Statistical Methods Programmed in MetaView

Version 4

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Data structure

Consider a meta-analysis of k studies. When the studies have a binary outcome the results of each study can be presented in a 2x2 table (Table 1) giving the numbers of subjects who do or do not experience the event in each of the two groups (here called intervention and control).

Table 1 Binary data

Study i	Event	No event	Total
Intervention	a_i	b_i	n_{1i}
Control	c_i	d_i	n_{2i}

If the outcome is a continuous measure, the number of subjects in each of the two groups, their mean response and the standard deviation of their responses are required to perform meta-analysis (Table 2).

Table 2 Continuous data

Study i	Group size	Mean response	Standard deviation
Intervention	n_{1i}	m_{1i}	sd_{1i}
Control	n_{2i}	m_{2i}	sd_{2i}

Formulae

Individual Study Responses: Binary outcomes

For study i denote the cell counts as in Table 1, and let $n_{1i} = a_i + b_i$, $n_{2i} = c_i + d_i$, and $N_i = n_{1i} + n_{2i}$. For the Peto method the individual odds ratios are given by

$$\hat{OR}_i = \exp\{(a_i - E[a_i])/v_i\}$$

with its logarithm having standard error

$$se\{\ln(\hat{O}R_i)\} = \sqrt{1/v_i}$$

where $E[a_i] = n_{1i}(a_i + c_i)/N_i$ (the expected number of events in the intervention group) and

$v_i = [n_{1i}n_{2i}(a_i + c_i)(b_i + d_i)]/[N_i^2(N_i - 1)]$ (the hypergeometric variance of a_i).

For other methods of combining trials, the odds ratio for each study is given by

$$\hat{O}R_i = a_i d_i / b_i c_i$$

the standard error of the log odds ratio being

$$se\{\ln(\hat{O}R_i)\} = \sqrt{1/a_i + 1/b_i + 1/c_i + 1/d_i}$$

The risk ratio for each study is given by

$$\hat{R}R_i = (a_i / n_{1i})/(c_i / n_{2i})$$

the standard error of the log risk ratio being

$$se\{\ln(\hat{R}R_i)\} = \sqrt{1/a_i + 1/c_i - 1/n_{1i} - 1/n_{2i}}$$

The risk difference for each study is given by

$\hat{R}D_i = (a_i / n_{1i}) - (c_i / n_{2i})$ with standard error $se(\hat{R}D_i) = \sqrt{a_i b_i / n_{1i}^3 + c_i d_i / n_{2i}^3}$

Where zero cells cause problems with computation of effects or standard errors, 0.5 is added to all cells (a_i, b_i, c_i, d_i) for that study, except when $a_i = c_i = 0$ or $b_i = d_i = 0$, when the relative effect measures $\hat{O}R_i$ and $\hat{R}R_i$ are undefined.

Individual Study Responses: Continuous outcomes

Denote the number of subjects, mean and standard deviation as in Table 2, and let

$$N_i = n_{1i} + n_{2i}$$

and

$$s_i = \sqrt{((n_{1i} - 1)sd_{1i}^2 + (n_{2i} - 1)sd_{2i}^2)/(N_i - 2)}$$

be the pooled standard deviation of the two groups. The weighted mean difference is given by

$W\hat{M}D = m_{1i} - m_{2i}$ with standard error $se(W\hat{M}D) = \sqrt{sd_{1i}^2 / n_{1i} + sd_{2i}^2 / n_{2i}}$

There are several popular formulations of the standardised mean difference. The one implemented in MetaView is Hedges adjusted g, which is very similar to Cohen's d, but includes an adjustment for small sample bias

$\hat{g}_i = ((m_{1i} - m_{2i})/s_i)(1 - 3/(4N_i - 9))$ with standard error $se(\hat{g}_i) = \sqrt{N_i /(n_{1i}n_{2i}) + \hat{g}_i^2 /(2(N_i - 3.94))}$.

Pooling Methods

Mantel-Haenszel Methods for Combining Trials

For each study, the effect size from each trial $\hat{\Theta}_i$ is given weight w_i in the analysis. The overall estimate of the pooled effect, $\hat{\Theta}_{MH}$ is given by

$$\hat{\Theta}_{MH} = \frac{\sum w_i \hat{\Theta}_i}{\sum w_i}$$

For combining odds ratios, each study's OR is given weight

$w_i = b_i c_i / N_i$,

and the logarithm of $\hat{O}R_{MH}$ has standard error given by

$$se\{\ln(\hat{O}R_{MH})\} = \sqrt{((PR)/R^2 + ((PS+QR)/(R \times S)) + (QS)/S^2)/2}$$

where

$R = \sum a_i d_i / N_i$; $S = \sum b_i c_i / N_i$;

$PR = \sum (a_i + d_i) a_i d_i / N_i^2$; $PS = \sum (a_i + d_i) b_i c_i / N_i^2$;

$QR = \sum (b_i + c_i) a_i d_i / N_i^2$; $QS = \sum (b_i + c_i) b_i c_i / N_i^2$

For combining risk ratios, each study's RR is given weight

$w_i = [c_i(a_i + b_i)] / N_i$,

and the logarithm of $\hat{R}R_{MH}$ has standard error given by

$$se\{\ln(\hat{R}R_{MH})\} = \sqrt{P/(R \times S)}$$

where

$P = \sum (n_{1i} n_{2i} (a_i + c_i) - a_i c_i N_i) / N_i^2$; $R = \sum a_i n_{2i} / N_i$; $S = \sum c_i n_{1i} / N_i$

For risk differences, each study's RD has the weight

$w_i = n_{1i} n_{2i} / N_i$

and $\hat{R}D_{MH}$ has standard error given by

$$se\{\hat{R}D_{MH}\} = \sqrt{(P/Q^2)}$$

where

$P = \sum (a_i b_i n_{2i}^3 + c_i d_i n_{1i}^3) / (n_{1i} n_{2i} N_i^2)$; $Q = \sum n_{1i} n_{2i} / N_i$

The heterogeneity statistic is given by

$$Q = \sum w_i' (\hat{\Theta}_i - \hat{\Theta}_{MH})^2$$

where $\hat{\Theta}$ is the log odds ratio, log relative risk or risk difference and the w_i' are the weights calculated as $1/se(\hat{\Theta}_i)^2$. Under the null hypothesis that there are no differences in treatment effect between trials this follows a chi-squared distribution on $k-1$ degrees of freedom (where k is the number of studies contributing to the meta-analysis) .

Inverse Variance Methods for Combining Trials

Inverse variance methods are used to pool both standardised mean differences, and weighted mean differences for continuous data. In the general formula the effect size is defined to be $\hat{\Theta}_i$ which is the trials SMD or WMD. The individual effect sizes are weighted according to the reciprocal of their variance (calculated as the square of the standard error given in the individual study section above) giving

$$w_i = 1/se(\hat{\Theta}_i)^2$$

These are combined to give a pooled estimate

$$\hat{\Theta}_{IV} = \frac{\sum w_i \hat{\Theta}_i}{\sum w_i}$$

with

$$se\{\hat{\Theta}_{IV}\} = 1/\sqrt{\sum w_i}$$

The heterogeneity statistic is given by a similar formula as for the Mantel-Haesznel method, using the inverse variance form of the weights, w_i

$$Q = \sum w_i (\hat{\Theta}_i - \hat{\Theta}_{IV})^2 \ .$$

Peto's Assumption Free Method for Combining Trials

Here, the overall odds ratio is given by

$$\hat{O}R_{Peto} = \exp\{\sum w_i \ln(\hat{O}R_i)/\sum w_i\},$$

where the odds ratio $\hat{O}R_i$ is calculated using the approximate method described in the individual trial section, and the weights, w_i are equal to the hypergeometric variances, v_i .

The logarithm of the odds ratio has standard error

$$se\{\ln(\hat{O}R_{Peto})\} = 1/\sqrt{\sum v_i}$$

The heterogeneity statistic is given by

$$Q = \sum v_i \{(\ln \hat{O}R_i)^2 - (\ln \hat{O}R_{Peto})^2\} \ .$$

DerSimonian and Laird Random Effects Models

Under the random effects model, the assumption of a common treatment effect is relaxed, and the effect sizes are assumed to have a distribution

$\Theta_i \approx N(\Theta, \tau^2)$.

The estimate of τ^2 is given by

$\hat{\tau}^2 = \max\{[Q-(k-1)]/[\sum w_i - (\sum (w_i^2))/\sum w_i],0\}$, where the w_i are the inverse variance weights (calculated as $1/se(\hat{\Theta}_i)^2$) for log OR, log RR, RD, WMD and SMD, as appropriate.

The estimate of the combined effect for the heterogeneity may be taken as either the Mantel-Haenszel or the inverse variance estimate. Again, for odds ratios and risk ratios, the effect size is taken as the natural logarithm of the OR and RR. Each study's effect size is given weight

$$w_i' = 1/(se(\hat{\Theta}_i)^2 + \hat{\tau}^2)$$

The pooled effect size is given by

$$\hat{\Theta}_{DL} = (\sum w_i' \hat{\Theta}_i)/(\sum w_i')$$

and

$$se\{\hat{\Theta}_{DL}\} = 1/\sqrt{\sum w_i'}$$

Note that in the case where the heterogeneity statistic Q is less than or equal to its degrees of freedom $(k-1)$, the estimate of the between trial variation, $\hat{\tau}^2$, is zero, and the weights reduce to the those as given by the inverse variance method.

Confidence intervals

The $100(1-\alpha)\%$ confidence interval for $\hat{\Theta}$ is given by

$\hat{\Theta} - se(\hat{\Theta})\Phi(1-\alpha/2)$, to $\hat{\Theta} + se(\hat{\Theta})\Phi(1-\alpha/2)$

where $\hat{\Theta}$ is the log odds ratio, log relative risk, risk difference,mean difference or standardised mean difference, and Φ is the standard normal deviate.

Test statistics

In all cases, the test statistic is given by

$$z = \hat{\Theta}/se(\hat{\Theta})$$

where the odds ratio or risk ratio is again considered on the log scale.

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