A comparison of meta-analysis using literature and using individual patient data

Thomas Mathew

Department of Mathematics and Statistics
University of Maryland
Baltimore, Maryland 21250

mathew@umbc.edu

Joint work with Kenneth Nordström, University of Oulu, Finland

Example 1 (Taken from Whitehead, 2003)

A study comparing two anaesthetics A and B with respect to the recovery times of patients undergoing short surgical procedures.

Data available from nine centers (log-transformed recovery times)

μ_A, μ_B: population mean log-recovery times for anaesthetics A and B, respectively.

To estimate $\mu_A - \mu_B$.

Center	Anaesthetic A			Anaesthetic B		
(Trial)	# patients	Mean	SD	# patients	Mean	SD
1	4	1.141	0.967	5	0.277	0.620
2	10	2.165	0.269	10	1.519	0.913
3	17	1.790	0.795	17	1.518	0.849
4	8	2.105	0.387	9	1.189	1.061
5	7	1.324	0.470	10	0.456	0.619
6	11	2.369	0.401	10	1.550	0.558
7	10	1.074	0.670	12	0.265	0.502
8	5	2.583	0.409	4	1.370	0.934
9	14	1.844	0.848	19	2.118	0.749

$\bar{y}_{A_j}$, $\bar{y}_{B_j}$: sample mean log-recovery times for Anaesthetic A and Anaesthetic B for the jth center.

n_{A_j}, n_{B_j}: corresponding sample sizes.

σ_j^2: Variability in the jth center. Can be estimated by pooling the pair of sample variances for each center.

$\hat{\sigma}_j^2$: the estimator so obtained.

$\bar{y}_{A_j} - \bar{y}_{B_j}$: estimator of $\mu_A - \mu_B$ from the jth center.

$\hat{\sigma}_j^2 \left(\frac{1}{n_{A_j}} + \frac{1}{n_{B_j}} \right)$: estimated variance of $\bar{y}_{A_j} - \bar{y}_{B_j}$.

Meta-analysis estimator of $\mu_A - \mu_B$ based on summary data: a weighted combination of $\bar{y}_{A_j} - \bar{y}_{B_j}$.

The estimator has value 0.627, with standard error 0.0990.

Meta-analysis estimator of $\mu_A - \mu_B$ based on the individual patient data (IPD):
a weighted combination of $\bar{y}_{A_j}$ – a weighted combination of $\bar{y}_{B_j}$

The estimator has value 0.679, with standard error 0.0982.

95% confidence intervals for $\mu_A - \mu_B$:

The interval (0.433, 0.821) based on summary data.

The interval (0.486, 0.874) based on the IPD.

Example 2 (Taken from Bower et al., 2003)

Data on the costs of counseling in primary care.

Data from different studies (trials) are available.

Short term costs for patients treated by counselors, and for those who remained under the care of a general practitioner.

μ_1, μ_2: the population average cost for patients treated by counselors, and for patients who remained under the care of a general practitioner, respectively.

To estimate $\mu_1 - \mu_2$.

Study (Trial)	Treated by counselor			Care by general practitioner		
	# patients	Mean	SD	# patients	Mean	SD
1	58	304	170	57	226	480
2	87	221	157	45	140	97
3	82	283	142	79	171	291
4	53	322	285	49	166	329

Meta-analysis estimate of $\mu_1 - \mu_2$ based on summary data: 94.09, with standard error 17.468.

95% confidence intervals for $\mu_1 - \mu_2$: (59.86, 128.33)

Meta-analysis estimate of $\mu_1 - \mu_2$ based on IPD: 117.050, with standard error 15.918

95% confidence intervals for $\mu_1 - \mu_2$: (85.85, 148.25)

The estimates and confidence intervals are quite different.

For testing a hypothesis concerning $\mu_1 - \mu_2$, the conclusion based on summary data, and that based on the IPD, can be different.

Angelillo and Villari (2003): "One issue that merits closer scrutiny is whether meta-analysis of published data is sufficient or whether individual patient data are necessary".

Olkin, I. and Sampson, A. (1998). Comparison of meta-analysis versus analysis of variance of individual patient data. *Biometrics* **54**, 317–322.

Mathew, T. and Nordström, K. (1999). On the equivalence of meta-analysis using literature and using individual patient data. *Biometrics* **55**, 1221–1223.

The above articles consider a two-way model without interaction, with fixed treatment effects and fixed study effects.

Conclusion in the above articles: For estimating the treatment contrasts, meta-analysis estimators based on summary data, and that based on the IPD, are the same.

What if there are covariates?

What if the study effects are random?

What if there are no study effects?

A general formulation

Consider k independent studies (or trials).

$\mathbf{y}_j$: vector of n_j responses from the jth trial.

$\mathbf{y}_1, \ldots, \mathbf{y}_k$: individual patient data (IPD).

Assume a linear model:

$$\mathrm{E}(\mathbf{y}_j) = W_j\boldsymbol{\beta} + Z_j\boldsymbol{\delta}_j = (W_j, Z_j)\begin{pmatrix} \boldsymbol{\beta} \\ \boldsymbol{\delta}_j \end{pmatrix} = X_j \begin{pmatrix} \boldsymbol{\beta} \\ \boldsymbol{\delta}_j \end{pmatrix}$$

$$\mathrm{Cov}(\mathbf{y}_j) = V_j,\ j = 1, \ldots, k$$

$\boldsymbol{\beta}$, $\boldsymbol{\delta}_j$: vectors of unknown parameters of dimension p and q_j

$X_j = (W_j, Z_j)$: design matrix

Assume V_j is completely known.

$$\mathrm{E}(\mathbf{y}_j) = X_j \begin{pmatrix} \boldsymbol{\beta} \\ \boldsymbol{\delta}_j \end{pmatrix}, \ \mathrm{Cov}(\mathbf{y}_j) = V_j, \ \text{where } X_j = (W_j, Z_j).$$

$\boldsymbol{\theta} = L\boldsymbol{\beta}$: parameter of interest.

Weighted least squares estimator of $(\boldsymbol{\beta}', \boldsymbol{\delta}_j')'$, based on the data from the jth trial:

$$\begin{pmatrix} \hat{\boldsymbol{\beta}}^{(j)} \\ \hat{\boldsymbol{\delta}}_j \end{pmatrix} = (X_j' V_j^{-1} X_j)^{-1} X_j' V_j^{-1} \mathbf{y}_j.$$

Known to be the best linear unbiased estimator (BLUE).

Write

$$\mathcal{I}^{(j)} = X_j' V_j^{-1} X_j = \begin{pmatrix} W_j' V_j^{-1} W_j & W_j' V_j^{-1} Z_j \\ Z_j' V_j^{-1} W_j & Z_j' V_j^{-1} Z_j \end{pmatrix} = \begin{pmatrix} \mathcal{I}_{11}^{(j)} & \mathcal{I}_{12}^{(j)} \\ \mathcal{I}_{21}^{(j)} & \mathcal{I}_{22}^{(j)} \end{pmatrix}$$

Then

$$\text{Cov} \begin{pmatrix} \hat{\boldsymbol{\beta}}^{(j)} \\ \hat{\boldsymbol{\delta}}_j \end{pmatrix} = (X_j' V_j^{-1} X_j)^{-1} = \mathcal{I}^{(j)^{-1}}.$$

$$\text{Cov}(\hat{\boldsymbol{\beta}}^{(j)}) = \mathcal{I}_{11\cdot 2}^{(j)^{-1}}, \quad \text{where} \quad \mathcal{I}_{11\cdot 2}^{(j)} = \mathcal{I}_{11}^{(j)} - \mathcal{I}_{12}^{(j)} \mathcal{I}_{22}^{(j)^{-1}} \mathcal{I}_{21}^{(j)}$$

The BLUE of $\boldsymbol{\theta} = L\boldsymbol{\beta}$ from the jth trial is $\hat{\boldsymbol{\theta}}^{(j)} = L\hat{\boldsymbol{\beta}}^{(j)}$.

$$\text{Cov}(\hat{\boldsymbol{\theta}}^{(j)}) = \text{Cov}(L\hat{\boldsymbol{\beta}}^{(j)}) = L\mathcal{I}_{11\cdot 2}^{(j)^{-1}} L'.$$

Summary data from the jth trial: $\hat{\boldsymbol{\theta}}^{(j)}$ and its covariance matrix $L\mathcal{I}_{11\cdot 2}^{(j)\ -1}L'$.

Meta-analysis estimator of $\boldsymbol{\theta} = L\boldsymbol{\beta}$ based on summary data:

$$\tilde{\boldsymbol{\theta}} = \left(\sum_{j=1}^{k}(L\ \mathcal{I}_{11\cdot 2}^{(j)\ -1}L')^{-1}\right)^{-1}\sum_{j=1}^{k}(L\ \mathcal{I}_{11\cdot 2}^{(j)\ -1}L')^{-1}\hat{\boldsymbol{\theta}}^{(j)}$$

$$\mathrm{Cov}(\tilde{\boldsymbol{\theta}}) = \left(\sum_{j=1}^{k}(L\ \mathcal{I}_{11\cdot 2}^{(j)\ -1}L')^{-1}\right)^{-1}.$$

Model for the IPD:

$\mathbf{y} = (\mathbf{y}_1', \ldots, \mathbf{y}_k')'$,

$W = (W_1', \ldots, W_k')'$,

$Z = \text{diag}(Z_1, \ldots, Z_k)$,

$\boldsymbol{\delta} = (\boldsymbol{\delta}_1', \ldots, \boldsymbol{\delta}_k')'$,

$V = \text{diag}(V_1, \ldots, V_k)$.

$$\text{E}(\mathbf{y}) = W\boldsymbol{\beta} + Z\boldsymbol{\delta} = (W, Z) \begin{pmatrix} \boldsymbol{\beta} \\ \boldsymbol{\delta} \end{pmatrix} = X \begin{pmatrix} \boldsymbol{\beta} \\ \boldsymbol{\delta} \end{pmatrix}$$

$$\text{Cov}(\mathbf{y}) = V, \text{ where } X = (W, Z).$$

Meta-analysis estimator of $\boldsymbol{\theta} = L\boldsymbol{\beta}$ based on IPD: BLUE of $\boldsymbol{\theta}$ obtained from the above model.

$$\mathrm{E}(\mathbf{y}) = X \begin{pmatrix} \boldsymbol{\beta} \\ \boldsymbol{\delta} \end{pmatrix}, \ \mathrm{Cov}(\mathbf{y}) = V, \quad \text{where } X = (W, Z).$$

$$\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\boldsymbol{\delta}} \end{pmatrix} = (X'V^{-1}X)^{-1}X'V^{-1}\mathbf{y}, \ \mathrm{Cov}\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\boldsymbol{\delta}} \end{pmatrix} = (X'V^{-1}X)^{-1}.$$

$$\hat{\boldsymbol{\theta}} = L\hat{\boldsymbol{\beta}} = (L, 0)\begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\boldsymbol{\delta}} \end{pmatrix} = (L, 0)(X'V^{-1}X)^{-1}X'V^{-1}\mathbf{y}$$

$$\mathrm{Cov}(\hat{\boldsymbol{\theta}}) = (L, 0)(X'V^{-1}X)^{-1}(L, 0)'.$$

Recall: $X_j = (W_j, Z_j)$ and

$$\mathcal{I}^{(j)} = X_j' V_j^{-1} X_j = \begin{pmatrix} W_j' V_j^{-1} W_j & W_j' V_j^{-1} Z_j \\ Z_j' V_j^{-1} W_j & Z_j' V_j^{-1} Z_j \end{pmatrix} = \begin{pmatrix} \mathcal{I}_{11}^{(j)} & \mathcal{I}_{12}^{(j)} \\ \mathcal{I}_{21}^{(j)} & \mathcal{I}_{22}^{(j)} \end{pmatrix}$$

$$\mathcal{I}_{11\cdot 2}^{(j)} = \mathcal{I}_{11}^{(j)} - \mathcal{I}_{12}^{(j)} {\mathcal{I}_{22}^{(j)}}^{-1} \mathcal{I}_{21}^{(j)}$$

$$\begin{aligned} X' V^{-1} X &= \sum_{j=1}^{k} (X_j' V_j^{-1} X_j) = \sum_{j=1}^{k} \mathcal{I}^{(j)} \\ \mathrm{Cov}(\hat{\boldsymbol{\theta}}) &= (L, 0)(X' V^{-1} X)^{-1} (L, 0)' \\ &= L \left(\sum_{j=1}^{k} \mathcal{I}_{11\cdot 2}^{(j)} \right)^{-1} L'. \end{aligned}$$

Based on summary data:

$$\begin{aligned}
\tilde{\boldsymbol{\theta}} &= \left(\sum_{j=1}^{k}(L\,{\mathcal{I}_{11\cdot 2}^{(j)}}^{-1}L')^{-1}\right)^{-1}\sum_{j=1}^{k}(L\,{\mathcal{I}_{11\cdot 2}^{(j)}}^{-1}L')^{-1}\hat{\boldsymbol{\theta}}^{(j)} \\
\mathrm{Cov}(\tilde{\boldsymbol{\theta}}) &= \left(\sum_{j=1}^{k}(L\,{\mathcal{I}_{11\cdot 2}^{(j)}}^{-1}L')^{-1}\right)^{-1}.
\end{aligned}$$

Based on IPD:

$$\begin{aligned}
\hat{\boldsymbol{\theta}} &= (L,0)(X'V^{-1}X)^{-1}X'V^{-1}\mathbf{y} \\
\mathrm{Cov}(\hat{\boldsymbol{\theta}}) &= L\left(\sum_{j=1}^{k}\mathcal{I}_{11\cdot 2}^{(j)}\right)^{-1}L'
\end{aligned}$$

For $\boldsymbol{\theta} = L\boldsymbol{\beta}$, $\hat{\boldsymbol{\theta}}$ is the BLUE based on the linear model for the IPD.

$\tilde{\boldsymbol{\theta}}$ is another unbiased estimator.

Hence $\mathrm{Cov}(\tilde{\boldsymbol{\theta}}) - \mathrm{Cov}(\hat{\boldsymbol{\theta}})$ is nonnegative definite.

That is

$$\left(\sum_{j=1}^{k}(L\,{\mathcal{I}_{11\cdot 2}^{(j)}}^{-1}L')^{-1}\right)^{-1} - L\left(\sum_{j=1}^{k}\mathcal{I}_{11\cdot 2}^{(j)}\right)^{-1}L'$$

is nonnegative definite.

Also follows from the concavity of the matrix function $g(A) = (LA^{-1}L')^{-1}$, for A p.d. (Marshall and Olkin, 1979, p. 469)

If the two matrices are equal, then the two estimators coincide, and there is no loss of information in using the summary data.

Result: The meta-analysis estimator based on the summary data, and that based on the IPD coincide if and only if the matrices $(L \, \mathcal{I}_{11\cdot 2}^{(j)\,-1} L')^{-1} L \, \mathcal{I}_{11\cdot 2}^{(j)\,-1}$ are equal for $j = 1, \ldots, k$.

The equality of the two estimators require a certain level of homogeneity across the trials.

The two estimators are equal if $L = I$. That is, if there are no common nuisance parameters across studies.

Application to some special models

To estimate a single treatment-control difference $\mu_1 - \mu_2$:

Assume there are no other effects or covariates.

$\bar{y}_{1j}$, $\bar{y}_{2j}$: sample means for the treatment and the control from the jth trial.

n_{1j}, n_{2j}: corresponding sample sizes.

σ_j^2: variability for the jth trial (usually an estimate).

Parameters in the mean: (μ_1, μ_2) or $(\mu_1 - \mu_2, \mu_2)$

μ_2 is a common nuisance parameter across the trials.

The two estimators of $\mu_1 - \mu_2$ coincide if and only if $\frac{n_{1j}}{n_{1j}+n_{2j}}$ are all the same for $j = 1, 2, ..., k$.

The fraction of observations for the treatment is the same across the different trials.

The condition is free of the variances!

Example 1 (continued)

A study comparing two anaesthetics A and B with respect to the recovery times of patients undergoing short surgical procedures.

Log-transformed recovery times available from nine centers.

μ_A, μ_B: population mean log-recovery times for anaesthetics A and B, respectively.

To estimate $\mu_A - \mu_B$.

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Based on IPD, the meta-analysis estimator of $\mu_A - \mu_B$ has value 0.679, with standard error 0.0982.

95% confidence intervals for $\mu_A - \mu_B$:

The interval (0.433, 0.821) based on summary data.

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Example 2 (continued)

Data on the costs of counseling in primary care available from four studies.

Short term costs for patients treated by counselors, and for those who remained under the care of a general practitioner.

μ_1, μ_2: population average cost for patients treated by counselors, and for patients who remained under the care of a general practitioner, respectively.

To estimate $\mu_1 - \mu_2$.

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To estimate several treatment-control differences:

Suppose several treatments are to be compared to the same control, **in the absence of any other effects or covariates**, based on data from k trials.

μ_i: mean for the ith treatment ($i = 1, 2, ..., m-1$),
μ_m: mean for the control.

To estimate the treatment$-$control differences $\mu_i - \mu_m$, $i = 1, 2, ..., m-1$.

$(\mu_1, \mu_2, ..., \mu_m) = (\mu_1 - \mu_m, \mu_2 - \mu_m, ..., \mu_{m-1} - \mu_m, \mu_m)$.

μ_m: A common nuisance parameter across the different studies.

Meta-analysis estimator based on summary data, and the meta-analysis estimator based on IPD coincide if and only if the fraction of observations for the ith treatment is the same across the different trials; $i = 1, 2, ..., m$.

A model with fixed treatment effects and fixed trial effects:

$y_{ij\alpha}$: the αth response on the ith treatment from the jth trial, $\alpha = 1, \ldots, n_{ij}$, $i = 1, 2, \ldots, m$, $j = 1, 2, \ldots, k$. Assume $n_{ij} > 0$ for all i and j.

τ_i: ith treatment effect

α_j: jth trial effect.

Assume

$$\mathrm{E}(y_{ij\alpha}) = \alpha_j + \tau_i.$$

$\mathbf{y}_{ij.}$: vector of n_{ij} responses on the ith treatment in the jth trial

$\mathbf{y}_{.j.} = (\mathbf{y}'_{1j.}, \ldots, \mathbf{y}'_{mj.})'$

Assume $\mathrm{Cov}(\mathbf{y}_{.j.}) = V_j$ (known)

Let the mth treatment represent a control

To estimate $\boldsymbol{\theta} = (\tau_1 - \tau_m, \ldots, \tau_{m-1} - \tau_m)'$

Write $\theta_i = \tau_i - \tau_m$, $i = 1, 2, \ldots, m-1$, so that $\tau_i = \theta_i + \tau_m$.

$$\mathrm{E}(y_{ij\alpha}) = \alpha_j + \tau_i = \alpha_j + \theta_i + \tau_m = \alpha'_j + \theta_i.$$

To estimate $\boldsymbol{\theta} = (\theta_1, \theta_2, ..., \theta_{m-1})'$.

The nuisance parameters are α'_j: $j = 1, 2, ..., k$.

No common nuisance parameters across the studies.

Meta-analysis estimator based on summary data, and the meta-analysis estimator based on IPD always coincide.

Result due to Olkin and Sampson (1998) and Mathew and Nordström (1999).

A model with fixed treatment effects and random trial effects:

Now the trail effects will contribute to the covariance matrix.

$$\mathrm{E}(y_{ij\alpha}) = \mu_i, \;\; i = 1, 2, ..., m.$$

To estimate $\boldsymbol{\theta} = (\mu_1 - \mu_m, \ldots, \mu_{m-1} - \mu_m)'$

$(\mu_1, \mu_2, \ldots, \mu_m)' = (\mu_1 - \mu_m, \ldots, \mu_{m-1} - \mu_m, \mu_m)'$

μ_m is a common nuisance parameter across the trials.

The two estimators of $\boldsymbol{\theta}$ coincide if and only if the fraction of observations for the ith treatment is the same across the different trials; $i = 1, 2, ..., m$

What if there are covariates?

Consider a simple model with one covariate, and without treatment-covariate interaction.

The problem is that of estimating a treatment−control difference.

y_{ij}: outcome for the ith patient in the jth trial.

Consider the model

$$y_{ij} = \beta_{0j} + \beta_1 x_{1ij} + \beta_2 x_{2ij} + \epsilon_{ij},$$

$i = 1, \ldots, n_j$ and $j = 1, \ldots, k$ (Higgins et al., 2001, Section 3.1)

β_{0j}: trial effects, assumed to be fixed

x_{1ij}: a dummy variable that indicates treatment group (treatment or control)

x_{2ij}: a single covariate

β_1: treatment$-$control difference

β_2: regression coefficient.

ϵ_{ij}'s are independent and identically distributed random variables with mean zero and variance σ^2.

To estimate β_1.

Meta-analysis estimator of β_1 based on summary data: Estimate β_1 and its variance from each trial, and combine the estimators.

Meta-analysis estimator of β_1 based on IPD: Estimate β_1 using the model for the entire data, consisting of all the y_{ij}'s.

Define

$$\bar{x}_{1j} = \frac{1}{n_j} \sum_{i=1}^{n_j} x_{1ij}, \ \bar{x}_{2j} = \frac{1}{n_j} \sum_{i=1}^{n_j} x_{2ij}.$$

The two estimators coincide if the quantities

$$\sum_{i=1}^{n_j}(x_{1ij} - \bar{x}_{1j})(x_{2ij} - \bar{x}_{2j}) \Big/ \sum_{i=1}^{n_j}(x_{2ij} - \bar{x}_{2j})^2$$

are all equal, for all $j = 1, \ldots, k$.

Requires a certain level of homogeneity with respect to the treatment allocation and the covariates across trials.

Patient-level homogeneity of the covariate within each trial implies the required condition.

Unrealistic in practice.

Thus equality of the two estimators is unlikely to hold when covariates are present.

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