The Equal-Effect and Random-Effects Model

The Random-Effects Model

- The EE-Model is quite straightforward, but **does it adequately reflect reality?**
- According to the EEM, if we were able to calculate the effect of each study without sampling error, each would have absolutely the same true effect size
- Often, this is too simplistic: there may be countless reasons that would make us expect that even the true effect is not absolutely the same in each study
  - E.g., differences in the population, interventions delivery, outcome measurement, etc.
- Thus, there may be countless “perturbations” that lead to somewhat higher or lower true effects that are difficult to determine a priori

→ We call this **between-study heterogeneity** of true effects

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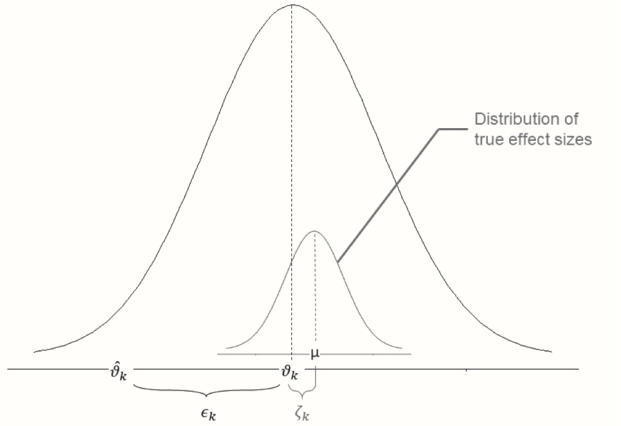
The REM can be seen as a „multilevel“ model:

- Level 1: $\hat{\theta}_k = \theta_k + \varepsilon_k$ or $\hat{\theta}_k \sim \mathcal{N}(\theta_k, \sigma_k^2)$
- Level 2: $\theta_k = \mu + \zeta_k$ or $\theta_k \sim \mathcal{N}(\mu, \tau^2)$*

By plugging the definition of θ_k into the first equation, we can also obtain a single formula (the **“marginal form”**):

$\theta_k = \mu + \zeta_k + \varepsilon_k$ or $\hat{\theta}_k \mid \mu, \tau^2, \sigma_k^2 \sim \mathcal{N}(\mu, \sigma_k^2 + \tau^2)$*

The **main challenge** is to **estimate** the variance of the distribution of true effect sizes, the **between-study heterogeneity variance** τ^2.



*assuming normality

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- Still, the most frequently used estimator is the one by DerSimonian and Laird, since it is implemented in software that has commonly been used by meta-analysts in the past, such as **RevMan** (a program developed by Cochrane) or **Comprehensive Meta-Analysis**.
- **But**: it has been found that this estimator can be biased, particularly when the number of studies is small and heterogeneity is high (Hartung 1999; Hartung and Knapp 2001a, 2001b; Follmann and Proschan 1999; Makambi 2004)
- This is problematic because meta-analyses often have few studies and high heterogeneity!
- Based on present evidence, **REML may be the best starting point for most meta-analyses**; especially when pooling continuous outcome effect sizes (Hedges' g, SMDs; Langan et al., 2019; Veroniki et al., 2016)

Common estimators of τ^2:

- **DerSimonian-Laird** ("DL") estimator (DerSimonian and Laird 1986)
- **Restricted Maximum Likelihood** ("REML"; Viechtbauer 2005)
- **Paule-Mandel** ("PM") procedure (Paule and Mandel 1982)
- **Empirical Bayes** ("EB") procedure (Sidik and Jonkman 2019)
- **Sidik-Jonkman** ("SJ") estimator (Sidik and Jonkman 2005)

The Equal-Effect and Random-Effects Model

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Once $\hat{\tau}^2$ is known, we can calculate random-effects weights w_k^* for each study. Then, inverse-variance pooling is used in the same way that we did in the EEM:

$$w_k^* = \frac{1}{\mathrm{SE}_k^2 + \tau^2} \quad \text{so that} \quad \hat{\theta} = \frac{\sum_{k=1}^{K} \hat{\theta}_k w_k^*}{\sum_{k=1}^{K} w_k^*}.$$

Statistical software is typically required to estimate τ^2.

Estimators fall into two categories:

- DerSimonian-Laird and Sidik-Jonkman estimator: based on closed-form expressions (i.e., τ^2 can be directly calculated using a formula)
- The (restricted) maximum likelihood, Paule-Mandel and empirical Bayes estimator find the optimal value of τ^2 through an iterative algorithm.

The Equal-Effect and Random-Effects Model

Which Model Should I Use?

- In practice, is it **very uncommon** to find studies that is **perfectly homogeneous**.
- In many fields, including health science, it is **conventional to always use a random-effects** model, since some degree of between-study heterogeneity can virtually always be anticipated.
- A fixed-effect model may only be used when we could **not detect any between-study heterogeneity** (we will discuss how this is done in Chapter 5) and when we have **very good reasons to assume that the true effect is fixed**.
  - For example: exact replications of a study, meta-analysis of study subsets

The Equal-Effect and Random-Effects Model

Which Model Should I Use?

- However, **this is not undisputed**. The random-effects model **pays more attention to small studies** when calculating the overall effect of a meta-analysis. Yet, small studies in particular are **often fraught with biases**
- This is why some have argued that the **fixed-effect model is (sometimes) preferable** (Poole and Greenland 1999; Furukawa, McGuire, and Barbui 2003).
- It also depends on whether we want to make **conditional** (fixed-effect**s**) or **unconditional inferences** (random-effects model)

$$\theta_k = \mu + \zeta_k + \varepsilon_k$$

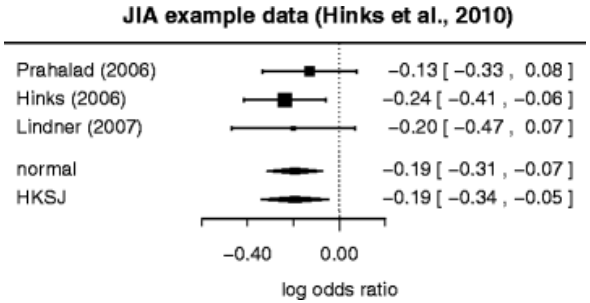
$$\theta_k = \mu + \varepsilon_k$$

The EEM is a special case of the REM in which τ^2 is (by definition) zero, so that $\zeta_k = 0$ falls out of the equation!

The Equal-Effect and Random-Effects Model

The Knapp-Hartung Adjustment

- In addition to selecting the τ^2 estimator, we also must decide if we want to apply so-called Knapp-Hartung adjustments (Knapp and Hartung 2003; Sidik and Jonkman 2002).
- These adjustments affect the way the standard error (and thus confidence intervals) of our pooled effect size $\hat{\theta}$ is calculated.
- These adjustments control for the uncertainty in our estimate of the between-study heterogeneity. Significance tests of the pooled effect usually assume a normal distribution (so-called **Wald-type tests**), while the Knapp-Hartung method is based on a t-distribution.
- Knapp-Hartung adjustments **can only be used in random-effects models**, and usually cause the confidence intervals of the pooled effect to become slightly larger.
- Applying a Knapp-Hartung adjustment is usually sensible **to control for false positives** (IntHout, Ioannidis, and Borm 2014; Langan et al. 2019)
- Also known as the **Hartung-Knapp-Sidik-Jonkman method (HKSJ)**



Röver, Knapp & Friede, 2015 (simplified)

The Forest Plot