Meta-Analysis with R
Fixed Effect and Random Effects Meta-Analysis

Qi Guo

Department of Mathematical Sciences
The University of Texas at Dallas

September, 15 2020

Introduction

Meta Analysis

Meta-analysis is a quantitative, formal, epidemiological study design used to systematically assess the results of previous research to derive conclusions about that body of research. Typically, but not necessarily, the study is based on randomized, controlled clinical trials.

- There are two main methods of meta-analysis, fixed effect model and random effects model.
- For both models the inverse variance method is introduced for estimation.
- All outcomes for introduce both fixed effect and random effects model are continuous.

Effect Measures for Continuous Outcomes

- Meta-analysis typically focuses on comparing two interventions, which we refer to as experimental and control.
- We denoted $\hat{\mu}_{ek}$, s^2_{ek},n_{ek} and $\hat{\mu}_{ck}$, s^2_{ck},n_{ck} denote the observed mean, standard deviation and sample size for study k, $k = 1, \cdots, K$.
- Two different types of effect measures for continuous outcomes: mean difference and standardised mean difference.
  1. The mean difference is typically used when all studies report the outcome on the same scale.
  2. The standardised mean difference can be used when studies measure the outcome on different scales.

Mean Difference

- For study k, the estimated mean difference is:

$$\hat{\mu}_k = \hat{\mu}_{ek} - \hat{\mu}_{ck}$$

- Variance estimate:

$$\hat{\text{Var}}(\hat{\mu}_k) = \frac{s_{ek}^2}{n_{ek}} + \frac{s_{ck}^2}{n_{ck}}$$

- An approximate two-sided $(1-\alpha)$ confidence interval for the mean difference is given by:

$$(\hat{\mu}_{ek} - \hat{\mu}_{ck}) \pm z_{1-\frac{\alpha}{2}} \sqrt{\frac{s_{ek}^2}{n_{ek}} + \frac{s_{ck}^2}{n_{ck}}}$$

Standardised Mean Difference

- A version of the standardised mean difference which is called Hedges's g based on the pooled sample variance. This standardised mean difference for study k is calculated as:

$$\hat{g}_k = (1 - \frac{3}{4n_k - 9}) \frac{\hat{\mu}_{ek} - \hat{\mu}_{ck}}{\sqrt{((n_{ek} - 1)s_{ek}^2 + (n_{ck} - 1)s_{ck}^2)/(n_k - 2)}}$$

  where $n_k = n_{ek} + n_{ck}$ and the factor $1 - 3/(4n_k - 9)$ corrects for the bias in the estimated standard error.
- Variance estimate:

$$\hat{\text{Var}}(\hat{g}_k) = \frac{n_k}{n_{ek} \cdot n_{ck}} + \frac{\hat{g}_k^2}{2(n_k - 3.94)}$$

- An approximate two-sided $(1 - \alpha)$ confidence interval for the mean difference is given by:

$$\hat{g}_k \pm z_{1-\frac{\alpha}{2}} S.E.(\hat{g}_k)$$

R Example

- Install the ‘meta‘ package in R. The variable names are:

Table 2.1 Variable names in R datasets for meta-analyses of continuous responses

Variable name	Notation	Description
`author`		First author of study
`year`		Year study published (if available)
`Ne`	n_e	Number of patients in the experimental (i.e. active) treatment arm
`Me`	$\hat{\mu}_e$	Mean response in the experimental treatment arm
`Se`	s_e	Standard deviation of the response in the experimental treatment arm
`Nc`	n_c	Number of patients in the control (often equivalent to placebo) arm
`Mc`	$\hat{\mu}_c$	Mean response in the control arm
`Sc`	s_c	Standard deviation of the response in the control arm

R Example

- The data:

```
> # 1. Read in the data:
> data2 <- read.csv("dataset02.csv")
> # 2. As usual, to view an object, type its name:
> data2
                author  Ne    Me    Se Nc    Mc    Sc
1    Blashki(75%150)  13  6.40  5.40 18 11.40  9.60
2     Hormazabal(86)  17 11.00  8.20 16 19.00  8.20
3   Jacobson(75-100)  10 17.50  8.80  6 23.00  8.80
4        Jenkins(75)   7 12.30  9.90  7 20.00 10.50
5     Lecrubier(100)  73 15.70 10.60 73 18.70 10.60
6        Murphy(100)  26  8.50 11.00 28 14.50 11.00
7          Nandi(97)  17 25.50 24.00 10 53.20 11.20
8      Petracca(100)  11  6.20  7.60 10 10.00  7.60
9       Philipp(100) 105 -8.10  3.90 46 -8.50  5.20
10     Rampello(100)  22 13.40  2.30 19 19.70  1.30
11       Reifler(83)  13 12.50  7.60 15 12.50  7.60
12       Rickels(70)  29  1.99  0.77 39  2.54  0.77
13     Robertson(75)  13 11.00  8.20 13 15.00  8.20
14      Rouillon(98)  78 15.80  6.80 71 17.10  7.20
15           Tan(70)  23 -8.50  8.60 23 -8.30  6.00
16 Tetreault(50-100)  11 51.90 18.50 11 74.30 18.50
17      Thompson(75)  11  8.00  8.10 18 10.00  9.70
> # 3. Calculate total sample sizes
> summary(data2$Ne+data2$Nc)
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
  14.00   26.00   31.00   53.06   54.00  151.00
```

R Example

- The R function by using the ‘SMD‘ method:

```
> print(metacont(Ne, Me, Se, Nc, Mc, Sc, sm="SMD",
+                data=data2, subset=1), digits=2)
  SMD         95%-CI     z  p-value
 -0.6 [-1.33; 0.13] -1.61   0.1083

Details:
- Inverse variance method
```

Fixed Effect Model

- The fixed effect model assumes that the estimated effects from the component studies in a meta-analysis come from a single homogeneous population.
- Let $k = 1, \cdots, K$ index study, $\hat{(}\theta_k)$ denote the intervention effect estimate from study k, and θ denote the intervention effect in the population, which we wish to estimate. Denote by $\hat{\sigma}_k^2$ the sample estimate of $\mathrm{Var}(\hat{\theta}_k)$.
- The fixed effect model is:

$$\hat{\theta}_k = \theta + \sigma_k \epsilon_k, \epsilon_k \sim N(0,1) i.i.d$$

Fixed Effect Model

- Consider the fixed effect estimate of θ, denoted by $\hat{\theta}_F$. Given estimates $(\hat{\theta}_k, \hat{\sigma}_k), k = 1, \cdots, K$, the maximum-likelihood estimate under model is:

$$\hat{\theta}_F = \frac{\sum_{k=1}^{K} \hat{\theta}_k / \hat{\sigma}_k^2}{\sum_{k=1}^{K} 1/\hat{\sigma}_k^2} = \frac{\sum_{k=1}^{K} w_k \hat{\theta}_k}{\sum_{k=1}^{K} w_k}$$

- Accordingly, $\hat{\theta}_F$ is a weighted average of the individual effect estimates $\hat{\theta}_k$ with weights $w_k = 1/\hat{\sigma}_k^2$. Therefore, this method is called the inverse variance method.

Fixed Effect Model

- The variance of $\hat{\sigma}_F$ is estimated by:

$$\hat{\text{Var}}(\theta_F) = \frac{1}{\sum_{k=1}^{K} w_k}$$

- A $(1-\alpha)$ confidence interval for $\hat{\theta}_F$ can be calculated by:

$$\hat{\theta}_F \pm z_{1-\frac{\alpha}{2}} S.E.(\hat{\theta}_F)$$

Random Effects Model

- The random effects model seeks to account for the fact that the study effect estimates $\hat{\theta}_k$ are often more variable than assumed in the fixed effect model. Under the random effects model.

$$\hat{\theta}_k = \theta + \mu_k + \sigma_k \epsilon_k, \quad \epsilon_k \sim N(0,1) i.i.d \quad \mu_k \sim N(0, \tau^2) i.i.d$$

  where the μ's and τ's are independent.
- A key assumption of the random effects model is that the μ_k we see in our data are not intrinsically associated with study k.
- A number of authors have argued that, as small studies are more susceptible to bias, the fixed effect estimate is (almost) always preferable.

Random Effects Model

- Define

$$Q = \sum_{k=1}^{K} w_k(\hat{\theta}_k - \hat{\theta}_F)^2$$

the weighted sum of squares about the fixed effect estimate with $w_k = 1/\hat{\sigma}_k^2$. This is usually referred to as either the homogeneity test statistic or the heterogeneity statistic. Then define

$$S = \sum_{k=1}^{K} w_k - \frac{\sum_{k=1}^{K} w_k^2}{\sum_{k=1}^{K} w_k}$$

If $Q < (K-1)$, then $\hat{\tau}^2$ is set to 0 and the random effects estimate $\hat{\theta}_R$ is set equal to the fixed effect estimate $\hat{\theta}_F$.

Random Effects Model

- Otherwise, the DerSimonian-Laird estimator of the between-study variance is defined as

$$\hat{\tau}^2 = \frac{Q - (K-1)}{S}$$

and the random effects estimate and its variance are given by

$$\hat{\theta}_R = \frac{\sum_{k=1}^{K} w_k^* \hat{\theta}_k}{\sum_{k=1}^{K} w_k^*}$$

$$\hat{\mathrm{Var}}(\hat{\theta}_R) = \frac{1}{\sum_{k=1}^{K} w_k^*}$$

with weights $w_k^* = 1/(\hat{\sigma}_k^2 + \hat{\tau}^2)$

Random Effects Model

- A $(1-\alpha)$ confidence interval for $\hat{\theta}_R$ can be calculated by

$$\hat{\theta}_R \pm z_{1-\frac{\alpha}{2}} S.E.(\hat{\theta}_R)$$

these formulas are used for the standardised mean difference.

- The method used to estimate the between-study variance τ^2 may have a large impact on the weighting of studies. The default is DerSimonian-Laird estimator(method.tau = "DL")

R Example

- The meta-analysis can be conducted using the “metacont” function:

```
> mc2 <- metacont(Ne, Me, Se, Nc, Mc, Sc, sm="SMD",
+                 data=data2)
```

```
> print(summary(mc2), digits=2)
Number of studies combined: k=17

                         SMD          95%-CI     z  p-value
Fixed effect model   -0.39 [-0.53; -0.25] -5.61 < 0.0001
Random effects model -0.59 [-0.87; -0.30] -4.04 < 0.0001

Quantifying heterogeneity:
tau^2 = 0.2309; H = 1.91 [1.5; 2.43]; I^2 = 72.5% [55.4%; 83.1%]

Test of heterogeneity:
     Q d.f.  p-value
 58.27   16 < 0.0001

Details on meta-analytical method:
- Inverse variance method
- DerSimonian-Laird estimator for tau^2
```

Prediction Intervals

- A $(1-\alpha)$ prediction interval can be calculated as

$$\hat{\theta}_R \pm t_{K-2,1-\frac{\alpha}{2}} \sqrt{\hat{\text{Var}}(\hat{\theta}_R) + \hat{\tau}^2}$$

where we include the estimate of τ in the variance, and $t_{K-2,1-\frac{\alpha}{2}}$ denotes the $1-\frac{\alpha}{2}$ quantile of the $t-$distribution with $K-2$ degrees of freedom.

```
> print(summary(mc1, prediction=TRUE), digits=2)
Number of studies combined: k=17

                          MD            95%-CI      z  p-value
Fixed effect model   -15.51 [-17.84; -13.18] -13.05 < 0.0001
Random effects model -15.64 [-18.14; -13.15] -12.30 < 0.0001
Prediction interval         [-19.94; -11.35]
*** Output truncated ***
```

Tests and Measures of Heterogeneity

- The most commonly used measures are calculated by the "metacont" function.
- The first Q, is the weighted sum of squares about the fixed effect estimate $\hat{\theta}_F$. Large values of Q indicate greater heterogeneity between the individual studies in a meta-analysis.
- Greater values of the between-study heterogeneity τ^2. Under the null hypothesis that $\tau^2 = 0$,

$$Q \sim \chi^2_{K-1}$$

and this can be used to calculate a $p-$value against this null hypothesis.

Tests and Measures of Heterogeneity

- Two related statistics are commonly quoted:

$$H^2 = \frac{Q}{K-1}$$

$$I^2 = (H^2 - 1)/H^2 \quad if \quad Q > (K-1) \quad 0 \quad o.w$$

- Under the null hypothesis that $\tau^2 = 0$, Q has mean $K-1$, so H^2 has mean 1; again large values of H^2 indicate greater heterogeneity. I^2 is a scaled version of H^2, lying between 0 and 1(or 0% and 100%). Again, large values are consistent with heterogeneity, although for given τ^2, values of I^2 will increase as the sample sizes of component trials increase.