ESTIMATION OF EFFECT SIZES WITH MULTIPLE TREATMENTS AND A COMMON CONTROL

by

L.J. Gleser
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Ingram Olkin, Project Director

Department of Statistics Stanford University Stanford, California
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ESTIMATION OF EFFECT SIZES WITH MULTIPLE TREATMENTS AND A COMMON CONTROL\footnote{Supported in part by National Science Foundation Grants DMS 90-02847 and DMS 93-01366.}

by

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Abstract

Experiments are often conducted with a single control and several treatments. Because an effect size is the difference between treatment and control statistics, the multiple effect sizes will be correlated by virtue of there being a single control. The analysis is further complicated by the fact that some studies will have common treatments, others will not. We provide an analysis based on a regression model that permits us to obtain estimates of the multiple effect sizes, and show in an example how to choose the best treatment.

Key words and phrases: meta-analysis, missing data, multivariate meta-analysis, regression analysis

AMS Classification: 62F99, 62P10, 62J05
Estimation of Effect Sizes with Multiple Treatments and a Common Control
Leon J. Gleser and Ingram Olkin

1. Introduction

Because of cost and efficiency considerations, experiments are often conducted with multiple treatments. In particular, this occurs when the efficacy of alternative doses is to be examined, as for example, when the treatment consists of taking one aspirin per day, two aspirins per day, one aspirin every other day, etc. It may also arise when several laboratories perform tests under different physical conditions (e.g., temperature, pressure, etc.), or when laboratories use different methods for chemical analysis.

A distinguishing feature is that although there are multiple treatment groups, there is usually only one control group in each study. As a consequence, the effect size for each treatment involves a common value for the control. This means that the estimates of effect size within studies will be correlated, although the estimates of effect size between studies remain independent. It is this correlational aspect that does not permit the use of standard methods for combining results of independent studies as treated in papers or texts. (For example, see Hedges and Olkin, 1985, Bailar and Mosteller, 1986.)

The data that motivated this paper contained seven studies with six treatments. It was not a designed set of studies, so that some studies had two treatments and others four. The following schematic diagram shows the treatments included (denoted by an asterisk) in each study.

Figure 1

<table>
<thead>
<tr>
<th>Study</th>
<th>C</th>
<th>E₁</th>
<th>E₂</th>
<th>E₃</th>
<th>E₄</th>
<th>E₅</th>
<th>E₆</th>
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</tr>
</tbody>
</table>

Study 1 contains treatment groups 1, 2, 3, and 5 whereas study 7 contains treatment groups 1 and 6.
This format may suggest an analysis based on missing observations, but the number of missing cells is large, they are generally not missing at random, and the computational methods to obtain exact maximum likelihood estimates, say, become exceedingly cumbersome. Instead we adopt a regression format based on large sample theory. This permits us to obtain estimates of effect sizes for each of the treatments as well as confidence intervals.

The model and an analysis is provided in Section 2; the results are applied to a data set in Section 3.

2. Models and Analysis

Suppose that each study consists of a single control group designated by \( C \), and up to \( m \) experimental or treatment groups denoted by \( E_1, \ldots, E_m \). The true mean and standard deviation of the control group are \( \mu_0 \) and \( \sigma_0 \); the true mean of the \( j \)-th experimental group is \( \mu_j^E \), \( j = 1, \ldots, m \). Because of possible differences in precision in the \( m \) experimental groups we permit the respective standard deviations \( \sigma_1, \ldots, \sigma_m \) to differ.

For the \( k \)-th study the sample sizes, means and standard deviations for the control and treatment groups are denoted

\[
\begin{align*}
    n_0^{(k)}, n_1^{(k)}, \ldots, n_m^{(k)}, \\
    \bar{y}_0^{(k)}, \bar{y}_1^{(k)}, \ldots, \bar{y}_m^{(k)}, \\
    s_0^{(k)}, s_1^{(k)}, \ldots, s_m^{(k)}.
\end{align*}
\]

As noted earlier, each study will contain a control group but only some of the treatments. From the schematic Figure 1 our data set contains 7 studies with 6 treatments. For simplicity of notation and description, we provide the relevant theoretical details for the example in Figure 1 using only the first three studies. This will serve to illustrate the procedure; extensions to other schematics will be evident. Our numerical results in Section 3 include all studies.

The population effect sizes to be estimated in this example are

\[
\delta_j = (\mu_0 - \mu_j^E)/\sigma_0, \quad j = 1, 2, 3. \tag{2.1}
\]

The sample estimates of \( \delta_j \) from study \( k \) are

\[
d_j^{(k)} = (\bar{y}_0^{(k)} - \bar{y}_j^{(k)})/s_0^{(k)}, \tag{2.2}
\]

with the proviso that we may not have estimates for each \( j \) and each \( k \). As an illustration, the first three studies in Figure 1 yield estimates

\[
\begin{align*}
    d^{(1)} &= (d_1^{(1)}, d_2^{(1)}, d_3^{(1)}, d_5^{(1)}), \\
    d^{(2)} &= (d_1^{(2)}, d_2^{(2)}), \\
    d^{(3)} &= (d_1^{(3)}, d_4^{(3)}, d_5^{(3)}).
\end{align*}
\]
Further, let
\[ \mathbf{d} = (\mathbf{d}^{(1)}, \mathbf{d}^{(2)}, \mathbf{d}^{(3)}) \).

Note that the vectors \( \mathbf{d}^{(1)}, \mathbf{d}^{(2)}, \mathbf{d}^{(3)} \) are mutually independent by virtue of the fact that they arise from different studies. The elements in each vector \( \mathbf{d}^{(k)} \) are rational functions of moments, so that for large samples, the vector will be approximately normally distributed with means corresponding to the treatments included in that study. In particular, in our example the large-sample means are
\[
\mathcal{E} \mathbf{d}^{(1)} \sim (\delta_1, \delta_2, \delta_3, \delta_5), \\
\mathcal{E} \mathbf{d}^{(2)} \sim (\delta_1, \delta_2), \\
\mathcal{E} \mathbf{d}^{(3)} \sim (\delta_1, \delta_4, \delta_5).
\]

Note that the \( d_j \) are not unbiased estimators of \( \delta_j \); however, for large samples the bias approaches zero (see Hedges and Olkin, 1985). The large-sample covariance matrix \( \Psi_\infty \) of \( \mathbf{d} = (\mathbf{d}^{(1)}, \mathbf{d}^{(2)}, \mathbf{d}^{(3)})' \) is block diagonal
\[ \Psi_\infty = \text{diag} \left( \Psi^{(1)}_\infty, \Psi^{(2)}_\infty, \Psi^{(3)}_\infty \right), \]
where the dimensionality of \( \Psi^{(k)}_\infty \) is that of \( \mathbf{d}^{(k)} \). A description of the elements of \( \Psi^{(k)}_\infty \) is given below.

**Proposition.** If \( \bar{y}_j \sim \mathcal{N}(\mu_j, \sigma_j^2/n_j), \quad j = 0, 1, \ldots, m \) are mutually independent, and independent of \( s_0^2/\sigma_0^2 \), which has a \( \chi^2_{n_0} \) distribution, then as \( n_0, n_1, \ldots, n_m \) approach infinity at a fixed rate,
\[ d_j = (\bar{y}_0 - \bar{y}_j)/s_0, \quad j = 1, \ldots, m \]
are asymptotically normal with means \( \delta_j = (\mu_0 - \mu_j)/\sigma_0 \), \( j = 1, \ldots, m \), and asymptotic covariance matrix \( \Psi_\infty = (\psi_{ij}) \) with elements
\[
\psi_{jj} = \frac{\sigma_j^2}{n_j \sigma_0^2} + \frac{1 + \frac{1}{2} \delta_j^2}{n_0}, \\
\psi_{jk} = \frac{1 + \frac{1}{2} \delta_j \delta_k}{n_0}, \quad j \neq k; \quad j, k = 1, \ldots, m. \quad (2.3)
\]

Because the \( d_j \) are rational functions of moments, the asymptotic variances and covariances can be obtained by a straightforward application of the delta method. Normality follows from the same facts.

Recall in our example that \( \Psi_\infty = \text{diag} \left( \Psi^{(1)}_\infty, \Psi^{(2)}_\infty, \Psi^{(3)}_\infty \right) \); to estimate \( \Psi^{(k)}_\infty \) we replace \( \sigma_0^{(k)}, \sigma_1^{(k)}, \ldots, \sigma_m^{(k)} \) by \( s_0^{(k)}, s_1^{(k)}, \ldots, s_m^{(k)} \), and \( \delta_1, \ldots, \delta_m \) by \( d_1^{(k)}, \ldots, d_m^{(k)} \). If only treatments
If $j_1, \ldots, j_r$ are present in study $k$, then $\Psi^{(k)}_\infty$ is defined to be the principal minor of $\Psi_\infty$ in (2.3) corresponding to treatments $j_1, \ldots, j_r$. Thus, in our example

$$
\Psi_\infty^{(2)} = \begin{pmatrix}
\frac{\sigma_1^2}{n_1} + \frac{1 + \frac{1}{2}\delta_1^2}{n_0} & \frac{1 + \frac{1}{2}\delta_1\delta_2}{n_0} \\
\frac{1 + \frac{1}{2}\delta_1\delta_2}{n_0} & \frac{\sigma_2^2}{n_2} + \frac{1 + \frac{1}{2}\delta_2^2}{n_0}
\end{pmatrix},
$$

which is estimated by

$$
\hat{\Psi}_\infty^{(2)} = \begin{pmatrix}
\frac{s_1^2}{n_1} + \frac{1 + \frac{1}{2}d_1^2}{n_0} & \frac{1 + \frac{1}{2}d_1d_2}{n_0} \\
\frac{1 + \frac{1}{2}d_1d_2}{n_0} & \frac{s_2^2}{n_2} + \frac{1 + \frac{1}{2}d_2^2}{n_0}
\end{pmatrix}.
$$

**Remark.** If the hypothesis $H: \sigma_0^2 = \sigma_1^2 = \cdots = \sigma_m^2$ is upheld, then the variances in (2.6) are replaced by

$$
\psi_{ij} = \frac{1}{n_j} + \frac{1 + \frac{1}{2}\delta_j^2}{n_0}, \quad j = 1, \ldots, m.
$$

When the test for homogeneity of variances holds and we use a pooled estimate of variance, $s_p^2 = \Sigma_{i=0}^m (n_i - 1)s_i^2 / \Sigma_{i=0}^m (n_i - 1)$, instead of $s_0^2$ in the denominator of (2.2), then the asymptotic variances and covariances in (2.3) are replaced by

$$
\psi_{jj} = \frac{1}{n_j} + \frac{1}{n_0} + \frac{1}{2} \frac{\delta_j^2}{n},
$$

$$
\psi_{jk} = \frac{1}{n_0} + \frac{1}{2} \frac{\delta_j \delta_k}{n}, \quad j \neq k,
$$

where $n = \Sigma_{0}^m n_i$ is the total sample size in which the effect size is calculated (including the control group).

**The Regression Model**

Using the regression framework

$$
d = \delta + e,
$$

where the error vector $e$ has mean 0 and covariance matrix $\Psi$. Regression models linearly relating the elements of $\delta$ to each other, or to specified covariates measured for the study, can be substituted for $d$ in (2.4), yielding a regression model

$$
d = \beta X + e.
$$
The regression model (2.5) represents the hypothesis that effect sizes $\delta^{(j)}_i$ for the $i$-th treatment on the $j$-th study have a common value $\beta_i$ across those studies $j$ where treatment $i$ was observed, $j = 1, \ldots, m$. The design matrix $X$ and slope vector applied to the example are

$$
X = \begin{pmatrix}
1 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\
0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\end{pmatrix},
$$

$$
\beta = (\beta_1, \beta_2, \beta_3, \beta_4, \beta_5, \beta_6).
$$

In this illustration the third block in the design matrix picks up the effect sizes $\beta_1, \beta_4$ and $\beta_6$.

The least squares estimator yields

$$
\hat{\beta} = d\hat{\Psi}^{-1}X'(X\hat{\Psi}^{-1}X')^{-1},
$$

where we have estimated the large-sample covariance matrix by its sample analog, which provides a consistent estimator.

The asymptotic best linear unbiased estimator $\tilde{\delta}$ of the effect size vector $\delta$ is

$$
\tilde{\delta} = (d\hat{\Psi}^{-1}\infty X')(X\hat{\Psi}^{-1}\infty X')^{-1}.
$$

(2.6)

This estimator can be obtained in a straightforward manner from a standard weighted least squares procedure. The asymptotic covariance matrix of $\tilde{\delta}$ is $T = (\tau_{ij}) = (X\hat{\Psi}^{-1}\infty X')^{-1}$, which is consistently estimated by $\hat{T} = (\hat{\tau}_{ij}) = (X\hat{\Psi}^{-1}\infty X')^{-1}$. Consequently, an approximate $100(1 - \alpha)\%$ confidence region for $\delta$ is

$$
\{\delta : (\tilde{\delta} - \delta)\hat{T}^{-1}(\tilde{\delta} - \delta)' \leq c_m\},
$$

(2.7)

where $c_m \equiv \chi^2_m(1 - \alpha)$ is the $100(1 - \alpha)$-th percentile of the central chi-squared distribution with $m$ degrees of freedom. Both the asymptotic covariance matrix and the approximate confidence region are usually available from the same software used to obtain $\tilde{\delta}$.

To obtain confidence intervals for $\delta_1, \ldots, \delta_m$ individually, we use the standard Scheffé projection method,

$$
\tilde{\delta}_j - \sqrt{c_m\hat{\Delta}_{jj}} \leq \delta_j \leq \tilde{\delta}_j + \sqrt{c_m\hat{\Delta}_{jj}}, \quad j = 1, \ldots, m.
$$

(2.8)
Remark. The estimator $\tilde{\delta}$ is asymptotically efficient and asymptotically equivalent to the maximum likelihood estimator. However the numerical computation of $\tilde{\delta}$ is considerably easier than that for the MLE.

3. An example: Studies of treatment of hypertension

The data in Table 1 deals with studies evaluating patient education methods used in protocols for the treatment of hypertension. The treatments were classified as

\begin{align*}
T_1 & : \text{one to one counseling} \\
T_2 & : \text{group education sessions} \\
T_3 & : \text{one to one counseling plus audio-visual aids} \\
T_4 & : \text{one to one counseling plus group education sessions} \\
T_5 & : \text{one to one counseling plus support from patient’s social network} \\
T_6 & : \text{one to one counseling plus self-monitoring of blood pressure}
\end{align*}

The goal in the first four treatments was to help patients adopt behaviors that, in conjunction with medical treatment, would improve blood pressure control. A blood pressure goal was set for each patient, and the data are proportions of patients under hypertension control who reach the goal.

All the studies were randomized, but most of the studies did not report their randomization procedures. The studies were from a wide variety of clinical settings, ranging from rural health clinics to private practices.
Table 1. Data for study of treatment of hypertension.

Sample Sizes

<table>
<thead>
<tr>
<th>Study</th>
<th>C</th>
<th>E₁</th>
<th>E₂</th>
<th>E₃</th>
<th>E₄</th>
<th>E₅</th>
<th>E₆</th>
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Sample Means

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<th>E₂</th>
<th>E₃</th>
<th>E₄</th>
<th>E₅</th>
<th>E₆</th>
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Sample Standard Deviations

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<th>E₂</th>
<th>E₃</th>
<th>E₄</th>
<th>E₅</th>
<th>E₆</th>
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<td>.06</td>
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</table>
From the data in Table 1, the vectors of effect sizes are obtained. Here $d^{(k)}$ is the vector of effect sizes from study $k$. The computations yield $d^{(1)} = (-0.154, 1.218, 1.693, 3.013)$, $d^{(2)} = (-1.789, -0.282)$, $d^{(3)} = (0.739, 2.33, 2.443)$, $d^{(4)} = (3.803, -4.225)$, $d^{(5)} = (-0.03, 1.4)$, $d^{(6)} = (-0.438, 0)$, $d^{(7)} = (2.688, 2.138)$.

Using these calculations and the sample standard deviations in Table 1, the following are the estimated asymptotic covariance matrices $\bar{\Psi}_\infty^{(k)}$ of the $d^{(k)}$:

$$\bar{\Psi}_\infty^{(1)} = \begin{pmatrix} 0.044 & 0.023 & 0.022 & 0.019 \\ 0.067 & 0.049 & 0.071 \\ 0.081 & 0.085 \\ 0.157 \end{pmatrix}, \quad \bar{\Psi}_\infty^{(2)} = \begin{pmatrix} 0.137 & 0.028 \\ 0.075 \end{pmatrix},$$

$$\bar{\Psi}_\infty^{(3)} = \begin{pmatrix} 0.186 & 0.233 & 0.238 \\ 0.495 & 0.481 \\ 0.525 \end{pmatrix}, \quad \bar{\Psi}_\infty^{(4)} = \begin{pmatrix} 0.183 & -0.147 \\ 0.222 \end{pmatrix},$$

$$\bar{\Psi}_\infty^{(5)} = \begin{pmatrix} 0.057 & 0.039 \\ 0.094 \end{pmatrix}, \quad \bar{\Psi}_\infty^{(6)} = \begin{pmatrix} 0.102 & 0.040 \\ 0.063 \end{pmatrix}, \quad \bar{\Psi}_\infty^{(7)} = \begin{pmatrix} 0.143 & 0.102 \\ 0.097 \end{pmatrix}.$$

Applying (2.6), where the matrix $X$ is the appropriate extension of the design matrix given for the first 3 studies,

$$\bar{\delta} = (-0.047, 0.510, 0.725, 1.660, 1.815, 0.179),$$

and the estimated asymptotic covariance matrix of $\bar{\delta}$ and its inverse are

$$\bar{T} \equiv (X \bar{\Psi}_\infty^{-1} X')^{-1} = \begin{pmatrix} 0.01049 & 0.00411 & 0.00329 & 0.00579 & 0.00458 & 0.00633 \\ 0.02652 & 0.00832 & 0.01520 & 0.01737 & 0.00248 \\ 0.02326 & 0.01587 & 0.01837 & 0.00199 \\ 0.09791 & 0.05378 & 0.00349 \\ 0.06374 & 0.00277 \\ 0.01988 \end{pmatrix},$$

$$\bar{T}^{-1} = \begin{pmatrix} 127.2 & -12.24 & -9.11 & -3.62 & 1.52 & -37.60 \\ 48.68 & -7.63 & .00 & -10.18 & .00 \\ 58.07 & .00 & -14.00 & .00 \\ 19.17 & -15.91 & .00 \\ 35.81 & .00 \\ 62.29 \end{pmatrix}.$$
are \(100(1 - \alpha)\%\) simultaneous confidence intervals for \(b\delta'\), where \(b\) is any vector with \(\sum b_i = 0\). Because treatment 1 is one-to-one counseling, whereas treatments 2–6 have additional components, we take contrasts of each treatment with treatment 1. This yields
\[
-0.008 \leq \delta_2 - \delta_1 \leq 1.222, \quad -0.224 \leq \delta_3 - \delta \leq 1.320,
\]
\[
0.672 \leq \delta_4 - \delta_1 \leq 2.742, \quad 1.103 \leq \delta_5 - \delta_1 \leq 2.711,
\]
\[
-0.217 \leq \delta_6 - \delta_1 \leq 0.669,
\]
from which we see that treatments 4 and 5 are superior to the mean effect.

Of central concern is the determination of the "best" treatment. By ordering the estimated effect sizes we have that \(\hat{\delta}_5 = 1.815\) is the largest effect size. But with what confidence can we say that this largest sample effect size corresponds to the largest population effect size? To answer this we use the procedure referred to as selecting and ordering populations. (For a general discussion of these procedures see Gibbons, Olkin and Sobel (1977); for the specific procedure used we refer to Section 15.2. See also Gupta and Panhappakesan (1979).)

The methodology for selecting the population that corresponds to the largest treatment effect size is known in the case that the treatments have homogeneous variances and homogeneous correlations. This is the assumption that the covariance matrix has an intraclass correlation structure, i.e., that
\[
T \equiv (X\Psi^{-1}\tilde{X}^{-1})^{-1} \equiv \xi^2 \begin{pmatrix}
1 & \rho & \cdots & \rho \\
\rho & \ddots & \ddots & \ddots \\
\vdots & \ddots & \ddots & \ddots \\
1 & \cdots & \cdots & \cdots
\end{pmatrix}.
\]

There are several procedures for testing this hypothesis; we use the standard likelihood ratio test (see e.g., Anderson (1984), Morrison (1990)).

In the context of the present example this assumption appears to be reasonable in that the treatments are very similar. The correlation matrix obtained from \(\tilde{T}\) exhibits some homogeneity in the sense that four correlations range between .05 and .3 and four correlations between .3 and .45.

From \(\tilde{T}\) we obtain as estimates
\[
\hat{\xi}^2 = \frac{\sum_1^6 \hat{\tau}_{ii}}{6} = 0.0403,
\]
\[
\hat{\rho} = \frac{\sum \hat{\tau}_{ij}/15}{\hat{\xi}^2} = 0.2709.
\]

Use of formula (15.21) and Table A.2 in Gibbons, Olkin and Sobel (1977) yields a probability of at least 0.96 that treatment 5 is the best whenever the largest and next largest \(\delta\)-values differ by at least 0.1.
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References


