EXERCISE

Applying fixed and random effects meta-analysis

Aims of the exercise

The purpose of this exercise is to demonstrate how meta-analysis can be used to estimate a combined treatment effect from multiple studies. Two alternative approaches will be used: the fixed effect and random effects models. These approaches make different assumptions about the combined effect and hence the calculations differ for estimating the pooled statistics.

The fixed effect model assumes that all studies are estimating the same underlying effect size. The difference between individual studies is due only to random (sampling) error within studies. The combined effect is the estimate of this common effect size. In contrast, the random effect model assumes that the effect size could vary between studies and hence the studies are estimating different effect sizes. These effects are assumed to vary at random and the studies provide a random sample of the relevant distribution of effects. The combined effect estimates the mean of this distribution. The random effects model includes two sources of variation: the between and within study variance.

As a first step, the exercise will get you to construct a 2x2 table for each individual study. This table provides the information required to calculate the outcome of interest – the odds ratio (OR). In order to combine the data it is necessary to transform the data to work with log odds ratio, providing a measure which is approximately normally distributed. The next step will be to estimate the weights applied to each individual study when the results are combined. This step will differ according to whether the fixed or random effects model is used. The final step in both approaches will be to estimate the pooled statistics.

Overview of steps to complete exercise

1. Constructing 2x2 tables from the individual studies and applying continuity correction to deal with zero counts.
2. Calculating ln(OR) and associated variance (within study) for each individual study.
3. Estimating the weights associated with the fixed effect model (allowing for within study variance only)
4. Estimating pooled statistics from a fixed effect model.
5. Estimating the between study variance.
6. Estimating the weights associated with the random effects model (allowing for within *and* between study variance).
7. Estimating pooled statistics from a random effects model.
8. Comparing results based on the alternative approaches.

1. Constructing 2x2 tables from the individual studies and applying continuity correction to deal with zero counts

In the template file (Exercise 5 – template.xls) you will find a new worksheet <*MetaAnalysis*>. At the top of this sheet, the results from ten studies are reported in a separate table. For each individual study, the numbers of patients in the control and treatment arms are reported together with the numbers of events in each arm. The outcome of interest in this example is mortality and measure of effect to be applied is the OR.

From the individual study data you will need to will need to estimate the data required to populate the 2x2 table for each individual study. The cells of this table and the formula for estimating the OR are reported below Table 1 in the worksheet.

An important issue to note is that the equation for the var LN(OR) is undefined if there are no events in either the treatment or control arms (i.e. one or more of a,b,c,d=0). The application of a continuity correction has been recommended to deal with these situations and should be done prior to estimating the combined outcome. This approach adds 0.5 to each cell of the 2x2 table. (*Note: This correction should only be applied to those studies with zero events in one or both arms. This correction will result in 1 being added to the overall sample size in both arms*).

The first task is to estimate the cells of the 2x2 table and apply the continuity correction.

(i) Use the data reported in Table 1, apply the continuity correction and complete the missing cells of the 2x2 table in range D36:J45.

2. Calculating ln(OR) and associated variance (within study) for each individual study.

The next task is to estimate the OR for each individual study using the 2x2 table data you have just calculated. The relevant formulae are reported at the bottom of Table 1. For each individual study:

(ii) In column L, estimate the LN(OR) for each individual study.
(iii) In column M, estimate the VAR LN(OR) for each individual study (see lecture notes for the formula).
(iv) In columns N-O, estimate the associated 95% confidence interval for LN(OR). By assuming that LN(OR) is normally distributed, the 95% confidence interval is given by:

a. $LN(OR) \pm 1.96 \times \sqrt{\text{var}(LN(OR))}$

(v) Finally, transform the estimates back to the natural scale in columns Q:S, by taking the exponential of the estimates in column L and N-O, for ease of interpretation.

3. Estimating the weights associated with the fixed effect model (allowing for within study variance)

The next step is to estimate the individual study weights to be applied within the fixed effect model. The approach that is used here uses the inverse variance weighting method. That is, the weight assigned to each individual study is simply the inverse of the variance (proportional to its precision) estimates that you have previously estimated.

For i=1,…,k independent studies to be combined, let T_i *(i.e. LN(OR))* be the observed effect size, θ_i the underlying population effect size, with variance v_i (i.e. Var(LN(OR))) for the *i*th study. For the fixed effect model, the assumption being made is that all population effect sizes are equal (i.e. $\theta_1 = \theta_2 \ldots = \theta_k = \theta$), where θ is the true common underlying effect size. The pooled estimate of the treatment effect is:

$$\bar{T}_{\cdot} = \frac{\sum_{i=1}^{k} w_i T_i}{\sum_{i=1}^{k} w_i}$$

The weights that minimise the variance of $\bar{T}_{\cdot}$, are inversely proportional to the variance in each study:

$$w_i = \frac{1}{v_i}$$

The estimate of the variance of the pooled estimate $\bar{T}_{\cdot}$ is given by the reciprocal of the sum of the weights:

$$\text{var}(\bar{T}_{\cdot}) = \frac{1}{\sum_{i=1}^{k} w_i}$$

Finally, if $\bar{T}_{\cdot}$ is assumed to be normally distributed, then the 95% confidence intervals for the population effect θ, is given by:

$$\bar{T}_{\cdot} \pm 1.96 \times \sqrt{\frac{1}{\sum_{i=1}^{k} w_i}}$$

Applying these formulae, your next task is to calculate the following:

(i) In column F (range F56:F65), calculate the weights assigned to each individual study
(ii) In cell F67, calculate the sum of the weights across studies.

(iii) In column G (range G56:G65), calculate the products $w_i T_i$ (effect size multiplied by weight) for each individual study.
(iv) In cell G67, calculate the sum of the products $w_i T_i$ across studies.

4. Estimating pooled statistics from a fixed effect model.

The final step is to estimate the pooled estimate of treatment effect.

Applying the previous formulae, calculate the following

(i) In cell L56, estimate the pooled (population) estimate for LN(OR)
(ii) In cell L57:58, estimate the corresponding variance and SE for LN(OR)
(iii) In cells L59:60, estimate the 95% confidence intervals for LN(OR)
(iv) In cells L63:65, transform the relevant estimates onto the natural scale for ease of interpretation.

5. Estimating the between study variance for a random effects model

The fixed effect model applied in the previous example assumes that all studies are estimating the same underlying effect size (i.e. $\theta_1 = \theta_2 \ldots = \theta_k = \theta$). The associated estimates reflect the random variation within each trial but do not reflect the potential heterogeneity *between* trials. There are a number of sources that may cause heterogeneity e.g. variation in the interventions themselves or overall management (e.g. dosing, timing of administration, differences in settings etc) and variation in the reporting of outcomes themselves (e.g. follow up times, definition of endpoints etc).

When the heterogeneity between trials exceeds that expected by chance, applying a fixed effect model will under-estimate the associated uncertainty surrounding the effect size estimates. Although statistical tests exist (e.g. standard χ^2 test) to formally assess the existence of heterogeneity, the subsequent interpretation of these tests can often be difficult (e.g. low power due to small number of trials). Instead, estimating the magnitude of the between-study variation has been proposed as a more informative approach.

The random effects model assumes that the studies are estimating different effect sizes and incorporates the additional variation due to this assumption. These effect sizes are assumed to vary at random and the distribution of these effects is assumed to be normally distributed.

In algebraic form, T_i is an estimate of effect size and θ_i is the true effect in the ith study:

$$T_i = \theta_{i+} e_i$$

where e_i is the error with which T_i estimates θ_i , and

$$\text{Var}\,(T_i) = \tau_\theta^{2} + v_i$$

where τ_θ^2 is the random effects variance (variance between studies) and v_i is the variance due to sampling error in the *i*th study (variance within study)

The approach employed within a random effects model is to apportion the observed variance into the two elements: the within and between study variance. Both elements are then used to estimate the subsequent weights applied when combining the individual study results.

In order to estimate the two separate elements, a series of steps are required. The approach employed will firstly require you to compute the total variance and then determine the within-studies variance (NB: you have already estimated the within-study variance previously). The difference between these two values is equal to the between-study variance, referred to as tau-squared (τ^2).

The first computational step is to estimate the total variance using the *Q* statistic. This is defined as:

$$Q = \sum_{i=1}^{k} w_i (T_i - \overline{T}_\cdot)^2$$

The following formula is equivalent to the one above but is more convenient for computation purposes:

$$Q = \sum_{i=1}^{k} w_i T_i^{\,2} - \frac{(\sum_{i=1}^{k} w_i T_i)^2}{\sum_{i=1}^{k} w_i}$$

In order to estimate *Q*, your first task is to calculate the following

(i) In column I (range I76:I85), calculate the products $w_i T_i^2$ (effect size^2 multiplied by weight) for each individual study.
(ii) Estimate the sum of these products in cell I87.
(iii) In cell E89 compute Q (*Hint: you have just calculated the first part of the equation in cell I87. The second part can be estimated from cells F87 and G87*).

As previously outlined, *Q* represents the total variance. Your next task is to estimate the separate variance elements which contribute to the total variance. The first step is to compare the value of *Q* to the degrees of freedom (*df=[k-1], where k = the number of studies*) for the meta analysis. If all the variance was due to within-study error, the expected value of *Q* would equal *df*. However, when Q exceeds the *df*, then the excess variance can be used to estimate tau-squared: It then follows that the between-study variance, is:

$\hat{\tau}^2 = 0$ if $Q \leq k - 1$ (Equation 1)

$$\hat{\tau}^2 = \left(Q-(k-1)\right)/U \text{ if } Q > k-1 \text{ (Equation 2)}$$

where:

$$U = \sum_{i=1}^{k} w_i - \frac{\sum_{i=1}^{k} w_i^2}{\sum_{i=1}^{k} w_i} \text{ (Equation 3)}$$

The numerator represents the excess (observed minus expected) variance. The denominator (*U*) is simply a scaling factor which ensures that the estimate of tau-squared is estimated in the same form as the within-study variance.

In order to estimate tau-squared, calculate the following:

(i) In cell E90, calculate the degrees of freedom (*df*)
(ii) In cell E91, calculate the numerator for tau-squared (Equation 2)
(iii) In column J (range J76:J85) calculate w_i^2 (i.e. weight^2) for each individual study and then estimate the sum in cell J87.
(iv) In cell E92, calculate the denominator for tau-squared (Equation 3)
(v) Finally, in cell E93, estimate tau-squared.

6. Estimating the weights for a random effects model (allowing for within *and* between study variance).

Within the fixed effects model estimate previously, the weights attached to each individual study were inversely proportional to the observed variance ($1/v_i$) in each study. Within the random effects model, these weights are now inversely proportional to the sum of the within and between study variances. That is:

$$w_i^* = \left[\frac{1}{(1/w_i) + \bar{\tau}^2}\right]$$

Your next task is to estimate these weights:

(i) In column F (range F100:F109) enter the value for tau-squared. Remember the same estimate for tau-squared is applied to all studies.
(ii) In column G (range G100:G109) calculate the total variance for each individual study – combining the within and between study variance estimates.
(iii) In column I (range I100:I109) calculate the weights for each individual study
(iv) In cell I111, calculate the sum of weights.

7. Estimating pooled statistics from a random effects model.

You have now undertaken all the steps needed to estimate the pooled statistics from a random effects model.

The combined treatment effect can now be calculated by:

$$\overline{T}_{.RND} = \frac{\sum_{i=1}^{k} w_i^* T_i}{\sum_{i=1}^{k} w_i^*}$$

and the variance of this estimate by:

$$\text{var}\left(\overline{T}_{.RND}\right) = \frac{1}{\sum_{i=1}^{k} w_i^*}$$

Finally, if $\overline{T}_{.RND}$ is assumed to be normally distributed, then the 95% confidence intervals for the random effect, is given by:

$$\overline{T}_{.RND} \pm 1.96 * \sqrt{\frac{1}{\sum_{i=1}^{k} w_i^*}}$$

Applying these formulae, calculate the following

(i) In column J (range J100:J109) calculate the products $w_i^* T_i$ (effect size multiplied by weight) for each individual study.
(ii) Estimate the sum of these products in cell J111.
(iii) In cell M100, estimate the pooled (population) estimate for LN(OR)
(iv) In cell M101:M102, estimate the corresponding variance and SE
(v) In cells M103:M104, estimate the 95% confidence intervals
(vi) In cells M107:M109, transform the relevant estimates onto the natural scale for ease of interpretation.

8. Compare results for alternative approaches.

Finally, it is helpful to compare the results of the fixed and random effects model in more detail to reinforce your understanding of the approaches.

(i) Firstly, report the mean, SE and 95% confidence intervals for the OR on the natural scale
(ii) Note that the confidence interval for the random effects is wider than that of the fixed effect. The wider interval is due to the additional between study variation that is incorporated within the random effects model. Although the interpretation of the separate models is similar and both are

statistically significant, the additional uncertainty surrounding the random effects model could impact on the overall decision uncertainty.

(iii) Finally it is helpful to explore the contribution made by individual studies to the combined effect using the different approaches. Begin by entering the weights applied to each individual study using a fixed and random effects model into columns H (range H23:H32) and J (range J23:J32)

(iv) In columns L (range L23:L32) and N (range N23:N32) estimate the % contribution each study makes to the overall sum of weights. Compare the different % contributions for individual studies. Also, examine the sample sizes for the different studies reported in column P. Note that the weighting of larger studies has been reduced (and vice-versa for the smaller studies) in the random effects model. This finding generally holds for all analyses and greater (smaller) differences between the two approaches will arise when the between study variance is high (low).

Note

In the solution file you will find an additional worksheet <*Validation*>. This reports a validation of the results using a commercially available software package (Comprehensive Meta Analysis www.meta-analysis.com).