate for $\psi = \sum_{j=1}^{p}(\kappa_j - 1)$, can be obtained from the method of moments estimator for κ_j taking $\hat{\kappa}_j = \sum_{s=1}^{S}(\hat{v}_{js} - \hat{v}_{j\cdot})^4/S$, where $\hat{\mathbf{v}}_s = (\hat{v}_{1s}, \ldots, \hat{v}_{ps}) = \mathbf{\Sigma}_s^{-1/2}(\mathbf{y}_s - \widehat{\boldsymbol{\beta}})$ and $\hat{v}_{j\cdot} = \sum_{s=1}^{S}\hat{v}_{js}/S$. We then have the test statistic for H_0 as

$$Z_S^{\star} = \frac{\sum_{s=1}^{S}(\mathbf{y}_s - \widehat{\boldsymbol{\beta}})' \mathbf{\Sigma}_s^{-1} (\mathbf{y}_s - \widehat{\boldsymbol{\beta}}) - Sp}{\sqrt{\sum_{j=1}^{p}(\widehat{\kappa}_j - 1) S}} \simeq \mathrm{N}(0, 1). \tag{13}$$

Eq. (13) follows from the Slutsky's theorem.

One can apply test (13) in the framework of (10) but only when $\mathbf{Z}$ is a special matrix such that $\mathbf{Z}'\mathbf{\Sigma}_b\mathbf{Z}$ extracts a main sub-matrix of $\mathbf{\Sigma}_b$. Then test (13) is applied to a respective subset of vector $\mathbf{y}_s$.

5. Example: carotenoids and lung cancer

In this section, we applied the methods developed in Sections 4–6 to a pooled analysis of seven prospective studies from around the world of dietary carotenoid intake and lung cancer that met minimal data quality and sample size criteria (Männistö et al., 2004). The studies were large, with cases/baseline cohort sizes 298/6771 (Holick et al., 2002), 149/56,837 (Rohan et al., 2002), 244/44,350 and 535/88,307 (Michaud et al., 2000), 433/33,828 (Steinmetz et al., 1993), 974/120,681 (Voorrips et al., 2000), 522/48,981 (Bandera et al., 1997), comprising 3155 cases and 399,765 participants in total. Most of the participating studies follow a prospective cohort design, and a few others follow a case-cohort design (Prentice, 1986). All the studies measured dietary intake through a semi-quantitative food frequency questionnaire, which was validated in a sub-study with weighed dietary records or 24-h recalls. The effect of average daily dietary intake of the five micronutrients, α-carotene, β-carotene, β-cryptoxanthin, lycopene, and lutein, on the incidence of lung cancer are investigated in this paper. The original data from each of the seven studies were re-analyzed in as uniform a way as possible, with the same model covariates defined in the same way, the same exclusion criteria, and the same statistical model. Two of the seven studies included women and men; each study was analyzed in the original publication as two independent cohorts defined on the basis of sex. To take advantage of the more extensive diet assessment completed in 1986, the cases and person–time accumulated in the Nurses' Health Study were divided into two groups for analysis (1980–1986 and 1986–1996) in the original publication. This led to 10 independent data sets used for the analysis in the original publication and here. Further details of the design of the Pooling Project of Prospective Studies of Diet and Cancer in Men and Women, and the methods used for analysis are given in Smith-Warner et al. (2005). Further details on the specific investigation of dietary carotenoids and lung cancer are given in Männistö et al. (2004) and references contained within that paper.

The vector $\widehat{\boldsymbol{\beta}}_s$ and the matrix $\widehat{\mathbf{\Sigma}}_s$ matrix from each of the seven studies were estimated directly at the pooling project study site and were then available to us for multivariate pooling. The study-specific estimates adjusted for confounding by five covariates: caloric intake (kcal/day), body mass index ($\mathrm{kg/m^2}$), alcohol intake (grams/day), number of cigarettes smoked per day for current smokers and the duration (years) of smoking among current smokers. We restricted the present analysis to current cigarette smokers.

Table 2
Estimates (SE) and AREs for carotenoids and lung cancer example

Variable coefficient	Maximum likelihood estimation			Estimating equations		
	Univariate	Multivariate MVML	ARE	Univariate	Multivariate MVEE1	ARE
β-Carotene$\times 10^4$	0.608 (0.260)	0.512 (0.251)	0.932	0.608 (0.329)	0.561 (0.324)	0.970
α-Carotene	−2.56 (1.06)	−0.593 (0.800)	0.569	−1.62 (1.78)	−1.16 (1.12)	0.396
β-Cryptoxanthin	−9.42 (2.30)	−9.37 (2.230)	0.940	−9.42 (1.72)	−9.81 (1.80)	1.100
Lycopene	−0.116 (0.07)	−0.133 (0.065)	0.862	−0.116 (0.056)	−0.132 (0.061)	1.187
Lutein	−0.311 (0.187)	−0.261 (0.151)	0.652	−0.311 (0.288)	−0.265 (0.160)	0.309

Before proceeding to the estimation phase, we first needed to investigate the evidence in the data for between-studies heterogeneity. Globally, we tested $H_0 : \mathbf{\Sigma}_b^{10\times 10} = \mathbf{0}$ and obtained a p-value of 0.001, indicating strong evidence of heterogeneity. We next investigated evidence in the data for between-studies heterogeneity in the 5×5 sub-matrix of interest corresponding to the five carotenoids, by testing $H_0 : \mathbf{Z}'\mathbf{\Sigma}_b\mathbf{Z} = \mathbf{0}$, where $\mathbf{Z}'$ is the 5×10 matrix of rank 5 consisting of the five row vectors $(1, 0, 0, 0, 0, \ldots, 0)$, $(0, 1, 0, 0, 0, \ldots, 0)$, $(0, 0, 1, 0, 0, \ldots, 0)$, $(0, 0, 0, 1, 0, \ldots, 0)$ and $(0, 0, 0, 0, 1, \ldots, 0)$, and obtained a p-value of 0.28, suggesting that the five effects of interest are homogeneous across studies and therefore can be pooled. In addition, we investigated evidence in the data for between-studies heterogeneity by forming univariate tests of no random between-studies effect in the five effects of interest, and obtained p-values of 0.04, 0.01, 0.34, 0.66, and 0.13 for β-carotene, α-carotene, β-cryptoxanthin, lycopene, and lutein, respectively. Finally, the p-values for the tests for heterogeneity for each covariate (calories, alcohol, BMI, number of cigarettes smoked per day, and duration of smoking) were 0.58, 0.48, 0.05, 0.001, and 0.0004, respectively. The heterogeneity was mainly driven by the smoking variables.

We therefore proceeded with estimation and inference allowing between-studies heterogeneity of effects in β-carotene, BMI, α-carotene, number of cigarettes smoked and the duration of smoking. Because of the multiple comparisons that were conducted and because there was no a priori reason to hypothesize between-studies heterogeneity in these particular effects, the borderline significant evidence for heterogeneity in β-carotene and BMI was not considered further, and all elements of $\mathbf{\Sigma}_b$ were fixed at zero except for the 3×3 sub-matrix $\mathbf{\Sigma}_0$ corresponding to carotene, number of cigarettes smoked and smoking duration. For these three variables, we then proceeded to estimate the six unique parameters of the sub-matrix Σ_0 along with the 10 regression parameters, for a total of 16 parameters.

Table 2 compares the $\widehat{\text{ARE}}$ of the univariate pooled estimates to the multivariate pooled analyses for the five micronutrients. The variance for the univariate estimate used in computing the ARE was evaluated at the corresponding elements of matrix $\hat{\mathbf{\Sigma}}_b$. Recall that the UVML corresponds to the MLE from the marginal univariate normal distribution where each micronutrient was analyzed separately (the between-studies variances were all assumed zero except for α -carotene). The standard errors of the MVML estimates were all smaller than the UVML estimates, with an estimated 6–43% improvement in efficiency evident. When using the EE approach, the estimated standard errors for the univariate estimating equations (UVEE) were all lower than that of the multivariate estimating equations (MVEE), except for β-cryptoxanthin and lycopene, where a small loss of efficiency was estimated.

6. A simulation study

In this section we describe the design and results of some simulations to assess small sample properties of our proposed estimators and test statistic. We set $p = 2$ for simplicity. The values of the within-study variances σ_{iis}, $i = 1, 2$, $s = 1, \ldots, S = 10$ where chosen to reflect the typical values given in the example of Section 5 for the variables β-cryptoxhanthin and lycopene, since these were the significant findings in this study. These values were 6.93, 1.30, 1.00, 2.29, 0.88, 0.31, 0.27, 1.80, 0.28, and 0.23 for $\sigma_{111}, \ldots, \sigma_{1110}$ (scaled up by 10^6) and 0.052, 0.039, 0.045, 0.015, 0.86, 0.088, 2.19, 0.032, 0.50, and 0.043 for $\sigma_{221}, \ldots, \sigma_{2210}$ (scaled up by 10^8). We simulated the values of $\mathbf{y}_s$ to follow a bivariate normal distribution with mean (β_1, β_2), variances $\sigma_{11s} + \sigma_{b11}$ and $\sigma_{22s} + \sigma_{b22}$ and covariance $\sigma_{12s} + \sigma_{b12}$. We set the within-study correlations, ρ_s, to be the same for all the studies. We studied the within- and between-studies correlations at a high and at a low value to illustrate the extreme situations. The values set for β_1 and β_2 were similar to

Table 3
Simulation results ($p = 2$); number of experiments, $M = 500$

	Relative bias (%)				Relative efficiency (%)				PD (%)	95% coverage				
	MVML	MVEE1	MVEE2	MVEE3	MVML	MVEE1	MVEE2	MVEE3		MVMLa	MVMLb	MVEE1	MVEE2	MVEE3
$S = 10$, $\rho_b = \rho_s = 0.9$														
$\widehat{\beta}_1$	−0.34	−0.23	−0.22	−10.2	79	89	128	292	56.0	79.8	86.0	92.8	80.4	52.8
$\widehat{\beta}_2$	−1.21	−1.76	−2.15	4.31	90	131	98	197	51.0	78.0	87.4	93.0	79.8	54.4
$S = 50$, $\rho_b = \rho_s = 0.9$														
$\widehat{\beta}_1$	−0.11	−0.06	−0.12	0.002	86	95	82	78	81.0	86.0	93.8	97.8	90.4	76.6
$\widehat{\beta}_2$	−0.29	−0.52	−0.57	−0.65	95	117	92	93	75.0	85.8	92.8	96.2	90.6	81.6
$S = 500$, $\rho_b = \rho_s = 0.9$														
$\widehat{\beta}_1$	0.04	0.23	0.04	0.04	86	24	83	84	99.4	90.2	95.4	94.2	95.0	93.2
$\widehat{\beta}_2$	−0.05	−0.47	0.003	0.004	96	114	93	93	99.2	87.6	94.8	96.2	93.8	93.8
$S = 10$, $\rho_b = \rho_s = 0.1$														
$\widehat{\beta}_1$	0.09	0.11	−0.06	−0.40	98	99	104	132	88.0	89.8	90.2	95.2	85.8	74.2
$\widehat{\beta}_2$	0.28	0.003	−0.22	0.10	99	105	98	100	74.0	89.6	90.2	92.0	89.4	71.4
$S = 50$, $\rho_b = \rho_s = 0.1$														
$\widehat{\beta}_1$	0.01	−0.01	0.01	−0.003	100	100	100	99	100	93.0	93.2	96.6	92.2	96.4
$\widehat{\beta}_2$	0.73	0.71	0.72	0.73	100	100	100	99	100	92.6	92.6	94.6	92.8	95.8

True values: $\beta_1 = 9.4$, $\beta_2 = 2.6$; $\sigma_{b1} = 2$, $\sigma_{b2} = 1$.

that of the values given in Table 2 with the true values $\beta_1 = 9.4$ and $\beta_2 = 2.6$ ($\times 10^4$). We varied the number of studies, S to 10, 50, and 500. For $S = 50$ and 500 we repeated the values for σ presented above, 5 and 50 times, respectively, to create the additional simulated studies. In Table 3, we display the result of the simulations for each of the methods proposed in this paper. Here MVML and MVEE1–3 are the multivariate maximum likelihood and EE methods as described schematically in Table 1 and Section 3. The relative bias is defined as percent $100(\bar{\hat{\beta}}_j - \beta_j)/\beta_j$, where β_j is the true value and $\bar{\hat{\beta}}_j$ is the sample mean of all the estimated β_j's. The 95% coverage is the percentage of times the true value is contained in the estimated 95% confidence interval formed with the corresponding variance estimator. For the test statistic $T = Z^2 \sim \chi^2_1$, where Z is given in (9), we calculated the rejection rate, that is, the percentage of the time the test statistic is rejecting the null hypothesis $H_0 : \mathbf{\Sigma}_b = \mathbf{0}$ following the procedure described in Section 3.

From the simulations, it is clear that all estimators had very small relative bias, ranging from 0.01 to 1.21, 0.003 to 1.76, 0.01 to 2.2, and 0.002 to 10.2 in absolute magnitude for the MVML and MVEE1–3, respectively. The relative efficiency (RE) was defined as the ratio of the empirical variance to MVML. These calculations reflect the small sample properties of the variance estimate, particularly when S is small, in addition to the RE of the approach. Therefore, some of these values may be greater than 100. The REs were always less than one for the MVML (0.79–0.96), when the between-studies correlation (ρ_b) was 0.9, but almost one when $\rho_b = 0.1$, as would be expected. The MVEE1 did not necessarily have an RE less than one. For β_1, the RE ranged from 0.89 to 1.78 and for β_2, it was always larger than one (1.02–1.31). For MVEE2–3, the RE went in either direction, ranging from 0.82–1.28 and 0.78–2.92, respectively. The MVML and MVEE1 estimated values of $\mathbf{\Sigma}_b$ were always positive as guaranteed by the estimation algorithm. The MVEE2–3 were not always, however, and the column marked PD shows the percentage of times out of all simulations that the estimated $\mathbf{\Sigma}_b$ was positive definite. For small S, the proportion of times $\widehat{\mathbf{\Sigma}}_b$ was not positive definite was large, suggesting that these estimators may be problematic in this setting.

The coverages for β_1 and β_2 shows that the variance estimate given by (4) is poor (MVMLa) when S is small, which had been noted previously by Hoewelingen (2002). The coverage was improved considerably by using the sandwich variance estimate (MVMLb). The MVEE2–3 had good coverage for the varying study sizes considered also. Overall, the improvement in both relative bias and coverage gets better for increasing study size with $S = 10$, 50, and 500 for $\rho_b = 0.9$ and $S = 10$–50 for $\rho_b = 0.1$.

Finally, we studied the performance of the test statistic in terms of the rejection rate for the test statistic (9) and power (data not shown). The test statistic had close to nominal level under H_0 for various values of S and within-study

correlations. We found that when $S = 10$, power was low unless at least one of the between-studies variance components was large. Power improved as the correlation between between-studies random effects decreased, as expected.

7. Discussion

We have shown theoretically and empirically that the multivariate pooling can increase the efficiency of estimates using model (2) under an assumption of multivariate normality of the random effects, and often without this assumption. Even with significant between-studies heterogeneity in the effects of only a few of the full model covariates, as in the lung cancer data in Table 2, we still saw a 6–43% gain in efficiency. A disadvantage of the ML method is that it requires an assumption of MV normality of the random effect and of the within-study sampling error. In contrast, the EE approach does not impose any distributional assumptions on the random effect or the within-studies sampling error. The lack of efficiency gain for a few of the covariate effects in Table 2 is likely due to small sample size because asymptotically the gain is guaranteed as follows from Section 3.

The test of between-studies homogeneity is an important part of pooling projects, IDP, and data consortia. We have developed two versions of the test, one for small S, to be used when the normal assumption is valid, and another for large S. Both are generalizations of the popular Q-test. The asymptotic test for between-studies homogeneity may not be valid in our example because we only had $S = 7$. However, Takkouche et al. (1999) studied by simulation the small sample properties of univariate tests of between-studies heterogeneity, and reported that the DerSimmonian and Laird statistic gave the correct type I error under the null, but has low statistical power when the number of studies was small. An analogous phenomena is observed in cluster randomized designs (Donner and Klar, 1994).

For data with $\mathbf{\Sigma}_b$ well away from zero, i.e. in the region where $\mathbf{\Sigma}_b$ is positive definite, the method of moments approach MVEE2–3 gives a simple non-iterative estimate of $\mathbf{\Sigma}_b$ and β. When $\mathbf{\Sigma}_b$ is near the boundary, i.e. when there is little if any between-studies heterogeneity, multivariate estimators may not converge as well as when the variances are away from the boundary. In these cases, it is perhaps best, as we did in Section 4, to set the appropriate elements of $\mathbf{\Sigma}_b$ to 0, and proceed with the resulting simpler estimator. The MVEE2–3 has the advantage of being computationally easier than the MVML, since these estimators for both $\boldsymbol{\beta}$ and $\mathbf{\Sigma}_b$ are non-iterative.

We have conducted a small simulation study that largely confirms the theory: when the correlation between estimates in studies is small, there is little gain from multivariate methods discussed in the paper relative to the standard univariate methods. When the correlation between estimates in the studies is high, efficiency improves by 15–20% by using multivariate methods compared to univariate. It is reasonable to assume that intermediate correlations will provide intermediate improvements in efficiency. More simulations and theoretical studies could be undertaken to fully investigate the effect of the correlation in the future.

A practical limitation of the methods described in this paper is that they require the ability to estimate the full covariance matrices from each study. These methods are most appropriate for use in pooling projects, IDP, and data consortia, such as the references in the Introduction section. In meta-analysis, only the summary effect estimates and their standard errors are available. Since data on covariances of multiple estimates are almost never supplied, the methods given here will generally not be applicable for meta-analysis. Greenland and Longnecker (1992) provide a somewhat *ad hoc* method to estimate the missing covariance terms; the usefulness of this approximation warrants further study. Hence, in addition to its validity advantages as previously discussed (e.g. Gordon et al., 1998), pooling may often have substantial efficiency advantages using the methods discussed in this paper. When the correlation between the estimates of pooled coefficients is not zero, multivariate pooling will usually result in improved estimates.

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Appendix A.

A.1. Proof of asymptotic normality of multivariate test for homogeneity

We consider the asymptotic distribution of the left-hand side of (9) under (8). Then, introducing random vectors $\mathbf{u}_s = \mathbf{y}_s - \boldsymbol{\beta}$ and $\mathbf{v}_s = \boldsymbol{\Sigma}_s^{-1/2}\mathbf{u}_s = \boldsymbol{\Sigma}_s^{-1/2}(\mathbf{y}_s - \boldsymbol{\beta})$, we notice that $E(\mathbf{v}_s) = \mathbf{0}$ and $cov(\mathbf{v}_s) = \mathbf{I}$. The left-hand side of (9) divided by $\sqrt{S}$, after some algebra, can be represented as

$$\frac{1}{\sqrt{S}}\sum_{s=1}^{S}\mathbf{v}_s'\mathbf{v}_s - \frac{2}{\sqrt{S}}\left(\sum \mathbf{v}_s'\boldsymbol{\Sigma}_s^{-1/2}\right)(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}) + \frac{1}{\sqrt{S}}\sum_{s=1}^{S}(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta})'\boldsymbol{\Sigma}_s^{-1}(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}). \tag{14}$$

It is then possible to show that these last two terms converge in probability to zero when $S \to \infty$. For example, for the second term, from the Chebyshev's inequality it suffices to show that $\lim_{S\to\infty} E[(2/\sqrt{S})(\sum \mathbf{v}_s'\boldsymbol{\Sigma}_s^{-1/2})(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta})]^2 = 0$. But we have

$$\begin{aligned} E\left[\frac{2}{\sqrt{S}}\left(\sum \mathbf{v}_s'\boldsymbol{\Sigma}_s^{-1/2}\right)(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta})\right]^2 &= \frac{4}{S}\left[\left(\sum \mathbf{v}_s'\boldsymbol{\Sigma}_s^{-1/2}\right)(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta})\right]^2 \\ &\leqslant \frac{4}{S}E\left[\left(\sum \mathbf{v}_s'\boldsymbol{\Sigma}_s^{-1/2}\right)\left(\sum \boldsymbol{\Sigma}_s^{-1/2}\mathbf{v}_s\right)\right]E[(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta})'(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta})]. \end{aligned}$$

Due to independence across studies we have for the first expected value

$$E\left[\left(\sum \mathbf{v}_s'\boldsymbol{\Sigma}_s^{-1/2}\right)\left(\sum \boldsymbol{\Sigma}_s^{-1/2}\mathbf{v}_s\right)\right] = \sum \mathrm{tr}(\boldsymbol{\Sigma}_s^{-1}).$$

The second expected value is easier, $E[(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta})'(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta})] = \mathrm{tr}(\sum \boldsymbol{\Sigma}_s^{-1})^{-1}$. Thus,

$$\begin{aligned} E\left[\frac{2}{\sqrt{S}}\left(\sum \mathbf{v}_s'\boldsymbol{\Sigma}_s^{-1/2}\right)(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta})\right]^2 &\leqslant \frac{4}{S}\sum \mathrm{tr}(\boldsymbol{\Sigma}_s^{-1})\mathrm{tr}\left(\sum \boldsymbol{\Sigma}_s^{-1}\right)^{-1} \leqslant \frac{4}{S}\frac{Sp}{a}\frac{pA}{S} \\ &= \frac{4p^2A}{aS} \to 0. \end{aligned}$$

Thus, the second term in (14) is negligible.

Next we use the fact that if for three random variables $Z_S = X_S + Y_S$, where $p\lim_{S\to\infty} Y_S = 0$, then the asymptotic distribution of Z_S and X_S coincide. Hence, the asymptotic distribution of the left-hand side (12) coincides with the asymptotic distribution of $\sum_{s=1}^{S}\mathbf{v}_s'\mathbf{v}_s$. We denote $\zeta_s = \mathbf{v}_s'\mathbf{v}_s$ and omitting subindex s, we obtain $E(\zeta) = E(\sum_{j=1}^{p} v_j^2) = \sum_{j=1}^{p} E(v_j^2) = p$ and

$$Var(\zeta) = Var\left(\sum_{j=1}^{p} v_j^2\right) = \sum_{j=1}^{p} Var(v_j^2) = \sum_{j=1}^{p}[E(v_j^4) - E^2(v_j^2)] = \sum_{j=1}^{p}(\kappa_j - 1).$$

Then, by the Central Limit Theorem, $(1/\sqrt{S})\sum_{s=1}^{S}(\zeta_s - p) \simeq \mathrm{N}(0, S\sum_{j=1}^{p}(\kappa_j - 1))$ when $S \to \infty$, which implies (12).

A.2. Proof of asymptotic RE of the multivariate maximum likelihood estimator (MVML)

We us the following fact on partitioned matrix inverse (Graybill, 1983, p. 184): if matrix $\mathbf{A}$ is partitioned as

$$\mathbf{A} = \begin{bmatrix} a_{11} & \mathbf{a}_{21}' \\ \mathbf{a}_{21} & \mathbf{A}_{22} \end{bmatrix},$$

then

$$\mathbf{A}^{-1} = \mathbf{B} = \begin{bmatrix} b_{11} & \mathbf{b}_{21}' \\ \mathbf{b}_{21} & \mathbf{B}_{22} \end{bmatrix},$$

where

$$b_{11} = \frac{1}{a_{11} - \mathbf{a}_{21}'\mathbf{A}_{22}^{-1}\mathbf{a}_{21}} = \frac{1}{a_{11}} + \frac{\mathbf{a}_{21}'\mathbf{B}_{22}\mathbf{a}_{21}}{a_{11}^2}, \tag{15}$$

$$\mathbf{b}_{21} = -\frac{1}{a_{11} - \mathbf{a}_{21}'\mathbf{A}_{22}^{-1}\mathbf{a}_{21}}\mathbf{A}_{22}^{-1}\mathbf{a}_{21} = -b_{11}\mathbf{A}_{22}^{-1}\mathbf{a}_{21}, \tag{16}$$

$$\mathbf{B}_{22} = \left(\mathbf{A}_{22} - \frac{1}{a_{11}}\mathbf{a}_{21}\mathbf{a}_{21}'\right)^{-1} = \mathbf{A}_{22}^{-1} + b_{11}\mathbf{A}_{22}^{-1}\mathbf{a}_{21}\mathbf{a}_{21}'\mathbf{A}_{22}^{-1}. \tag{17}$$

The proof of multivariate efficiency relies on the following Lemma, where $\mathbf{V}_s = \mathbf{\Sigma}_b + \mathbf{\Sigma}_s$.

Lemma 1. *Let* $\{\mathbf{V}_s, s = 1, \ldots, S\}$ *be* $p \times p$ *positive definite symmetric matrices of the same size and* v_{s11} *denote the* $(1, 1)$*th element. Then*

$$\frac{1}{\sum_{s=1}^{S} 1/v_{s11}} \geqslant \left[\left(\sum_{s=1}^{S} \mathbf{V}_s^{-1}\right)^{-1}\right]_{11}, \tag{18}$$

where the right-hand side denotes the $(1, 1)$*th element of the inverse matrix. The inequality turns into equality if either all* $\mathbf{V}_s$ *are the same or the off-diagonal elements in the first row and column are zero.*

Proof. Partition the S matrices as follows:

$$\mathbf{V}_s = \begin{bmatrix} v_{11s} & \mathbf{v}_{21s}' \\ \mathbf{v}_{21s} & \mathbf{V}_{22s} \end{bmatrix}, \quad s = 1, \ldots, S,$$

where $\mathbf{v}_{21s}$ is the first $(p-1) \times 1$ vector column and $\mathbf{V}_{22s}$ is the $(p-1) \times (p-1)$ sub-matrix starting from the second row. Using formulas (15)–(17) we obtain

$$\sum_{s=1}^{S} \mathbf{V}_s^{-1} = \begin{bmatrix} \sum_{s=1}^{S} q_s & -\sum_{s=1}^{S} q_s \mathbf{v}_{21s}' \mathbf{V}_{22s}^{-1} \\ -\sum_{s=1}^{S} q_s \mathbf{V}_{22s}^{-1}\mathbf{v}_{21s} & \sum_{s=1}^{S}\left(\mathbf{V}_{22s} - \frac{1}{v_{11s}}\mathbf{v}_{21s}\mathbf{v}_{21s}'\right)^{-1} \end{bmatrix},$$

where $q_s = 1/(v_{11s} - \mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s})$. Using (15) for reciprocal of the (1, 1)th element we obtain

$$\begin{aligned} &\frac{1}{[(\sum_{s=1}^{S} \mathbf{V}_s^{-1})^{-1}]_{11}} \\ &\quad = \sum_{s=1}^{S} q_s - \left[\sum_{s=1}^{S} q_s \mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\right]' \left[\sum_{s=1}^{S}\left(\mathbf{V}_{22s} - \frac{1}{v_{11s}}\mathbf{v}_{21s}\mathbf{v}_{21s}'\right)^{-1}\right]^{-1} \left[\sum_{s=1}^{S} q_s \mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\right]. \end{aligned}$$

Hence, inequality (18) is equivalent to

$$\begin{aligned} &\sum_{s=1}^{S} q_s - \left[\sum_{s=1}^{S} q_s \mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\right]' \left[\sum_{s=1}^{S}\left(\mathbf{V}_{22s} - \frac{1}{v_{11s}}\mathbf{v}_{21s}\mathbf{v}_{21s}'\right)^{-1}\right]^{-1} \left[\sum_{s=1}^{S} q_s \mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\right] \\ &\quad \geqslant \sum_{s=1}^{S} 1/v_{s11}, \end{aligned}$$

or

$$\begin{aligned} &\left[\sum_{s=1}^{S} q_s \mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\right]' \left[\sum_{s=1}^{S}\left(\mathbf{V}_{22s} - \frac{1}{v_{11s}}\mathbf{v}_{21s}\mathbf{v}_{21s}'\right)^{-1}\right]^{-1} \left[\sum_{s=1}^{S} q_s \mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\right] \\ &\quad \leqslant \sum_{s=1}^{S}\left(q_s - \frac{1}{v_{s11}}\right) = \sum_{s=1}^{S} \frac{\mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}}{(v_{11s} - \mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s})v_{11s}}. \end{aligned}$$

But

$$\left(\mathbf{V}_{22s} - \frac{1}{v_{11s}}\mathbf{v}_{21s}\mathbf{v}_{21s}'\right)^{-1} = \mathbf{V}_{22s}^{-1} + \frac{1}{v_{11s} - \mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}}\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1}$$
$$= \mathbf{V}_{22s}^{-1} + q_s\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1}.$$

Thus we need to prove

$$\left[\sum_{s=1}^{S} q_s\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\right]'\left[\sum_{s=1}^{S}(\mathbf{V}_{22s}^{-1} + q_s\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1})\right]^{-1}\left[\sum_{s=1}^{S} q_s\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\right]$$
$$\leqslant \sum_{s=1}^{S}\left(q_s - \frac{1}{v_{s11}}\right).$$

Since

$$q_s - \frac{1}{v_{s11}} = \frac{q_s^2\mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}}{1 + q_s\mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}},$$

we need to prove that

$$\left[\sum_{s=1}^{S} q_s\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\right]'\left[\sum_{s=1}^{S}(\mathbf{V}_{22s}^{-1} + q_s\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1})\right]^{-1}\left[\sum_{s=1}^{S} q_s\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}\right]$$
$$\leqslant \sum_{s=1}^{S}\frac{q_s^2\mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}}{1 + q_s\mathbf{v}_{21s}'\mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}}.$$

Letting $\mathbf{x}_s = \mathbf{V}_{22s}^{-1}\mathbf{v}_{21s}$ and $\mathbf{A}_s = \mathbf{V}_{22s}$, the original inequality becomes equivalent to

$$\left(\sum_{s=1}^{S} q_s\mathbf{x}_s\right)'\left(\sum_{s=1}^{S}\left(\mathbf{A}_s^{-1} + q_s\mathbf{x}_s\mathbf{x}_s'\right)\right)^{-1}\left(\sum_{s=1}^{S} q_s\mathbf{x}_s\right) \leqslant \sum_{s=1}^{S}\frac{q_s^2\mathbf{x}_s'\mathbf{A}_s\mathbf{x}_s}{1 + q_s\mathbf{x}_s'\mathbf{A}_s\mathbf{x}_s}. \tag{19}$$

To prove this we use inequality

$$\left(\sum_{s=1}^{S}\mathbf{u}_s\right)'\left(\sum_{s=1}^{S}\mathbf{Q}_s\right)^{-1}\left(\sum_{s=1}^{S}\mathbf{u}_s\right) \leqslant \sum_{s=1}^{S}\mathbf{u}_s'\mathbf{Q}_s^{-1}\mathbf{u}_s, \tag{20}$$

which follows from Cauchy inequality. Notice that (20) turns into equality if $\mathbf{u}_s$ and $\mathbf{Q}_s$ do not change with s. Letting $\mathbf{u}_s = q_s\mathbf{x}_s$ and $\mathbf{Q}_s = \mathbf{A}_s^{-1} + q_s\mathbf{x}_s\mathbf{x}_s'$ we obtain that the left-hand side of (19) is less or equal $\sum_{s=1}^{S} q_s^2\mathbf{x}_s'(\mathbf{A}_s^{-1} + q_s\mathbf{x}_s\mathbf{x}_s')^{-1}\mathbf{x}_s$. But

$$\mathbf{x}_s'(\mathbf{A}_s^{-1} + q_s\mathbf{x}_s\mathbf{x}_s')^{-1}\mathbf{x}_s = \mathbf{x}_s'\left(\mathbf{A}_s - \frac{q_s}{1 + q_s\mathbf{x}_s'\mathbf{A}\mathbf{x}_s}\mathbf{A}_s\mathbf{x}_s\mathbf{x}_s'\mathbf{A}_s\right)\mathbf{x}_s = \frac{\mathbf{x}_s'\mathbf{A}_s\mathbf{x}_s}{1 + q_s\mathbf{x}_s'\mathbf{A}_s\mathbf{x}_s},$$

which proves (19) and consequently (18). The inequality (19) turns into equality if either all $\mathbf{V}_s$ are the same ($\mathbf{V}_{22s}$=const, $\mathbf{v}_{21s} = \text{const}$, $q_s = \text{const}$) or the off-diagonal elements in the first row and column are zero ($\mathbf{v}_{21s} = \mathbf{0}$).

A.3. Proof of equivalence of ML and EE under symmetry

We aim to prove that if the distribution of $\mathbf{y}_s$ is symmetric, under standard regularity conditions, the EE approach, given by Eqs. (5) and (6), is asymptotically equivalent to the maximum likelihood (ML) estimator for $\boldsymbol{\beta}$. We prove that, as follows from the sandwich formula $Cov(\widehat{\theta}) = (\mathbf{A}^{-1})\mathbf{B}(\mathbf{A}^{-1})'$, where matrices $\mathbf{A}$ and $\mathbf{B}$ are defined by (7), the covariance matrix of $\widehat{\boldsymbol{\beta}}$ from EE is equal to $(\sum_{s=1}^{S}(\boldsymbol{\Sigma}_b + \boldsymbol{\Sigma}_s)^{-1})^{-1}$, the covariance matrix of the ML estimator. In

addition to standard regularity conditions for ML and EE (Schervish, 1995), we assume that the components of the normalized vector $(\mathbf{\Sigma_b}+\mathbf{\Sigma}_s)^{-1/2}(\mathbf{y}_s-\boldsymbol{\beta})=\eta$ are independent with the third moment equal to zero. From the symmetry condition, $E(\eta_i\eta_j^2)=E(\eta_i^3)=0$ for all $i, j=1,2,\ldots,p$.

Matrices $\mathbf{A}$ and $\mathbf{B}$ are given by

$$\mathbf{A}=E\begin{bmatrix}\dfrac{\partial\mathbf{U}}{\partial\boldsymbol{\beta}} & \dfrac{\partial\mathbf{U}}{\partial\boldsymbol{\sigma}}\\ \dfrac{\partial\mathbf{T}}{\partial\boldsymbol{\beta}} & \dfrac{\partial\mathbf{T}}{\partial\boldsymbol{\sigma}}\end{bmatrix},\quad \mathbf{B}=Cov\begin{bmatrix}\mathbf{U}\\ \mathbf{T}\end{bmatrix}=\begin{bmatrix}Cov(\mathbf{U}) & Cov(\mathbf{U},\mathbf{T})\\ Cov(\mathbf{T},\mathbf{U}) & Cov(\mathbf{T})\end{bmatrix}.$$

Taking the derivative of the EE for $\boldsymbol{\beta}$ presented in Table 1 with respect to $\boldsymbol{\sigma}$, it is easy to see that $E(\partial\mathbf{U}/\partial\sigma)=0$. Also it is easy to see that $E(\partial\mathbf{U}/\partial\beta)=Cov(\mathbf{U})=\sum_{s=1}^{S}(\mathbf{\Sigma}_b+\mathbf{\Sigma}_s)^{-1}$. Now we use the symmetry condition to prove that $Cov(\mathbf{U},\mathbf{T})=\mathbf{0}$. The product of $\mathbf{U}$ and $\mathbf{T}$ can be expressed as a linear combination of the terms $\eta_i\eta_j^2$. Since $E(\eta_i\eta_j^2)=0$ for all i, j, we have $Cov(\mathbf{U},\mathbf{T})=\mathbf{0}$. Finally, the asymptotic covariance matrix of the EE estimator of $\boldsymbol{\theta}$ is

$$\begin{bmatrix}Cov(\mathbf{U}) & \mathbf{0}\\ E\left(\dfrac{\partial\mathbf{T}}{\partial\boldsymbol{\beta}}\right) & E\left(\dfrac{\partial\mathbf{T}}{\partial\boldsymbol{\sigma}}\right)\end{bmatrix}^{-1}\begin{bmatrix}Cov(\mathbf{U}) & \mathbf{0}\\ \mathbf{0} & Cov(\mathbf{T})\end{bmatrix}\begin{bmatrix}Cov(\mathbf{U}) & E\left(\dfrac{\partial\mathbf{T}}{\partial\boldsymbol{\beta}}\right)\\ \mathbf{0} & E\left(\dfrac{\partial\mathbf{T}}{\partial\boldsymbol{\sigma}}\right)\end{bmatrix}^{-1}.$$

Using standard formulas for the block matrix inverse (Schott, 2005), we find that the (1, 1)th block of the above matrix is $Cov^{-1}(\mathbf{U})=(\sum_{s=1}^{S}(\mathbf{\Sigma}_b+\mathbf{\Sigma}_s)^{-1})^{-1}$, the asymptotic covariance matrix of the MLE. Thus, EE and ML are asymptotically equivalent estimators of $\boldsymbol{\beta}$.

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