

# Statistical algorithms in Review Manager 5

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## Data structure

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

Table 1: Binary data

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

If the outcome is a continuous measure, the number of participants 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
Experimental	$n_{1i}$	$m_{1i}$	$sd_{1i}$
Control	$n_{2i}$	$m_{2i}$	$sd_{2i}$

If the outcome is analysed by comparing observed with expected values (for example using the Peto method or a log-rank approach for time-to-event data), then 'O - E' statistics and their variances are required to perform the meta-analysis. Group sizes may also be entered by the review author, but are not involved in the analysis.

Table 3: O minus E and variance

Study $i$	O minus E	Variance of (O minus E)	Group size (experimental)	Group size (control)
	$Z_i$	$V_i$	$n_{1i}$	$n_{2i}$

For other outcomes a generic approach can be used, the user directly specifying the values of the intervention effect estimate and its standard error for each study (the standard error may be calculable from a confidence interval). 'Ratio' measures of effect effects (e.g. odds ratio, risk ratio, hazard ratio, ratio of means) will normally be expressed on a log-scale, 'difference' measures of

effect (e.g. risk difference, differences in means) will normally be expressed on their natural scale. Group sizes can optionally be entered by the review author, but are not involved in the analysis.

Table 4: Generic data

Study $i$	Estimate of effect	Standard error of estimate	Group size (experimental)	Group size (control)
	$\hat{\theta}_i$	$SE\{\hat{\theta}_i\}$	$n_{1i}$	$n_{2i}$

## Formulae for individual studies

### Individual study estimates: dichotomous outcomes

#### Peto odds ratio

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

$$OR_{Peto,i} = \exp\left\{\frac{Z_i}{V_i}\right\}.$$

The logarithm of the odds ratio has standard error

$$SE\{\ln(OR_{Peto,i})\} = \sqrt{\frac{1}{V_i}},$$

where  $Z_i$  is the ‘O – E’ statistic:

$$Z_i = a_i - E[a_i],$$

with

$$E[a_i] = \frac{n_{1i}(a_i + c_i)}{N_i}$$

(the expected number of events in the experimental intervention group), and

$$V_i = \frac{n_{1i}n_{2i}(a_i + c_i)(b_i + d_i)}{N_i^2(N_i - 1)}$$

(the hypergeometric variance of  $a_i$ ).

#### Odds ratio

For methods other than the Peto method, the odds ratio for each study is given by

$$OR_i = \frac{a_i d_i}{b_i c_i},$$

the standard error of the log odds ratio being

$$SE\{\ln(OR_i)\} = \sqrt{\frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i}}.$$

#### Risk ratio

The risk ratio for each study is given by

$$RR_i = \frac{a_i / n_{1i}}{c_i / n_{2i}},$$

the standard error of the log risk ratio being

$$SE\{\ln(RR_i)\} = \sqrt{\frac{1}{a_i} + \frac{1}{c_i} - \frac{1}{n_{1i}} - \frac{1}{n_{2i}}}.$$

### Risk difference

The risk difference for each study is given by

$$RD_i = \frac{a_i}{n_{1i}} - \frac{c_i}{n_{2i}},$$

with standard error

$$SE\{RD_i\} = \sqrt{\frac{a_i b_i}{n_{1i}^3} + \frac{c_i d_i}{n_{2i}^3}}.$$

### Empty cells

Where zeros 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  $OR_i$  and  $RR_i$  are undefined.

### Individual study estimates: continuous outcomes

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

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

and

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

be the pooled standard deviation across the two groups.

### Difference in means (mean difference)

The difference in means (referred to as mean difference) is given by

$$MD_i = m_{1i} - m_{2i},$$

with standard error

$$SE\{MD_i\} = \sqrt{\frac{sd_{1i}^2}{n_{1i}} + \frac{sd_{2i}^2}{n_{2i}}}.$$

### Standardized difference in means (standardized mean difference)

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

$$SMD_i = \frac{m_{1i} - m_{2i}}{s_i} \left(1 - \frac{3}{4N_i - 9}\right),$$

with standard error

$$SE\{SMD_i\} = \sqrt{\frac{N_i}{n_{1i}n_{2i}} + \frac{SMD_i^2}{2(N_i - 3.94)}}.$$

## Individual study estimates: O – E and variance

For study  $i$  the effect estimate is given by

$$\hat{\theta}_i = \frac{Z_i}{V_i},$$

with standard error

$$SE\{\hat{\theta}_i\} = \sqrt{\frac{1}{V_i}}.$$

The effect estimate is either of a log odds ratio or a log hazard ratio, depending on how the observed and expected values were derived.

## Individual study estimates: Generic method

As the user directly enters the intervention effect estimates and their standard errors no further processing is needed. All types of intervention effects are eligible for this method, but it might be most useful when intervention effects have been calculated in a way which makes special consideration of design (e.g. cluster randomized and cross-over trials), are adjusted for other effects (adjusted effects from non-randomized studies) or are not covered by existing methods (e.g. ratios of means, relative event rates).

## Meta-analysis methods

All summations are over  $i$ , from 1 to the number of studies, unless otherwise specified.

### Mantel-Haenszel methods for combining results across studies

#### Odds ratio

The Mantel-Haenszel summary log odds ratio is given by

$$\ln(OR_{MH}) = \ln\left(\frac{\sum w_{MH,i} OR_i}{\sum w_{MH,i}}\right), \quad (1)$$

and the Mantel-Haenszel summary odds ratio by

$$OR_{MH} = \frac{\sum w_{MH,i} OR_i}{\sum w_{MH,i}},$$

where each study's odds ratio is given weight

$$w_{MH,i} = \frac{b_i c_i}{N_i}.$$

The summary log odds ratio has standard error given by

$$SE\{\ln(OR_{MH})\} = \sqrt{\frac{1}{2} \left( \frac{E}{R^2} + \frac{F+G}{RS} + \frac{H}{S^2} \right)}, \quad (2)$$

where

$$R = \sum \frac{a_i d_i}{N_i}; \quad S = \sum \frac{b_i c_i}{N_i};$$

$$E = \sum \frac{(a_i + d_i)a_i d_i}{N_i^2}; F = \sum \frac{(a_i + d_i)b_i c_i}{N_i^2};$$

$$G = \sum \frac{(b_i + c_i)a_i d_i}{N_i^2}; H = \sum \frac{(b_i + c_i)b_i c_i}{N_i^2}.$$

## Risk ratio

The Mantel-Haenszel summary log risk ratio is given by

$$\ln(RR_{MH}) = \ln \left( \frac{\sum w_{MH,i} RR_i}{\sum w_{MH,i}} \right), \quad (3)$$

and the Mantel-Haenszel summary risk ratio by

$$RR_{MH} = \frac{\sum w_{MH,i} RR_i}{\sum w_{MH,i}},$$

where each study's risk ratio is given weight

$$w_{MH,i} = \frac{c_i(a_i + b_i)}{N_i}.$$

The summary log risk ratio has standard error given by

$$SE\{\ln(RR_{MH})\} = \sqrt{\frac{P}{RS}}, \quad (4)$$

where

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

## Risk difference

The Mantel-Haenszel summary risk difference is given by

$$RD_{MH} = \frac{\sum w_{MH,i} RD_i}{\sum w_{MH,i}}, \quad (5)$$

where each study's risk difference is given weight

$$w_{MH,i} = \frac{n_{1i}n_{2i}}{N_i}.$$

The summary risk difference has standard error given by

$$SE\{RD_{MH}\} = \sqrt{\frac{J}{K^2}}, \quad (6)$$

where

$$J = \sum \frac{a_i b_i n_{2i}^3 + c_i d_i n_{1i}^3}{n_{1i} n_{2i} N_i^2}; K = \sum \frac{n_{1i} n_{2i}}{N_i}.$$

## Test for heterogeneity

The heterogeneity test statistic is given by

$$Q_{MH} = \sum w_i (\hat{\theta}_i - \hat{\theta}_{MH})^2,$$

where  $\hat{\theta}$  represents the log odds ratio, log risk ratio or risk difference and the  $w_i$  are the weights calculated as  $1/\text{SE}\{\hat{\theta}_i\}^2$  rather than the weights used for the Mantel-Haenszel meta-analyses. Under the null hypothesis that there are no differences in intervention effect among studies this follows a chi-squared distribution with  $k - 1$  degrees of freedom (where  $k$  is the number of studies contributing to the meta-analysis).

The statistic  $I^2$  is calculated as

$$I^2 = \max \left\{ 100\% \times \frac{Q_{MH} - (k-1)}{Q_{MH}}, 0 \right\}$$

This measures the extent of inconsistency among the studies' results, and is interpreted as approximately the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error.

## Inverse-variance methods for combining results across studies

Inverse-variance methods are used to pool log odds ratios, log risk ratios and risk differences as one of the analysis options for binary data, to pool all mean differences and standardized mean differences for continuous data, and also for combining intervention effect estimates in the generic method. In the general formula the intervention effect estimate is denoted by  $\hat{\theta}_i$ , which is the study's log odds ratio, log risk ratio, risk difference, mean difference or standardized mean difference, or the estimate of intervention effect in the generic method. 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

$$w_i = \frac{1}{(\text{SE}\{\hat{\theta}_i\})^2}.$$

These are combined to give a summary estimate

$$\hat{\theta}_{IV} = \frac{\sum w_i \hat{\theta}_i}{\sum w_i}. \quad (7)$$

with

$$\text{SE}\{\hat{\theta}_{IV}\} = \frac{1}{\sqrt{\sum w_i}}. \quad (8)$$

The heterogeneity statistic is given by a similar formula as for the Mantel-Haenszel method:

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

Under the null hypothesis that there are no differences in intervention effect among studies this follows a chi-squared distribution with  $k - 1$  degrees of freedom (where  $k$  is the number of studies contributing to the meta-analysis).  $I^2$  is calculated as

$$I^2 = \max \left\{ 100\% \times \frac{Q_{IV} - (k-1)}{Q_{IV}}, 0 \right\}.$$

## Peto's method for combining results across studies

The Peto summary log odds ratio is given by

$$\ln(OR_{Peto}) = \frac{\sum V_i \ln(OR_{Peto,i})}{\sum V_i}. \quad (9)$$

and the summary odds ratio by

$$OR_{Peto} = \exp \left\{ \frac{\sum V_i \ln(OR_{Peto,i})}{\sum V_i} \right\},$$

where the odds ratio  $OR_{Peto,i}$  is calculated using the approximate method described in the individual study section, and  $V_i$  are the hypergeometric variances.

The log odds ratio has standard error

$$SE\{\ln(OR_{Peto})\} = \frac{1}{\sqrt{\sum V_i}}. \quad (10)$$

The heterogeneity statistic is given by

$$Q_{Peto} = \sum V_i \left\{ (\ln OR_{Peto,i})^2 - (\ln OR_{Peto})^2 \right\}.$$

Under the null hypothesis that there are no differences in intervention effect among studies this follows a chi-squared distribution with  $k - 1$  degrees of freedom (where  $k$  is the number of studies contributing to the meta-analysis).  $I^2$  is calculated as

$$I^2 = \max \left\{ 100\% \times \frac{Q_{Peto} - (k-1)}{Q_{Peto}}, 0 \right\}.$$

## O – E and variance method for combining studies

This is an implementation of the Peto method, which allows its application to time-to-event data as well as binary data. The summary effect estimate is given by

$$\hat{\theta} = \frac{\sum V_i \hat{\theta}_i}{\sum V_i}, \quad (11)$$

where the estimate,  $\hat{\theta}_i$ , from study  $i$  is calculated from  $Z_i$  and  $V_i$  as for individual studies. The summary effect is either a log odds ratio or a log hazard ratio (the user should specify which). The effect estimate (on a non-log scale) is given by

$$\text{effect estimate} = \exp \left\{ \frac{\sum V_i \hat{\theta}_i}{\sum V_i} \right\},$$

and is either an odds ratio or a hazard ratio.

The effect estimate (on the log scale) has standard error

$$SE\{\hat{\theta}\} = \frac{1}{\sqrt{\sum V_i}}. \quad (12)$$

The heterogeneity statistic is given by

$$Q_{Peto} = \sum V_i (\hat{\theta}_i^2 - \hat{\theta}^2).$$

Under the null hypothesis that there are no differences in intervention effect among studies this follows a chi-squared distribution with  $k - 1$  degrees of freedom (where  $k$  is the number of studies contributing to the meta-analysis).  $I^2$  is calculated as

$$I^2 = \max \left\{ 100\% \times \frac{Q_{Peto} - (k-1)}{Q_{Peto}}, 0 \right\}.$$

## DerSimonian and Laird random-effects models

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

$$\theta_i \sim N(\theta, \tau^2).$$

The estimate of  $\tau^2$  is given by

$$\hat{\tau}^2 = \max \left\{ \frac{Q - (k-1)}{\sum w_i - (\sum w_i^2) / \sum w_i}, 0 \right\},$$

where the  $w_i$  are the inverse-variance weights, calculated as

$$w_i = \frac{1}{\text{SE}\{\hat{\theta}_i\}^2},$$

for log odds ratio, log risk ratio, risk difference, mean difference, standardized mean difference, or for the intervention effect in the generic method, as appropriate.

For continuous data and for the generic method,  $Q$  is  $Q_{IV}$ . For binary data, either  $Q_{IV}$  or  $Q_{MH}$  may be taken. Both are implemented in RevMan 5 (and this is the only difference between random-effects methods under ‘Mantel-Haenszel’ and ‘inverse-variance’ options). Again, for odds ratios, risk ratios and other ratio effects, the effect size is taken on the natural logarithmic scale.

Each study’s effect size is given weight

$$w'_i = \frac{1}{\text{SE}\{\hat{\theta}_i\}^2 + \hat{\tau}^2}.$$

The summary effect size is given by

$$\hat{\theta}_{DL} = \frac{\sum w'_i \hat{\theta}_i}{\sum w'_i}, \quad (13)$$

and

$$\text{SE}\{\hat{\theta}_{DL}\} = \frac{1}{\sqrt{\sum w'_i}}. \quad (14)$$

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 study variation,  $\hat{\tau}^2$ , is zero, and the weights coincide with those given by the inverse-variance method.

## Confidence intervals

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

$$\hat{\theta} - \text{SE}\{\hat{\theta}\} \Phi(1-\alpha/2) \quad \text{to} \quad \hat{\theta} + \text{SE}\{\hat{\theta}\} \Phi(1-\alpha/2),$$

where  $\hat{\theta}$  is the log odds ratio, log risk ratio, risk difference, mean difference, standardized mean difference or generic intervention effect estimate, and  $\Phi$  is the standard normal deviate. For log odds ratios, log risk ratios and generic intervention effects entered on the log scale (and identified



as such by the review author), the point estimate and confidence interval limits are exponentiated for presentation.

## Test statistics

### Test for presence of an overall intervention effect

In all cases, the test statistic is given by

$$Z = \frac{\hat{\theta}}{SE(\hat{\theta})},$$

where the odds ratio, risk ratio and other ratio measures are again considered on the log scale. Under the null hypothesis that there is no overall effect of intervention effect this follows a standard normal distribution.

### Test for comparison of subgroups

The test is valid for all methods. It is based on the notion of performing a test for heterogeneity across *subgroups* rather than across *studies*. Let  $\hat{\theta}_j$  be the summary effect size for subgroup  $j$ , with standard error  $SE\{\hat{\theta}_j\}$ . The summary effect size may be based on either a fixed-effect or a random-effects meta-analysis. For fixed-effect meta-analyses, these numbers correspond to above equations (1) and (2); (3) and (4); (5) and (6); (7) and (8); (9) and (10); or (11) and (12), each applied within each subgroup. For random-effects meta-analyses, these numbers correspond to equations (13) and (14), each applied within each subgroup. Note that for ratio measures, all computations here are performed on the log scale.

First we compute a weight for each subgroup:

$$w_j = \frac{1}{SE\{\hat{\theta}_j\}^2},$$

then we perform a (fixed-effect) meta-analysis of the summary effect sizes across subgroups:

$$\hat{\theta}_{tot} = \frac{\sum w_j \hat{\theta}_j}{\sum w_j}.$$

The test statistic for differences across subgroups is given by

$$Q_{int} = \sum w_j (\hat{\theta}_j - \hat{\theta}_{tot})^2.$$

Under the null hypothesis that there are no differences in intervention effect across subgroups this follows a chi-squared distribution with  $S-1$  degrees of freedom (where  $S$  is the number of subgroups with summary effect sizes).

$I^2$  for differences across subgroups is calculated as

$$I^2 = \max \left\{ 100\% \times \frac{Q_{int} - (S-1)}{Q_{int}}, 0 \right\}.$$

This measures the extent of inconsistency across the subgroups' results, and is interpreted as approximately the proportion of total variation in subgroup estimates that is due to genuine variation across subgroups rather than sampling error.

*Note.* An alternative formulation for fixed-effect meta-analyses (inverse variance and Peto methods only) is as follows. The  $Q$  statistic defined by either  $Q_{IV}$  or  $Q_{Peto}$  is calculated separately for each of the  $S$  subgroups and for the totality of studies, yielding statistics  $Q_1, \dots, Q_S$  and  $Q_{tot}$ . The test statistic is given by

$$Q_{int} = Q_{tot} - \sum_{j=1}^S Q_j .$$

This is identical to the test statistic given above, in these specific situations.

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