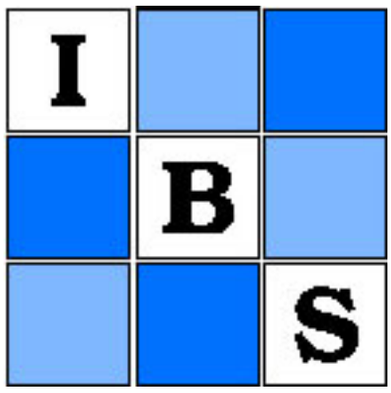

BIOMETRICS 54, 317–322
March 1998

Comparison of Meta-Analysis Versus Analysis of Variance of Individual Patient Data

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SUMMARY

Meta-analysis is a method of synthesizing the results of independent studies. We consider the case in which there are multiple treatments and a control, with the goal of estimating the relative effect of each treatment based on continuous outcomes. Even when all data are available, rather than only summary data, it has become common to use meta-analytic estimators of treatment contrasts. Alternatively, we could use a two-way analysis of variance model with no interaction in which one factor is study and one factor is treatment. For the unbalanced case, we obtain the surprising result that the standard meta-analysis estimates of treatment contrasts are identical to the least squares estimators of treatment contrasts in the linear model. Because a meta-analysis of individual patient data can be considerably more costly in terms of data retrieval than a meta-analysis of summary data, this equivalence provides for cost-efficient analysis.

1. Introduction

Consider the setting in which we have k independently conducted studies where, within each study, the same m treatments are compared. The goal is to appropriately synthesize results across studies in order to estimate treatment differences for continuous outcome data. In the setting where only summary data are available from the studies, meta-analytical techniques are appropriate. If we have access to all the data, i.e., where individual patient data are available, we might alternatively consider analysis of variance (ANOVA) techniques.

A natural question is whether a meta-analysis with literature summary data (often referred to as MAL) yields different results than a meta-analysis of individual patient data (often referred to as MAP). Jeng, Scott, and Burmeister (1995) and Stewart and Parmar (1993) show for particular examples that empirical results can differ in conclusions depending on the pool of studies being used or the measures extracted from each study, etc. Steinberg et al. (1997) illustrate that, when the pool of studies are essentially identical and the same measures are used, the effect size estimates for appropriate procedures are in close agreement for MAP and MAL. More specifically, if one uses summary data and individual patient data from the same set of studies, under what models will both approaches yield identical results? A general review of meta-analysis procedures is given by D'Agostino and Weintraub (1995), who also illustrate a meta-analysis on continuous response data.

A particular area in which the equivalence of results is important is in the development of new pharmaceutical products. In license applications, the Food and Drug Administration (FDA) and European regulatory agencies require integrated safety and efficacy analyses. Sometimes the

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Key words: Integrated efficacy analysis; Meta-analysis of literature; Meta-analysis of patients; Multiple treatment contrasts; Research synthesis; Unbalanced ANOVA.

sponsor or reviewers will accomplish this using meta-analysis on numbers of very similar studies, where all data are available in-house. Jones and Lewis (1992) and Jones (1995) provide discussions of the use of meta-analysis in regulated pharmaceutical trials.

Our focus in this paper is to evaluate in a straightforward setting the merits of using meta-analysis when individual patient data are available. To this end, we purposely avoid such issues as tests for homogeneity, whether to use random or fixed effects, and so forth.

More specifically, we consider a fixed effects model for treatment and study and let $y_{ij\alpha}$ denote the αth response on the ith treatment for the jth study, $\alpha = 1, \ldots, n_{ij}$; $i = 1, \ldots, m$; $j = 1, \ldots, k$, where $y_{ij\alpha}$, $\alpha = 1, \ldots, n_{ij}$, are independently and identically distributed with common variance σ^2, i.e., the within study variances are all the same. We assume homogeneity of treatment differences across studies, namely, that $\mathrm{E}(y_{ij\alpha} - y_{i'j\alpha'}) = \tau_i - \tau_{i'}$ for all j, α, and α'.

Because our main concern is with estimating these contrasts in main effects, rather than interactions, we assume for simplicity that within-study estimates of variances are not available. For further simplicity, we require all treatments to appear in all studies, i.e., $n_{ij} > 0$, $i = 1, \ldots, m$; $j = 1, \ldots, k$.

It is common in these settings for one of the treatments to serve as a baseline treatment or control, and we designate the mth treatment to serve this role. Consequently, we are concerned with an analysis that focuses on the pairwise treatment contrasts relative to the mth treatment, namely, the vector

$$\boldsymbol{\delta} = (\delta_1, \ldots, \delta_{m-1})' \equiv (\tau_1 - \tau_m, \tau_2 - \tau_m, \ldots, \tau_{m-1} - \tau_m)'. \tag{1}$$

If summary data for each study, i.e., $\bar{y}_{ij\cdot}$, $i = 1, \ldots, m$, $j = 1, \ldots, k$, were all that were available, we would use certain meta-analytic techniques to estimate $\boldsymbol{\delta}$. The appropriate estimator is a matrix-weighted average of individual study contrast estimators, where the matrices depend on sample sizes. If all the individual patient data are available, we can estimate $\boldsymbol{\delta}$ based on least squares estimators (LSE) from a two-way additive ANOVA model.

In the balanced case, in which there is a common or proportionate number of observations for each treatment–study combination, a direct computation shows that the results of a meta-analysis and an ANOVA of the individual patient data yield the same contrast estimates. The seeming difficulty in comparing the two estimators of $\boldsymbol{\delta}$ in the unbalanced case has been the elusiveness in obtaining usable solutions to the normal equations in the unbalanced two-way additive ANOVA (see Searle, 1987, p. 102). Because meta-analysis provides a closed-form solution for contrasts, it might be suspected that in the unbalanced case the meta-analysis estimator differs from the linear model estimator. It might appear then that the individual patient analysis would be more appropriate in that it utilizes all the data.

The surprising result we obtain is that, in the unbalanced case, meta-analysis and the individual patient analysis provide the same estimator of the contrasts and that the meta-analytic approach yields a readily computed estimator of contrasts for the linear model.

2. The Meta-Analytic Procedure

Gleser and Olkin (1994) consider a more general form of our model, whereby not all treatments are used in every study. In our setting, their approach yields the following meta-analytic procedure to synthesize treatment comparisons across studies.

Within the jth study, estimate the vector $\boldsymbol{\delta}$ of contrasts by

$$\mathbf{d}^{(j)} = (\bar{y}_{1j\cdot} - \bar{y}_{mj\cdot}, \ldots, \bar{y}_{m-1,j\cdot} - \bar{y}_{mj\cdot})'. \tag{2}$$

A key point is that the within-study estimates of the contrasts are correlated by virtue of having a common mean $\bar{y}_{mj}$. The covariance matrix is readily obtained as

$$\mathrm{cov}\left(\mathbf{d}^{(j)}\right) = \sigma^2 \Sigma_j \equiv \sigma^2 \left[\mathrm{diag}\left(\frac{1}{n_{1j}}, \ldots, \frac{1}{n_{m-1,j}}\right) + \frac{1}{n_{mj}} \mathbf{e}\mathbf{e}'\right], \tag{3}$$

where $\mathbf{e}$ is the unit vector. Using a regression format, Gleser and Olkin (1994, equation (22-8), p. 344) obtain the estimate of $\boldsymbol{\delta}$ across studies to be

$$\hat{\boldsymbol{\delta}} = \left(H'\Sigma^{-1}H\right)^{-1} H'\Sigma^{-1}d, \tag{4}$$

where, in our case, H is a column vector consisting of k blocks, each block being I_{m-1}, the identity matrix of order $m-1$, i.e., $H = (I_{m-1}, \ldots, I_{m-1})'$; $\Sigma = \sigma^2 \mathrm{diag}\,(\Sigma_1, \ldots, \Sigma_k)$; and $d = (\mathbf{d}^{(1)}, \ldots, \mathbf{d}^{(k)})$.

In (4), $(H'\Sigma^{-1}H) = \Sigma_1^{-1} + \cdots + \Sigma_k^{-1}$, so that the solution to (4) takes the simple form

$$\hat{\boldsymbol{\delta}} = \left(\Sigma_1^{-1} + \cdots + \Sigma_k^{-1}\right)^{-1} \left(\Sigma_1^{-1}\mathbf{d}^{(1)} + \cdots + \Sigma_k^{-1}\mathbf{d}^{(k)}\right), \tag{5}$$

which is a matrix-weighted linear combination of the individual study estimates, taking into account the corresponding sample sizes. It follows that

$$\mathrm{E}(\hat{\boldsymbol{\delta}}) = \boldsymbol{\delta} \quad \text{and} \quad \mathrm{cov}\,(\hat{\boldsymbol{\delta}}) = \sigma^2\left(\Sigma_1^{-1} + \cdots + \Sigma_k^{-1}\right)^{-1}. \tag{6}$$

See also Fleiss (1993) for further discussion of these estimators for univariate contrasts.

3. The Procedure for the Individual Patient Data Analysis

Reframing the preceding in a linear model format, we have the effect of studies as additive, resulting in the well-known two-way ANOVA model with no interaction. The lack of interaction terms corresponds to the assumption in the meta-analysis of the homogeneity of treatment contrasts among studies. With arbitrary sample sizes across the treatments and studies, this model is often referred to as an unbalanced model (e.g., Searle, 1987), with the admonition by Searle (1987, p. 102) that "except in special cases, solutions to the [normal] equations ... have no simple form." The resultant recommendation to numerically solve the normal equations is certainly satisfactory for data analysis but clearly causes difficulties in evaluating the efficiency in the linear model of the estimator $\hat{\boldsymbol{\delta}}$ given by (5). To this end, we develop a slight variation of Searle's (1987, Section 9.2) analysis of this two-way model.

The linear model is written as

$$y_{ij\alpha} = \mu + \tau_i + \nu_j + \epsilon_{ij\alpha}, \qquad \alpha = 1, \ldots, n_{ij},\ i = 1, \ldots, m,\ j = 1, \ldots, k, \tag{7}$$

where $\tau_1, \ldots, \tau_m$ are the fixed treatment effects, $\nu_1, \ldots, \nu_k$ are the fixed study effects, and where the $n = \Sigma n_{ij}$ random variables $\{\epsilon_{ij\alpha}\}$ are independently and identically distributed with mean 0 and common variance σ^2. Write $\Sigma_{\alpha=1}^{n_{ij}} y_{ij\alpha} = y_{ij\cdot}$ and $y_{ij\cdot}/n_{ij} = \bar{y}_{ij\cdot}$ and so forth.

The normal equations for this model contain $m+k+1$ variables but are of rank $m+k-1$. Using a particular generalized inverse to $X'X$, where X is the corresponding $n \times (m+k+1)$ design matrix, Searle (1987, Section 9.2) obtains somewhat simplified normal equations (Searle, 1987, equation (79), p. 348) and gives the variances of the treatment contrasts (Searle, 1987, equation (86), p. 349) in a nonsimplified fashion.

We derive in the Appendix the following useful form for the covariance matrix of the LSE of δ:

$$\mathrm{cov}\,(\underset{\mathrm{N}}{\hat{\delta}}) \equiv \mathrm{cov}\,(\hat{\tau}_1^*, \ldots, \hat{\tau}_{m-1}^*) = \sigma^2\left(D_1 - N^* D_2^{-1} N^{*\prime}\right)^{-1}, \tag{8}$$

where

$$D_1 = \mathrm{diag}\,(n_{1\cdot}, \ldots, n_{m-1,\cdot}), \tag{9}$$

$$D_2 = \mathrm{diag}\,(n_{\cdot 1}, \ldots, n_{\cdot k}), \tag{10}$$

$$N^* = \begin{pmatrix} n_{11} & \cdots & n_{1k} \\ \vdots & \vdots & \vdots \\ n_{m-1,1} & \cdots & n_{m-1,k} \end{pmatrix} \equiv (\mathbf{n}_1^*, \cdots, \mathbf{n}_k^*). \tag{11}$$

4. Equivalence of the Meta-Analysis and Pooled Analysis Estimators

The direct way to show the equivalence of the two estimators is to first solve the normal equations (A6) and (A7). This method appears to be algebraically difficult (Searle, 1987). However, we can use the Gauss–Markov theorem in a straightforward manner to show this equivalence. Specifically, to demonstrate that $\hat{\boldsymbol{\delta}}$ given by (5) is in fact the LSE for the ANOVA model, it suffices by the Gauss–Markov theorem to observe

(i) $\mathrm{E}(\hat{\boldsymbol{\delta}}) = (\tau_1 - \tau_m, \ldots, \tau_{m-1} - \tau_m)'$, i.e., that $\hat{\boldsymbol{\delta}}$ is unbiased,
(ii) $\hat{\boldsymbol{\delta}}$ is a linear estimator in $\bar{y}_{11\cdot}, \ldots, \bar{y}_{mk\cdot}$,
(iii) diagonal elements of $\mathrm{cov}\,(\hat{\boldsymbol{\delta}})$ and the diagonal elements of the covariance matrix of the LSE, respectively, match; i.e., the meta-analysis estimator that is linear and unbiased achieves the least squares variance.

To show (iii), it is sufficient to show that the inverses of the covariance matrices given by (6) and (8) match, namely,

$$\Sigma_1^{-1} + \cdots + \Sigma_k^{-1} = D_1 - N^* D_2^{-1} N^{*'}. \tag{12}$$

It is well known (e.g., Graybill, 1983, Theorem 8.9.3) that $(A + \underset{N}{b}\,\underset{N}{b}')^{-1} = A^{-1} - A^{-1}\,\underset{N}{b}\,\underset{N}{b}'A^{-1}/(a + \underset{N}{b}'A^{-1}\,\underset{N}{b})$, so that from (3),

$$\Sigma_j^{-1} = \text{diag}\,(n_{1j}, \ldots, n_{m-1,j}) - \mathbf{n}_j^* \mathbf{n}_j^{*'}/n_{\cdot j}. \tag{13}$$

Further, note that

$$N^* D_2^{-1} N^{*'} = \sum_1^k \mathbf{n}_j^* \mathbf{n}_j^{*'}/n_{\cdot j}, \tag{14}$$

so that, from (12),

$$\begin{aligned} \Sigma_1^{-1} + \cdots + \Sigma_k^{-1} &= \text{diag}\,(n_{1\cdot}, \ldots, n_{m-1,\cdot}) - \sum_1^k \mathbf{n}_j^* \mathbf{n}_j^{*'}/n_{\cdot j} \\ &= D_1 - N^* D_2^{-1} N^{*'}, \end{aligned} \tag{15}$$

which was to be shown.

This establishes that the technique of meta-analysis that utilizes summary information from each study provides the same estimator of treatment contrasts that would be obtained if we used all the data from all studies and analyzed them in a standard linear model format. We summarize this as follows.

PROPOSITION: *The meta-analysis estimators for treatment contrasts based on data from k independent and homogeneous studies are the least squares estimators of treatment constrasts in the two-way fixed-effects ANOVA model with no interaction.*

An apparent secondary result is an explicit representation of the treatment contrasts in this unbalanced two-way model with no interaction.

5. Commentary

Previously, Hedges (1983) noted a result that implies that, asymptotically, the two approaches we noted must have the same covariances. What we have shown is that, when there is no interaction, meta-analysis and pooled analysis provide the same estimates of contrasts. This then can be viewed as a small sample counterpart to Hedges' result.

It is important to note that pooled analyses (MAP) can permit other study features to be explored. For instance, one can explore effects of covariates that may not be suitably reported in summaries. Thus, our result should not be viewed to imply that individual patient data should immediately be reduced to summary data. What is stated is that meta-analysis suffices to determine the efficacy of treatments versus controls among multiple homogeneous studies. The present analysis was based on effect sizes for continuous outcomes. Other types of data and other measures of effect will require further examination.

ACKNOWLEDGEMENTS

The authors want to thank Dr Kay Larholt for helpful discussions, comments, and literature citations and Professors Shayle Searle and Larry Hedges for careful readings of a draft version of this manuscript. The work of the first named author was done in part while a visiting scientist with the Centers for Disease Control and Prevention and was also supported in part by National Science Foundation grant DMS 93-01366. The work of the second named author was done while visiting Stanford University and was supported in part by NSA grant MDA-904-95-H-1011.

RÉSUMÉ

La méta-analyse est une méthode conçue pour synthétiser les résultats de plusieurs études indépendantes. Nous considérons ici le cas où il y a plusieurs groupes de traitements et un groupe contrôle, le but étant d'estimer l'effet relatif de chacun des traitements sur une variable continue. Même

lorsque toutes les données individuelles sont disponibles, l'usage s'est répandu de construire les estimateurs des contrastes entre traitements à partir des résultats agrégés au niveau de chaque étude. Une autre approche consisterait à utiliser sur les données individuelles un modèle d'analyse de variance à 2 facteurs sans interaction avec un facteur étude et un facteur traitement. Dans le cas d'effectifs déséquilibrés, nous constatons, non sans surprise, que les estimateurs habituels de la méta-analyse sont identiques aux estimateurs des moindres carrés du modèle d'analyse de variance. Du fait qu'une analyse à partir des données individuelles peut être considérablement plus coûteuse à mettre en oeuvre (parce qu'il faut récupérer les données) qu'une analyse à partir des résultats agrégés, cette équivalence des estimateurs fournit l'opportunité, dans certains cas, d'une forte réduction des coûts.

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Received August 1996; *revised July* 1997; *accepted September* 1997.

Appendix

To obtain the covariance matrix of the LSE of $\boldsymbol{\delta}$ in a form useful for our argument in Section 4, we summarize the calculations here. First we parameterize the model by setting $\mu = 0$ and $\tau_m = 0$, denoting the remaining parameters by $\tau_1^*, \ldots, \tau_{m-1}^*, \nu_1^*, \ldots, \nu_k^*$. For $i = 1, 2, \ldots, m-1$, the parameter τ_i^* now represents $\tau_i - \tau_m$, which is estimable with LSE $\hat{\tau}_i^* - \hat{\tau}_m^* = \hat{\tau}_i^* - 0 = \hat{\tau}_i^*$. The resulting model is of full rank and we can obtain

$$\operatorname{cov}(\hat{\tau}_1^*, \ldots, \hat{\tau}_{m-1}^*, \hat{\nu}_1^*, \ldots, \hat{\nu}_k^*) = \sigma^2 \begin{pmatrix} D_1 & N^* \\ N^{*\prime} & D_2 \end{pmatrix}^{-1}, \tag{A1}$$

where $(\hat{\tau}_1^*, \ldots, \hat{\tau}_{m-1}^*, \hat{\nu}_1^*, \ldots, \hat{\nu}_k^*)$ are the LSEs for the reparameterized model,

$$D_1 = \operatorname{diag}(n_{1\cdot}, \ldots, n_{m-1,\cdot}), \tag{A2}$$

$$D_2 = \operatorname{diag}(n_{\cdot 1}, \ldots, n_{\cdot k}), \tag{A3}$$

$$N^* = \begin{pmatrix} n_{11} & \cdots & n_{1k} \\ \vdots & \vdots & \vdots \\ n_{m-1,1} & \cdots & n_{m-1,k} \end{pmatrix} \equiv (\mathbf{n}_1^*, \cdots, \mathbf{n}_k^*). \tag{A4}$$

In particular,

$$\operatorname{cov}(\hat{\tau}_1^*, \ldots, \hat{\tau}_{m-1}^*) = \sigma^2 \left(D_1 - N^* D_2^{-1} N^{*\prime} \right)^{-1}, \tag{A5}$$

which is (8).

The actual LSE, $\hat{\tau}_1^*, \ldots, \hat{\tau}_{m-1}^*, \hat{\nu}_1^*, \ldots, \hat{\nu}_k^*$ (Searle, 1987, equations (65) and (68), p. 102; note that Searle indexes studies by i and treatments by j), are given by first solving (A6) below:

$$c_{ii}\hat{\tau}_i^* + \sum_{\substack{i'=1 \\ i' \neq i}}^{m-1} c_{ii'}\hat{\tau}_{i'}^* = r_i, \tag{A6}$$

where

$$r_i = y_{i\cdot\cdot} - \sum_{j=1}^{k} n_{ij}\bar{y}_{\cdot j\cdot} \ ,$$

$$c_{ii} = n_{i\cdot} - \sum_{j=1}^{k} \frac{n_{ij}^2}{n_{\cdot j}},$$

and for $i \neq i'$,

$$c_{ii'} = -\sum_{j=1}^{k} n_{ij}n_{i'j}/n_{\cdot j},$$

and then substituting into and solving

$$\hat{\nu}_j^* = \bar{y}_{\cdot j\cdot} - \frac{1}{n_{\cdot j}} \sum_{i=1}^{m-1} n_{ij}\hat{\tau}_i^*, \qquad j = 1, \ldots, k, \tag{A7}$$

for the $\{\hat{\nu}_j^*\}$.

Furthermore, if we extend the $(m+k-1)\times(m+k-1)$ matrix in (A1) to an $(m+k+1)\times(m+k+1)$ matrix by adding a first row and column of 0's and an $(m+1)$st row and column of 0's, we obtain a generalized inverse to $X'X$ for the full model and also have that $(0, \hat{\tau}_1^*, \ldots, \hat{\tau}_{m-1}^*, 0, \hat{\nu}_1^*, \ldots, \hat{\nu}_k^*)$ is a solution to the normal equations corresponding to the full model parameters. It thus follows by standard arguments that the covariance matrix of the LSE of $\boldsymbol{\delta}$ is given by cov $(\hat{\tau}_1^*, \ldots, \hat{\tau}_{m-1}^*)$.