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COMBINING MULTIVARIATE ESTIMATORS OF THE MEAN VECTOR

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Abstract

Meta-analysis is a standard statistical method used to combine the conclusions of individual studies that are related and the results of single study alone can not answered to deal with issues. The data are summarized by one or more outcome measure estimates along with their standard errors.

The multivariate model and the variations between studies are not considered in most articles.

Here we discuss multivariate effects models: a multivariate fixed effects model and a multivariate random effects model.

Keywords: meta-analysis, the fixed effects model, the random effects model.

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1. Introduction

Meta-analysis is a statistical method put in the context of mixed likelihood methods to estimate all relevant parameters [3].

In the medical literature, meta-analysis is usually applied to the results of clinical trials, but we present a theory, the application of which is not only limited to clinical trials.

Methods for meta-analysis of summary data are discussed in Section 2 and Section 3. The statistical methods are generally based on standard fixed or random effects models. In Section 4, we discuss results in medical trials.

Section 5 examines the application of the methods. The collection consists of seven studies, each examines the efficacy of three medicines in the treatment of hypertension. The medicines include the same component in different amount. In each study the number of patients whom medicines or a control drug did not help is recorded. To calculate the example we use SAS PROC.

2. The fixed effects model

Suppose that in each of m studies there are measures on k response variables for each subject (see Table 1).

Table 1.

Study 1	Study 2	...	Study m
Y_{11}	Y_{21}	...	Y_{m1}
Y_{12}	Y_{22}	...	Y_{m2}
$\vdots$	$\vdots$	$\vdots$	$\vdots$
Y_{1k}	Y_{2k}	...	Y_{mk}

Let

$$\mathbf{Y}_j = \begin{bmatrix} Y_{1j} \\ Y_{2j} \\ \vdots \\ Y_{mj} \end{bmatrix}, \quad j = 1, 2, \ldots, k,$$

and denote the estimated outcome measure by

$$\mu = \begin{bmatrix} \mu_1 \\ \mu_2 \\ \vdots \\ \mu_m \end{bmatrix}.$$

A general model is then specified by

$$\mathbf{Y}_j = \mu + \mathbf{e}_j,$$

where

$$\mathbf{e}_j = \begin{bmatrix} e_{1j} \\ e_{2j} \\ \vdots \\ e_{mj} \end{bmatrix}$$

indicate the error of the summary statistic and we assume that for a given $i = 1, 2, \ldots, m$, e_{ij} are supposed to be independent with mean zero and variance $\sigma_{ii}^{2(j)}$, $e_{ij} \sim N(0, \sigma_{ii}^{2(j)})$, but $\mathbf{e}_j$ are dependent for different j, $j = 1, 2, \ldots, k$.

This means that the estimated effect size $\mathbf{Y}_j$, $j = 1, 2, \ldots, k$, is normally distributed with the mean μ and variance

$$\mathbf{\Sigma}_j = \begin{bmatrix} \sigma_{11}^{2(j)} & \sigma_{12}^{2(j)} & \ldots & \sigma_{1m}^{2(j)} \\ \sigma_{21}^{2(j)} & \sigma_{22}^{2(j)} & \ldots & \sigma_{2m}^{2(j)} \\ \vdots & \vdots & \vdots & \vdots \\ \sigma_{m1}^{2(j)} & \sigma_{m2}^{2(j)} & \ldots & \sigma_{mm}^{2(j)} \end{bmatrix}, \quad j = 1, 2, \ldots, k.$$

Let $\mathbf{S}_j$, $j = 1, 2, \ldots, k$, denote the estimator of $\mathbf{\Sigma}_j$. Then, the estimator of μ is a simple weighted average of $\mathbf{Y}_j$, with the weights proportional to $\mathbf{\Omega}_j = \mathbf{S}_j^{-1}$. Hence

$$\hat{\mu} = \left(\sum_{j=1}^{k} \mathbf{\Omega}_j \right)^{-1} \sum_{j=1}^{k} \mathbf{\Omega}_j \mathbf{Y}_j$$

and $\hat{Var}(\hat{\mu}) = \mathbf{\Omega}^{-1}$, where $\mathbf{\Omega} = \sum_{j=1}^{k} \mathbf{\Omega}_j$.

When $\mathbf{\Sigma}_j$ is assumed known, the estimator $\hat{\mu} \,|\, \mathbf{\Sigma} \sim N(\mu, \mathbf{\Sigma}^{-1})$ (adequately to one-dimensional model [1], [4]) and the statistic to testing $H_0 : \mu = \mu_0$ is $(\hat{\mu} - \mu_0)' \, \mathbf{\Omega} \, (\hat{\mu} - \mu_0) \underset{H_0}{\sim} \chi_m^2$.

3. The random effects model

Assume, that $\mathbf{Y}_1, \mathbf{Y}_2, \ldots, \mathbf{Y}_k$, are not equal, but are m-normally distributed. This gives the following model

$$\mathbf{Y}_j = \mathbf{X}_j + \epsilon_j, \ \mathbf{X}_j = \mu + \xi_j,$$

where for a given i, $i = 1, 2, \ldots, m$ ϵ_{ij} and ξ_{ij}, $j = 1, 2, \ldots, k$, are independent and normally distributed $N(0, \sigma_{ii}^{2(j)})$, $N(0, \sigma_\xi^{2(i)})$, respectively. Hence $\mathbf{Y}_j = \mu + \epsilon_j + \xi_j$ and $\mathbf{Y}_j \sim N(0, \mathbf{\Sigma}_j + \mathbf{\Sigma}_\xi)$, where

$$\mathbf{\Sigma}_\xi = \begin{bmatrix} \sigma_\xi^{2(1)} & 0 & \ldots & 0 \\ 0 & \sigma_\xi^{2(2)} & \ldots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \ldots & \sigma_\xi^{2(m)} \end{bmatrix}.$$

Then, the optimal weights are equal

$$\mathbf{T}_j = \left(\mathbf{\Sigma}_j + \mathbf{\Sigma}_\xi\right)^{-1}, \ j = 1, 2, \ldots, k$$

$$\text{and } \mathbf{T} = \sum_{j=1}^{k} \mathbf{T}_j.$$

The best unbiased estimator has the form (under known $\mathbf{T}_j$)

$$\widetilde{\mu} = \left(\sum_{j=1}^{k} \mathbf{T}_j\right)^{-1} \sum_{j=1}^{k} \mathbf{T}_j \mathbf{Y}_j$$

with $Var(\widetilde{\mu}) = \mathbf{T}^{-1}$. The estimator $\widetilde{\mu} \sim N(\mu, \mathbf{T}^{-1})$ and the statistic to testing $H_0 : \mu = \mu_0$ is $(\widetilde{\mu} - \mu_0)' \, \mathbf{T} \, (\widetilde{\mu} - \mu_0) \underset{H_0}{\sim} \chi_m^2$.

3.1. Method of Moments

In a traditional random effects meta-analysis we usually use the method of moments based on the estimator of $\boldsymbol{\Sigma}_\xi$.

The unbiased estimator of $\sigma_\xi^{2(i)}$ (DerSimonian and Laird (1986) [2]) is

$$\bar{\sigma}_\xi^{2(i)} = \frac{\omega_i}{\omega_i^2 - \sum_{j=1}^{k} \omega_{ij}^2} \left\{ \sum_{j=1}^{k} \omega_{ij} \left(Y_{ij} - \sum_{j=1}^{k} \frac{\omega_{ij} Y_{ij}}{\omega_i} \right)^2 - (k-1) \right\},$$

where $\omega_{ij} = \frac{1}{\sigma_{ii}^{2(j)}}$, $\omega_i = \sum_{j=1}^{k} \omega_{ij}$, $i = 1, 2, \ldots, m$.

In practice, ω_{ij} is unknown. We replace $\sigma_{ii}^{2(j)}$ by $\hat{\sigma}_{ii}^{2(j)}$, $j = 1, 2, \ldots, k$, and we obtain the reference unbiased estimator of $\sigma_\xi^{2(i)}$ with the realization $\tilde{\sigma}_\xi^{2(i)}$. Since the estimator $\tilde{\sigma}_\xi^{2(i)}$ can become negative with positive probability, $\tilde{\sigma}_\xi^{2(i)}$ is substituted by the truncated estimator $\hat{\sigma}_\xi^{2(i)} = max\{0, \tilde{\sigma}_\xi^{2(i)}\}$. Note that $Q_{hom}^{(i)} = \sum_{j=1}^{k} \hat{\omega}_{ij}(Y_{ij} - \hat{\mu}_i)^2$ is approximately χ_{k-1}^2-distributed. Hence

$$E\left(Q_{hom}^{(i)}\right) = k - 1 + \sigma_\xi^{2(i)} \left(\sum_{j=1}^{k} \hat{\omega}_{ij} - \sum_{j=1}^{k} \hat{\omega}_{ij}^2 \Big/ \sum_{j=1}^{k} \hat{\omega}_{ij} \right).$$

Suppose that $\bar{\sigma}_\xi^{2(i)}$ is obtained by solving

$$q_{\hat{\omega}}^{(i)} = k - 1 + \bar{\sigma}_\xi^{2(i)} \left(\sum_{j=1}^{k} \hat{\omega}_{ij} - \sum_{j=1}^{k} \hat{\omega}_{ij}^2 \Big/ \sum_{j=1}^{k} \hat{\omega}_{ij} \right)$$

giving

$$\bar{\sigma}_{\xi}^{2(i)} = \frac{q_{\hat{\omega}}^{(i)} - (k-1)}{\sum_{j=1}^{k} \hat{\omega}_{ij} - \sum_{j=1}^{k} \hat{\omega}_{ij}^{2} \Big/ \sum_{j=1}^{k} \hat{\omega}_{ij}} .$$

According to DerSimonian and Laird the random weights are

$$\hat{\mathbf{T}}_j = \left(\hat{\mathbf{\Sigma}}_j + \hat{\mathbf{\Sigma}}_{\xi}\right)^{-1}, \text{ and } \hat{\mathbf{T}} = \sum_{j=1}^{k} \hat{\mathbf{T}}_j, \; j = 1, 2, \ldots, k.$$

The estimator of μ is then given by

$$\breve{\mu} = \hat{\mathbf{T}}^{-1} \sum_{j=1}^{k} \hat{\mathbf{T}}_j \mathbf{Y}_j.$$

3.2. Method of Maximum Likelihood (ML)

This is a method for estimating variance components in a general linear model. This is considered as an alternative to the DerSimonian and Laird method.

The standard random effects model has the form $\mathbf{Y}_j = \mu + \epsilon_j + \xi_j, \; j = 1, 2, \ldots, k$, where ϵ_{ij} and ξ_{ij} are independent for a given i. Hence $\mathbf{Y}_j \sim N(\mu, \mathbf{\Sigma}_j + \mathbf{\Sigma}_{\xi})$. We assume that $\sigma_{ii}^{2(j)}$ is treated as known and constant. For a given $i, \; i = 1, 2, \ldots, m$ the log - likelihood function is

$$\log L\left(\mu_i, \sigma_{\xi}^{2(i)}\right) = -\frac{1}{2} \sum_{j=1}^{k} \log\left(2\pi\left(\sigma_{ii}^{2(j)} + \sigma_{\xi}^{2(i)}\right)\right) - \frac{1}{2} \sum_{j=1}^{k} \frac{(Y_{ij} - \mu_i)^2}{\sigma_{ii}^{2(j)} + \sigma_{\xi}^{2(i)}},$$

$$\mu_i \in \mathbf{R}, \; \sigma_{\xi}^{2(i)} \geq 0.$$

We want to find the maximum likelihood estimators $\hat{\mu}_{ml}$ and $\hat{\sigma}_{\xi ml}^{2}$.

We obtain

$$\hat{\mu}_m^{(i)} = \sum_{j=1}^{k} \frac{Y_{ij}}{\hat{\sigma}_{ii}^{2(j)} + \hat{\sigma}_{\xi m}^{2(i)}} \Bigg/ \sum_{j=1}^{k} \frac{1}{\hat{\sigma}_{ii}^{2(j)} + \hat{\sigma}_{\xi m}^{2(i)}},$$

$$\hat{\sigma}_{\xi m}^{2(i)} = \sum_{j=1}^{k} \frac{\left(Y_{ij} - \hat{\mu}_m^{(i)}\right)^2 - \hat{\sigma}_{ii}^{2(j)}}{\left(\hat{\sigma}_{ii}^{2(j)} + \hat{\sigma}_{\xi m}^{2(i)}\right)^2} \Bigg/ \sum_{j=1}^{k} \frac{1}{\left(\hat{\sigma}_{ii}^{2(j)} + \hat{\sigma}_{\xi m}^{2(i)}\right)^2}.$$

The ML estimator of $\mu_{ml}^{(i)}$ and $\sigma_{\xi ml}^{2(i)}$ is the solution to

$$\left(\hat{\mu}_{ml}^{(i)}, \hat{\sigma}_{\xi ml}^{2(i)}\right) = \begin{cases} \left(\hat{\mu}_{ml}^{(i)}, \hat{\sigma}_{\xi ml}^{2(i)}\right), & \hat{\sigma}_{\xi ml}^{2(i)} > 0 \\ (\hat{\mu}_i, 0), & \hat{\sigma}_{\xi ml}^{2(i)} \le 0 \end{cases}.$$

The solution must be obtained iteratively. In this paper, the iterations are initialized with $\hat{\sigma}_{\xi m}^{2(i)} = \hat{\sigma}_{\xi}^{2(i)} + 0.01$, and SAS PROC MIXED is used. The estimator of μ is then given by

$$\breve{\mu}_{ml} = \hat{\mathbf{T}}_{ml}^{-1} \sum_{j=1}^{k} \hat{\mathbf{T}}_j^{(ml)} \mathbf{Y}_j,$$

where

$$\hat{\mathbf{T}}_j^{(ml)} = \left(\hat{\mathbf{\Sigma}}_j + \hat{\mathbf{\Sigma}}_{\xi ml}\right)^{-1}, \ j = 1, 2, \ldots, k,$$

and

$$\hat{\mathbf{T}}_{ml} = \sum_{j=1}^{k} \hat{\mathbf{T}}_j^{(ml)}.$$

3.3. Method of Restricted Maximum Likelihood (REML)

Let the overall effect μ be diverse between $\mathbf{Y}_1,\ \mathbf{Y}_2, \ldots,\ \mathbf{Y}_k$. Recall that the standard effects model has $\mathbf{Y}_j \sim N(\mu, \mathbf{\Sigma}_j + \mathbf{\Sigma}_\xi)$. We want to maximize the following function for a given $i,\ i = 1, 2, \ldots, m$

$$\log L\left(\mu_i, \sigma_\xi^{2(i)}\right) \propto \sum_{j=1}^{k}\left\{\log\left(\sigma_{ii}^{2(j)} + \sigma_\xi^{2(i)}\right) + \frac{(Y_{ij}-\mu_i)^2}{\sigma_{ii}^{2(j)} + \sigma_\xi^{2(i)}}\right\} +$$

$$+\log\left(\sum_{j=1}^{k}\frac{1}{\sigma_{ii}^{2(j)} + \sigma_\xi^{2(i)}}\right),\ \mu_i \in \mathbf{R},\ \sigma_\xi^{2(i)} \geq 0.$$

The REML estimators of μ_i and $\sigma_\xi^{2(i)}$ are the solution to

$$\hat{\mu}_r^{(i)} = \sum_{j=1}^{k}\frac{Y_{ij}}{\hat{\sigma}_{ii}^{2(j)} + \hat{\sigma}_{\xi r}^{2(i)}}\Big/\sum_{j=1}^{k}\frac{1}{\hat{\sigma}_{ii}^{2(j)} + \hat{\sigma}_{\xi r}^{2(i)}},$$

$$\hat{\sigma}_{\xi r}^{2(i)} = \sum_{j=1}^{k}\frac{\frac{k}{k-1}\left(Y_{ij}-\hat{\mu}_r^{(i)}\right)^2 - \hat{\sigma}_{ii}^{2(j)}}{\left(\hat{\sigma}_{ii}^{2(j)} + \hat{\sigma}_{\xi r}^{2(i)}\right)^2}\Big/\sum_{j=1}^{k}\frac{1}{\left(\hat{\sigma}_{ii}^{2(j)} + \hat{\sigma}_{\xi r}^{2(i)}\right)^2}.$$

We find the estimators $\hat{\mu}_r^{(i)}$ and $\hat{\sigma}_{\xi r}^{2(i)}$ iteratively. The iterations are initialized with $\hat{\sigma}_{\xi r}^{2(i)} = \hat{\sigma}_\xi^{2(i)} + 0.01$, and SAS PROC MIXED is used in this paper. The estimator of μ is then given by

$$\breve{\mu}_{reml} = \hat{\mathbf{T}}_{reml}^{-1}\sum_{j=1}^{k}\hat{\mathbf{T}}_j^{(reml)}\mathbf{Y}_j,$$

where

$$\hat{\mathbf{T}}_j^{(reml)} = \left(\hat{\mathbf{\Sigma}}_j + \hat{\mathbf{\Sigma}}_{\xi reml}\right)^{-1},\ j = 1, 2, \ldots, k$$

and

$$\hat{\mathbf{T}}_{reml} = \sum_{j=1}^{k}\hat{\mathbf{T}}_j^{(reml)}.$$

4. Results of medical trials

Meta-analysis is usually used to clinical trails. Then data are usually received from binary trials. We can use the following table.

Table 2. Columns 2-4 show the sample sizes, $f_{ij}^{(.)} + s_{ij}^{(.)} = n_{ij}^{(.)}$. Column 5 gives the proportion $p_{ij}^{(.)} = \frac{f_{ij}^{(.)}}{n_{ij}^{(.)}}$.

Procedure	Number disease cases	Number no disease cases	Number cases	
A	$f_{ij}^{(A)}$	$s_{ij}^{(A)}$	$n_{ij}^{(A)}$	$p_{ij}^{(A)} = \frac{f_{ij}^{(A)}}{n_{ij}^{(A)}}$
B	$f_{ij}^{(B)}$	$s_{ij}^{(B)}$	$n_{ij}^{(B)}$	$p_{ij}^{(B)} = \frac{f_{ij}^{(B)}}{n_{ij}^{(B)}}$
	$f_{ij}^{(.)}$	$s_{ij}^{(.)}$	$n_{ij}^{(.)}$	

The estimator of Y_{ij}, $j = 1, 2, \ldots, k$, for given i, $i = 1, 2, \ldots, m$ is $\hat{\mu}_{ij} = \frac{f_{ij}^{(A)}}{n_{ij}^{(A)}} - \frac{f_{ij}^{(B)}}{n_{ij}^{(B)}}$ with the variance $v_{ii}^{(j)} = \frac{f_{ij}^{(A)} s_{ij}^{(A)}}{n_{ij^3}^{(A)}} + \frac{f_{ij}^{(B)} s_{ij}^{(B)}}{n_{ij^3}^{(B)}}$ (see Table 2).

The log-odds method has $OR = \frac{p^{(A)}}{1-p^{(A)}} / \frac{p^{(B)}}{1-p^{(B)}} = \frac{p^{(A)}(1-p^{(B)})}{(1-p^{(A)})p^{(B)}}$. Hence,

$$\hat{\mu}_{ij} = \ln(OR_{ij}) = \ln\left(\frac{f_{ij}^{(A)} s_{ij}^{(B)}}{f_{ij}^{(B)} s_{ij}^{(A)}}\right), \ j = 1, 2, \ldots, k.$$

The corresponding within-trial, computed from the inverse of the matrix of second derivatives of the log - likelihood, is

$$\hat{\sigma}_{ii}^{2(j)} = v\hat{a}r(\ln(OR_{ij})) = \frac{1}{f_{ij}^{(A)}} + \frac{1}{s_{ij}^{(A)}} + \frac{1}{f_{ij}^{(B)}} + \frac{1}{s_{ij}^{(B)}},$$

which is also known as Woolf's formula.

Since $\hat{\mu}_i$ is normally distributed and $\hat{\mu}_{lj}$ and $\hat{\mu}_{sj}$ are dependent for $l \neq s,\ l, s = 1, 2, \ldots, m$, we can calculate the correlation between vectors

$$\begin{bmatrix} \hat{\mu}_{l1} \\ \hat{\mu}_{l2} \\ \vdots \\ \hat{\mu}_{lk} \end{bmatrix} \quad \text{and} \quad \begin{bmatrix} \hat{\mu}_{s1} \\ \hat{\mu}_{s2} \\ \vdots \\ \hat{\mu}_{sk} \end{bmatrix}$$

from

$$r_{ls} = \frac{\sum_{j=1}^{k} \left(\hat{\mu}_{lj} - \bar{\hat{\mu}}^{(l)}\right)\left(\hat{\mu}_{sj} - \bar{\hat{\mu}}^{(s)}\right)}{\sqrt{\sum_{j=1}^{k} \left(\hat{\mu}_{lj} - \bar{\hat{\mu}}^{(l)}\right)^2 \sum_{j=1}^{k} \left(\hat{\mu}_{sj} - \bar{\hat{\mu}}^{(s)}\right)^2}},$$

where $\bar{\hat{\mu}}^{(l)} = \frac{1}{l} \sum_{j=1}^{k} \hat{\mu}_{lj}$.

5. Examples and comparison of methods

To illustrate the above methods we make use of data: the efficacy of three medicines in the treatment of hypertension (see Table 3). The medicines include the same component in different amount. We use SAS PROC.

Table 3. Columns show the sample sizes and observed proportions.

Study	Treatment 1			Treatment 2			Treatment 3			Control		
	$f_{1j}^{(A)}$	$n_{1j}^{(A)}$	$p_{1j}^{(A)}$	$f_{2j}^{(A)}$	$n_{2j}^{(A)}$	$p_{2j}^{(A)}$	$f_{3j}^{(A)}$	$n_{3j}^{(A)}$	$p_{3j}^{(A)}$	$f_{1j}^{(B)}$	$n_{1j}^{(B)}$	$p_{1j}^{(B)}$
1	44	716	0.0615	33	669	0.0493	46	721	0.0638	56	710	0.0789
2	94	730	0.1288	26	581	0.0448	56	667	0.0840	59	415	0.1422
3	51	576	0.0885	44	774	0.0569	31	545	0.0569	68	587	0.1158
4	121	742	0.1631	89	689	0.1292	59	712	0.0829	114	733	0.1555
5	44	754	0.0584	23	376	0.0612	45	541	0.0832	58	770	0.0753
6	32	341	0.0938	46	456	0.1009	41	452	0.0907	29	311	0.0933
7	151	991	0.1524	120	887	0.1353	131	886	0.1479	149	1000	0.1490

From the studies we receive the log-odds ratio and estimated variances (see Table 4).

Table 4. Columns give the log-odds ratio and variance estimates for each of the studies.

	$\hat{\mu}_{1j} =$ $\ln OR_{1j}$	$\hat{\sigma}^2_{1j} =$ $v\hat{a}r\,(\ln OR_{1j})$	$\hat{\mu}_{2j} =$ $\ln OR_{2j}$	$\hat{\sigma}^2_{2j} =$ $v\hat{a}r\,(\ln OR_{2j})$	$\hat{\mu}_{3j} =$ $\ln OR_{3j}$	$\hat{\sigma}^2_{3j} =$ $v\hat{a}r\,(\ln OR_{3j})$
1	-0.2683	0.04360	-0.5009	0.05126	-0.2283	0.04261
2	-0.1145	0.03197	-1.2635	0.06002	-0.5924	0.03925
3	-0.2992	0.03815	-0.7765	0.04073	-0.7758	0.05084
4	0.0564	0.02026	-0.2164	0.02329	-0.7121	0.02887
5	-0.2734	0.04278	-0.2233	0.06496	0.1077	0.04288
6	0.0070	0.07252	0.0871	0.06221	-0.0304	0.06485
7	0.0263	0.01570	-0.1125	0.01752	-0.0091	0.01685

The multivariate fixed effects method and tree multivariate random effects methods have all been used to combine these data. Below we have estimated values of μ and its variation. For the random effects methods the estimate of $\sigma_\xi^{2(1)}$ is equal 0 and estimates of $\sigma_\xi^{2(2)}$ and $\sigma_\xi^{2(3)}$ are larger than 0.

The estimates from the fixed effects model are:

$$\hat{\mu} = \begin{bmatrix} -0.13726 \\ -0.31386 \\ -0.2967 \end{bmatrix} \quad \text{and} \quad \hat{Var}(\hat{\mu}) = \begin{bmatrix} 0.00927 & 1.48882 & 0.14624 \\ 1.48882 & 0.0864 & 2.07132 \\ 0.14624 & 2.07132 & 0.00995 \end{bmatrix}.$$

When we use the random effects model we receive the following estimates.

(1) DerSimonian and Laird:

$$\breve{\mu} = \begin{bmatrix} -0.13718 \\ -0.26403 \\ -0.29704 \end{bmatrix} \quad \text{and} \quad \hat{Var}(\breve{\mu}) = \begin{bmatrix} 0.00749 & 0.76561 & 0.07894 \\ 0.76561 & 0.14427 & 0.58201 \\ 0.07894 & 0.58201 & 0.02311 \end{bmatrix}.$$

(2) ML:

$$\breve{\mu}_{ml} = \begin{bmatrix} -0.13714 \\ -0.28285 \\ -0.2982 \end{bmatrix} \quad \text{and} \quad \hat{Var}(\breve{\mu}_{ml}) = \begin{bmatrix} 0.00754 & 0.78287 & 0.08583 \\ 0.78287 & 0.13035 & 0.64466 \\ 0.08583 & 0.64466 & 0.02005 \end{bmatrix}.$$

(3) REML:

$$\breve{\mu}_{reml} = \begin{bmatrix} -0.13759 \\ -0.27627 \\ -0.29749 \end{bmatrix} \quad \text{and} \quad \hat{Var}(\hat{\mu}_{reml}) = \begin{bmatrix} 0.00747 & 0.720 & 0.07972 \\ 0.720 & 0.13197 & 0.55238 \\ 0.07972 & 0.55238 & 0.02275 \end{bmatrix}.$$

6. Conclusions

In this paper, we have considered and combined several estimators for the common mean μ. Here, one example was used. As we see, different estimation methods can lead to proportionally the same results.

In practice, we often need methods for multivariate model but for simplification calculation variation between studies is ignored.

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