Basic Meta-Analysis Models

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Example

Example: Meier (1953) (reanalyzed in Jordan and Krishnamoorthy, 1996) considered four experiments about the percentage of albumin in plasma protein in human subjects

Percentage of albumin in plasma protein

Experiment	n_i	Mean	Variance
A	12	62.3	12.986
B	15	60.3	7.840
C	7	59.5	33.433
D	16	61.5	18.513

Common Mean Problem

- Let us consider k independent normal populations where the ith population follows a normal distribution with mean $\mu \in I\!R$ and variance $\sigma_i^2 > 0$, $i = 1, \ldots, k$.

- Let $\bar{Y}_i$ denote the sample mean in the ith population, S_i^2 the sample variance, and n_i the sample size, $i = 1, \ldots, k$.

- Then, we have

$$\bar{Y}_i \sim N\left(\mu\,,\,\frac{\sigma_i^2}{n_i}\right) \quad \text{and} \quad \frac{(n_i-1)\,S_i^2}{\sigma_i^2} \sim \chi^2_{n_i-1},\ i = 1, \ldots, k,$$

  and the statistics are all mutually independent.
  Note that $(\bar{Y}_i, S_i^2, i = 1, \ldots, k)$ is minimal sufficient for $(\mu, \sigma_1^2, \ldots, \sigma_k^2)$ even though it is not complete.

Estimates of μ

- If the population variances $\sigma_1^2, \ldots, \sigma_k^2$ are completely known, the maximum likelihood estimator of μ is given by

$$\hat{\mu} = \frac{\sum_{i=1}^k \frac{n_i}{\sigma_i^2}\,\bar{Y}_i}{\sum_{j=1}^k \frac{n_j}{\sigma_j^2}}.$$

- The above estimator is also the minimum variance unbiased estimator under normality as well as the best linear unbiased estimator without normality for estimating μ.

- The variance of $\hat{\mu}$ is given by $\quad \mathrm{Var}\,(\hat{\mu}) = \dfrac{1}{\sum_{i=1}^k \frac{n_i}{\sigma_i^2}}.$

Estimates of μ

- Graybill-Deal (1959) estimator of μ is given as

$$\hat{\mu}_{GD} = \frac{\sum_{i=1}^{k} \frac{n_i}{S_i^2} \bar{Y}_i}{\sum_{j=1}^{k} \frac{n_j}{S_j^2}}.$$

  Clearly, $\hat{\mu}_{GD}$ is an unbiased estimator of the common mean μ.

- For calculating the variance of $\hat{\mu}_{GD}$, it holds

$$\begin{aligned} \mathsf{Var}\left(\hat{\mu}_{GD}\right) &= \mathsf{E}\left[\mathsf{Var}\left(\hat{\mu}_{GD}|S_1,\ldots,S_k\right)\right] + \mathsf{Var}\left[\mathsf{E}\left(\hat{\mu}_{GD}|S_1,\ldots,S_k\right)\right] \\ &= \mathsf{E}\left[\left(\sum_{i=1}^{k} \frac{n_i\,\sigma_i^2}{S_i^4}\right) \Big/ \left(\sum_{i=1}^{k} \frac{n_i}{S_i^2}\right)^2\right]. \end{aligned}$$

Estimates of μ

Meier (1953) derived a first order approximation of the variance of $\hat{\mu}_{GD}$ as

$$\mathsf{Var}\left(\hat{\mu}_{GD}\right) = \frac{1}{\sum_{i=1}^{k} \frac{n_i}{\sigma_i^2}} \left[1 + 2\sum_{i=1}^{k} \frac{1}{n_i - 1}\, c_i\,(1-c_i) + O\left(\sum_{i=1}^{k} \frac{1}{(n_i-1)^2}\right)\right]$$

with

$$c_i = \frac{n_i \;/\; \sigma_i^2}{\sum_{j=1}^{k} n_j \;/\; \sigma_j^2},\ \ i = 1,\ldots,k.$$

Estimates of μ

- Is $\hat{\mu}_{GD}$ a uniformly better unbiased estimator of μ than is each $\bar{Y}_i$, $i = 1,\ldots,k$? Is Var$(\hat{\mu}_{GD}) \leq \sigma_i^2/n_i$, $i = 1,\ldots,k$ for all $\sigma_1^2,\ldots,\sigma_k^2$?

- Graybill and Deal (1959) showed for $k = 2$ that $\hat{\mu}_{GD}$ is a uniformly better unbiased estimator of μ than is $\bar{Y}_1$ or $\bar{Y}_2$ if and only if n_1 and n_2 are each greater than 10.

- Norwood and Hinkelmann (1977): $\hat{\mu}_{GD}$ is a uniformly better estimator of μ than each $\bar{Y}_i$ if and only if each sample size n_i, $i = 1,\ldots,k > 2$, is greater than 10 or $n_i = 10$ for some i and n_j greater than 18 for all $j \neq i$.

Variance Estimates

Sinha (1985) derived an unbiased estimator of the variance of $\hat{\mu}_{GD}$ that is a convergent series. A first order approximation of this estimator is

$$\widehat{\mathsf{Var}}_{(1)}\left(\hat{\mu}_{GD}\right) = \frac{1}{\sum_{i=1}^{k} \frac{n_i}{S_i^2}} \left[1 + \sum_{i=1}^{k} \frac{4}{n_i+1} \left(\frac{n_i \;/\; S_i^2}{\sum_{j=1}^{k} n_j \;/\; S_j^2} - \frac{n_i^2 \;/\; S_i^4}{\left(\sum_{j=1}^{k} n_j \;/\; S_j^2\right)^2}\right)\right].$$

This estimator is comparable to Meier's (1953) approximate estimator:

$$\widehat{\mathsf{Var}}_{(2)}\left(\hat{\mu}_{GD}\right) = \frac{1}{\sum_{i=1}^{k} \frac{n_i}{S_i^2}} \left[1 + \sum_{i=1}^{k} \frac{4}{n_i-1} \left(\frac{n_i \;/\; S_i^2}{\sum_{j=1}^{k} n_j \;/\; S_j^2} - \frac{n_i^2 \;/\; S_i^4}{\left(\sum_{j=1}^{k} n_j \;/\; S_j^2\right)^2}\right)\right].$$

Variance Estimates

Two further estimators of the variance of $\hat{\mu}_{GD}$ which can be easily adapted for later purposes.

- The "classical" meta-analysis variance estimator

$$\widehat{\mathsf{Var}}_{(3)}\left(\hat{\mu}_{GD}\right) = \frac{1}{\sum_{i=1}^{k} \frac{n_i}{S_i^2}}.$$

- Hartung (1999): approximate variance estimator

$$\widehat{\mathsf{Var}}_{(4)}\left(\hat{\mu}_{GD}\right) = \frac{1}{k-1} \sum_{i=1}^{k} \frac{n_i \ / \ S_i^2}{\sum_{j=1}^{k} n_j \ / \ S_j^2} \left(\bar{Y}_i - \hat{\mu}_{GD}\right)^2.$$

Homogeneity Testing

- Crucial assumption: Common mean in ALL the studies or populations
- Homogeneity hypothesis:

$$H_0 : \mu_1 = \cdots = \mu_k$$

- Assuming equal error variances: ANOVA F-test
- Unequal error variances: modifications of F-test proposed by Brown and Forsythe (1974), Mehrotra (1997), Asiribo and Gurland (1990).

Homogeneity Testing

- Cochran (1937) suggested the test statistic

$$Q_C = \sum_{i=1}^{k} \hat{v}_i \left(\bar{Y}_{i.} - \sum_{j=1}^{k} h_j \, \bar{Y}_{j.}\right)^2,$$

where $\hat{v}_i = n_i/S_i^2$, $h_i = \hat{v}_i / \sum_{i=1}^{k} \hat{v}_i$.

- Reject H_0 at level α if $Q_C > \chi^2_{k-1;\alpha}$.
- Cochran's test is often used as the standard test for testing homogeneity of effect sizes in meta-analysis.
- In the common mean problem, Cochran's test can be very liberal, see Hartung, Argac, and Makambi (2002).

Homogeneity Testing

- Welch (1951):

$$Q_W = \frac{Q_C}{(k-1) + 2\,\frac{k-2}{k+1} \sum_{i=1}^{k} \frac{1}{n_i - 1} (1 - h_i)^2}.$$

- Under H_0, $Q_W \overset{approx.}{\sim} F_{k-1,\nu_g}$

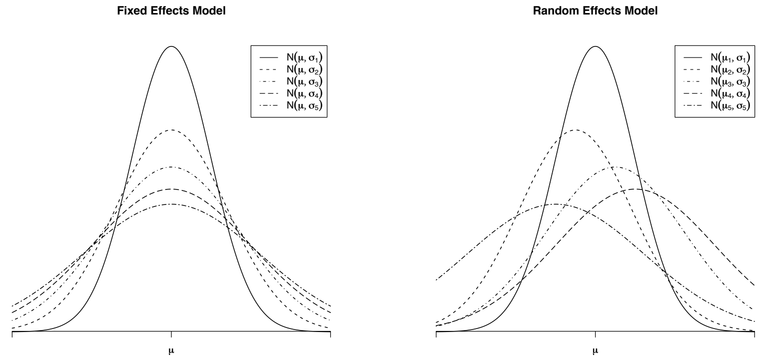
$$\nu_g = \frac{(k^2-1)/3}{\sum_{i=1}^{k} \frac{1}{n_i - 1} \, (1-h_i)^2}.$$

- This test rejects H_0 at level α if $Q_W > F_{k-1,\nu_g;\alpha}$.

One-Way Random Effects Model

- 1.) What do we do when the true means may differ from study to study?
- 2.) In conducting several studies, we have restriction in randomization. Is there any study-by-subject interaction present?
- Yes in 1.) or 2.) $\rightarrow$ one-way random effects model

One-Way Random Effects Model



One-Way Random Effects Model

- Let $\bar{Y}_i$ denote the sample mean in the ith population, S_i^2 the sample variance, and n_i the sample size, $i = 1, \ldots, k$. Then, we have

$$\bar{Y}_i \sim N\left(\mu \ , \ \tau^2 + \frac{\sigma_i^2}{n_i}\right) \quad \text{and} \quad \frac{(n_i - 1)\ S_i^2}{\sigma_i^2} \sim \chi^2_{n_i - 1}, \ i = 1, \ldots, k,$$

  where $\tau^2 \geq 0$ stands for the variability between the populations and is also called the heterogeneity parameter.

- The expected value μ is generally called overall mean.
- Note that $(\bar{Y}_i, S_i^2, i = 1, \ldots, k)$ are minimally sufficient statistics in the one-way random effects model.

Estimates of μ

- If the variances τ^2 and σ_i^2, $i = 1, \ldots, k$, are completely known, the maximum likelihood estimator for μ is given as

$$\hat{\mu} = \frac{\sum_{i=1}^{k} (\tau^2 + \sigma_i^2/n_i)^{-1}\ \bar{Y}_i}{\sum_{i=1}^{k} (\tau^2 + \sigma_i^2/n_i)^{-1}}$$

- The above estimator is also the minimum variance unbiased estimator under normality as well as the best linear unbiased estimator without normality for estimating μ in one-way random effects model.
- The variance of $\hat{\mu}$ is given by

$$\text{Var}(\hat{\mu}) = \left[\sum_{i=1}^{k} (\tau^2 + \sigma_i^2/n_i)^{-1}\right]^{-1}$$

Estimates of μ

- In practice, the within-population variances σ_i^2, $i = 1, \ldots, k$, can be unbiasedly estimated using the sample variances S_i^2.
- The heterogeneity parameter τ^2, however, has to be estimated using the sufficient statistics $(\bar{Y}_i, S_i^2)$, $i = 1, \ldots, k$.

Estimates of τ^2

- ANOVA-type estimator (see Rao, Kaplan, and Cochran, 1981):

$$\hat{\tau}_{AN}^2 = \frac{1}{k-1} \sum_{i=1}^{k} \left(\bar{Y}_i - \bar{Y}\right)^2 - \frac{1}{k} \sum_{i=1}^{k} \frac{S_i^2}{n_i}$$

  with $\bar{Y} = \sum_{i=1}^{k} \bar{Y}_i / k$.

- The estimator τ_{AN}^2 may lead to a negative estimate of τ^2, and hence it is used by enforcing non-negativity in practice, i.e., $\max\{0, \hat{\tau}_{AN}^2\}$.
- In meta-analysis, known as Hedges estimator.

Estimates of τ^2

- A widely used estimator for τ^2: DerSimonian and Laird (1986) estimator

$$\hat{\tau}_{DSL}^2 = \frac{Q_C - (k-1)}{\sum_{i=1}^{k} \hat{v}_i - \sum_{i=1}^{k} \hat{v}_i^2 / \sum_{i=1}^{k} \hat{v}_i}$$

  where $\hat{v}_i = n_i / S_i^2$ and Q_C is Cochran's homogeneity test statistic.

- The estimator $\hat{\tau}_{DSL}^2$ may also yield a negative estimate for the heterogeneity parameter, and hence the truncated version $\max\{0, \hat{\tau}_{DSL}^2\}$ is usually used.

Estimates of τ^2

- Consider

$$\mathsf{E}\left[\sum_{i=1}^{k} a_i \left(\bar{Y}_i - \bar{Y}_a\right)^2\right] = k - 1.$$

  with $a_i = 1/(\tau^2 + \sigma_i^2/n_i)$ and $\bar{Y}_a = \sum_{i=1}^{k} a_i\, \bar{Y}_i / \sum_{j=1}^{k}$.

- By substituting $S_1^2, \ldots, S_k^2$ for $\sigma_1^2, \ldots, \sigma_k^2$, we get the Mandel-Paule (1970) estimating equation

$$Q(\tau^2) = \sum_{i=1}^{k} \tilde{w}_i \left[\bar{Y}_i - \bar{Y}_{\tilde{w}}\right]^2 = k - 1,$$

  where $\bar{Y}_{\tilde{w}} = \sum_{i=1}^{k} \tilde{w}_i \bar{Y}_i / \sum_{i=1}^{k} \tilde{w}_i$ and $\tilde{w}_i = 1/(\tau^2 + S_i^2/n_i)$.

Estimates of τ^2

- The solution of

$$Q(\tau^2) = \sum_{i=1}^{k} \tilde{w}_i \left[\bar{Y}_i - \bar{Y}_{\tilde{w}}\right]^2 = k - 1,$$

say $\hat{\tau}^2_{MP}$, is called the Mandel-Paule estimator for τ^2.

- The solution is unique and exists provided that $Q(0) > k - 1$, see for instance, Hartung and Knapp (2005). If $Q(0) < k-1$, the Mandel-Paule estimator is set to zero.

Estimates of τ^2

- Sidik and Jonkman (2005) proposed an always non-negative heterogeneity estimator

$$\hat{\tau}^2 = \frac{1}{k-1} \sum_{i=1}^{k} (r_i + 1)^{-1} \left(\bar{Y}_i - \hat{Y}_r\right)^2.$$

with $r_i = \sigma_i^2/(n_i\, \tau^2)$ and $\hat{Y}_r = \sum_{i=1}^{k} (r_i + 1)^{-1}\, \bar{Y}_i / \sum_{j=1}^{k} (r_j + 1)^{-1}$.

- Note r_i depends on σ_i^2 and τ^2. Compute a crude estimator of τ^2, say $\hat{\tau}_0^2$, and estimate the ratio r_i by $\hat{r}_i = S_i^2/(n_i\, \hat{\tau}_0^2)$.

- Sidik and Jonkman (2005): $\hat{\tau}_0^2 = \frac{1}{k} \sum_{i=1}^{k} \left(\bar{Y}_i - \bar{Y}\right)^2$, $\bar{Y} = \sum_i Y_i/k$

Estimates of τ^2

- All the above estimators do not need normality assumption.

- Mandel-Paule estimator is close to (conditional) restricted maximum likelihood (REML) estimator under normality, see Ruhkin, Biggerstaff, and Vangel (2000).

- Which estimate of the heterogeneity parameter should we use?
  Is it an important question?
  Heterogeneity is only a nuisance parameter, isn't it?

Confidence Intervals on τ^2

- Normality assumption is needed.

- Likelihood based methods can be applied: Wald-type or profile likelihood confidence intervals.

- Wald-type confidence intervals cannot be recommended though statistical packages usually provide this type of confidence intervals.

- Candidate: profile REML confidence interval

- Competitor: Q-profiling method proposed by Knapp, Biggerstaff, Hartung (2006) and, independently, by Viechtbauer (2007)

Confidence Intervals on τ^2

- Confidence interval based on the (conditional) restricted log-likelihood; conditional means: substitute the observed sample variance $s_1^2, \ldots, s_k^2$ for $\sigma_1^2, \ldots, \sigma_k^2$ and then treated as known.

- It holds for the restricted log-likelihood for τ^2

$$l_R(\tau^2) \propto -\frac{1}{2}\sum_{i=1}^{k} \ln(\tau^2 + s_i^2/n_i) - \frac{1}{2}\sum_{i=1}^{k} \frac{1}{\tau^2 + s_i^2/n_i} - \frac{1}{2}\sum_{i=1}^{k} \frac{(\bar{Y}_i - \hat{\mu})^2}{\tau^2 + s_i^2/n_i}$$

Confidence Intervals on τ^2

- The estimating equation for τ^2 is given by

$$\hat{\tau}^2 = \frac{\sum_{i=1}^{k} \tilde{w}_i^2 \left[(\bar{Y}_i - \hat{\mu})^2 - s_i^2/n_i\right]}{\sum_{i=1}^{k} \tilde{w}_i^2} + \frac{1}{\sum_{i=1}^{k} \tilde{w}_i}$$

  $\tilde{w}_i = 1/(\tau^2 + s_i^2/n_i)$.
  Let $\hat{\tau}^2_{\text{REML}}$ denote the REML estimate.

- Then, a $100(1-\alpha)$% confidence interval for τ^2 is given by

$$\begin{aligned} CI_{REML}(\tau^2) &: \left\{\tilde{\tau}^2 \mid -2\left[l_R(\tilde{\tau}^2) - l_R(\hat{\tau}^2_{\text{REML}})\right] < \chi^2_{1;\alpha}\right\} \\ &= \left\{\tilde{\tau}^2 \mid l_R(\tilde{\tau}^2) > l_R(\hat{\tau}^2_{\text{REML}}) - \chi^2_{1;\alpha} \;/\; 2\right\} \end{aligned}$$

Confidence Intervals on τ^2

- Q-profiling method: Recall from the estimating equation of the Mandel-Paule estimator the statistic

$$Q(\tau^2) = \sum_{i=1}^{k} \tilde{w}_i \left[\bar{Y}_i - \bar{Y}_{\tilde{w}}\right]^2$$

  where $\bar{Y}_{\tilde{w}} = \sum_{i=1}^{k} \tilde{w}_i \bar{Y}_i / \sum_{i=1}^{k} \tilde{w}_i$ and $\tilde{w}_i = 1/(\tau^2 + S_i^2/n_i)$.

- Approximate $100(1-\alpha)$% confidence interval on τ^2

$$CI_Q(\tau^2) = \left\{\tau^2 \geq 0 \;\middle|\; \chi^2_{k-1;\alpha/2} \leq Q(\tau^2) \leq \chi^2_{k-1;1-\alpha/2}\right\}$$

Confidence Intervals on τ^2

- To determine the bounds of the confidence interval $CI_Q(\tau^2)$ one has to solve the two equations for τ^2, namely

lower bound:	$Q(\tau^2) = \chi^2_{k-1;\alpha/2}$
upper bound:	$Q(\tau^2) = \chi^2_{k-1;1-\alpha/2}$

- Simulation studies by Hartung and Knapp (2005), Knapp, Biggerstaff, and Hartung (2006) as well as Viechtbauer (2007) show that the interval $CI_Q(\tau^2)$ generally outperforms the other intervals with respect to attaining the nominal confidence coefficient. The profile restricted maximum likelihood interval $CI_{REML}(\tau^2)$ behaves well in attaining the nominal confidence coefficient in several scenarios and seems to be the only real competitor to the interval $CI_Q(\tau^2)$.

Inference on the Overall Mean μ

- Standard approximate confidence interval for μ in meta-analysis:

$$CI_1(\mu) : \hat{\mu}_{RE} = \bar{Y}_{\hat{w}} = \frac{\sum_{i=1}^k \hat{w}_i \, \bar{Y}_i}{\sum_{i=1}^k \hat{w}_i} \pm \left(\sum_{i=1}^k \hat{w}_i \right)^{-1/2} z_{1-\alpha/2}$$

  with $\hat{w}_i = (\hat{\tau}^2 + S_i^2/n_i)^{-1}$.

- As is well known, in small to moderate number of samples, this confidence interval suffers from the same weaknesses as its fixed effects counterpart. Namely, the actual confidence coefficient is below the nominal one. Consequently, the corresponding test on the overall mean yields too many unjustified significant results.

Inference on the Overall Mean μ

- Hartung and Knapp (2001a,b): approximate $100(1-\alpha)\%$-confidence interval for μ

$$CI_2(\mu) : \bar{Y}_{\hat{w}} = \frac{\sum_{i=1}^k \hat{w}_i \, \bar{Y}_i}{\sum_{i=1}^k \hat{w}_i} \pm \sqrt{\hat{Q}^*} \, t_{k-1,1-\alpha/2}$$

  with

$$\hat{Q}^* = \frac{1}{k-1} \frac{\sum_{i=1}^k \hat{w}_i \, (\bar{Y}_i - \bar{Y}_{\hat{w}})^2}{\sum_{i=1}^k \hat{w}_i}$$

Generic Meta-Analysis Models

- Fixed-effect model
- Random-effects model

Let us consider k independent studies, then we have for $i = 1, 2, \ldots, k$

θ_i	—	true effect size in the ith study
$\hat{\theta}_i$	—	estimated effect size in the ith study
$\sigma^2(\hat{\theta}_i)$	—	true variance of $\hat{\theta}_i$, which may depend on θ_i
$\hat{\sigma}^2(\hat{\theta}_i)$	—	estimate of $\sigma^2(\hat{\theta}_i)$

Generic Meta-Analysis Models

In the ith study:

$$\hat{\theta}_i \sim \mathcal{N}\left(\theta_i, \sigma^2(\hat{\theta}_i)\right), \qquad \hat{\sigma}^2(\hat{\theta}_i) \text{ given}$$

Justification for normality assumption:

- Central limit theorem
- Asymptotic normality of maximum-likelihood estimator

Fixed-Effect Model

Homogeneity assumption: $\theta_1 = \theta_2 = \cdots = \theta_k =: \theta$

Fixed-effect model is given by

$$\hat{\theta}_i \sim \mathcal{N}\left(\theta, \hat{\sigma}^2(\hat{\theta}_i)\right),\ i = 1, 2, \ldots, k.$$

(Conditional) ML estimate and (conditional) BLUE for θ is

$$\hat{\theta}_{FE} = \frac{\sum_{i=1}^k v_i\, \hat{\theta}_i}{\sum_{i=1}^k v_i}, \quad v_i = \frac{1}{\hat{\sigma}^2(\hat{\theta}_i)},\ i = 1, 2, \ldots, k,$$

with

$$\mathrm{Var}\left(\hat{\theta}_{FE}\right) = \frac{1}{\sum_{i=1}^k v_i}.$$

Fixed-Effect Model

Homogeneity test problem:

$$H_0 : \theta_1 = \theta_2 = \cdots = \theta_k \qquad \text{versus} \qquad H_1 : \exists(i,j)\ \theta_i \neq \theta_j, i \neq j.$$

Cochran's Q:

$$Q = \sum_{i=1}^k v_i \left(\hat{\theta}_i - \hat{\theta}_{FE}\right)^2$$

is approximately χ^2-distributed with $k-1$ degrees of freedom.

Reject H_0 at (approximate) level α, if $Q > \chi^2_{k-1;1-\alpha}$.

Generally, use results from common mean problem and replace $\bar{Y}_i$ by $\hat{\theta}_i$ and S_i/n_i by $\hat{\sigma}^2(\hat{\theta}_i)$.

Random-Effects Model

Random-effects model:

$$\hat{\theta}_i \sim \mathcal{N}\left(\theta, \tau^2 + \hat{\sigma}^2(\hat{\theta}_i)\right),\ i = 1, 2, \ldots, k,$$

and τ^2 is the between-study variance, also called heterogeneity parameter.

(Conditional) ML estimator and (conditional)BLUE for θ for known τ^2

$$\tilde{\theta}_{RE} = \frac{\sum_{i=1}^k w_i\, \hat{\theta}_i}{\sum_{i=1}^k w_i}, \quad w_i = \frac{1}{\tau^2 + \hat{\sigma}^2(\hat{\theta}_i)},\ i = 1, 2, \ldots, k,$$

Generally, use results from one-way random effects model and replace $\bar{Y}_i$ by $\hat{\theta}_i$ and S_i/n_i by $\hat{\sigma}^2(\hat{\theta}_i)$.

Random-Effects Model

Estimators of τ^2 available in R package *meta*:

- DerSimonian-Laird
- Paule-Mandel (Mandel-Paule see above)
- Maximum-likelihood (use R package *metafor*)
- Restricted maximum-likelihood (use R package *metafor*)
- Hunter-Schmidt (use R package *metafor*)
- Sidik-Jonkman (use R package *metafor*)
- Hedges (use R package *metafor*)
- Empirical Bayes (use R package *metafor*)

Random-Effects Model

By plugging in an estimate of τ^2 in the above formula, we obtain

$$\hat{\theta}_{RE} = \frac{\sum_{i=1}^{k} \hat{w}_i \, \hat{\theta}_i}{\sum_{i=1}^{k} \hat{w}_i}, \quad \hat{w}_i = \frac{1}{\hat{\tau}^2 + \hat{\sigma}^2(\hat{\theta}_i)}, \; i = 1, 2, \ldots, k,$$

with 'classical' variance estimate

$$\widehat{\mathsf{Var}}\left(\hat{\theta}_{RE}\right) = \frac{1}{\sum_{i=1}^{k} \hat{w}_i}.$$

Random-Effects Model

Approximate $(1-\alpha)$-confidence interval for θ

$$\hat{\theta}_{RE} \pm \sqrt{\widehat{\mathsf{Var}}\left(\hat{\theta}_{RE}\right)}\; z_{1-\alpha/2}.$$

Hartung-Knapp-Sidik-Jonkman-interval (Hartung, Knapp (2001, Statist. Med.), Sidik, Jonkman (2002, Statist. Med.):

$$\hat{\theta}_{RE} \pm \sqrt{\widehat{\mathsf{Var}_m}\left(\hat{\theta}_{RE}\right)}\; t_{k-1;1-\alpha/2}.$$

with

$$\widehat{\mathsf{Var}_m}\left(\hat{\theta}_{RE}\right) = \frac{1}{\sum_{i=1}^{k} \hat{w}_i} \frac{1}{k-1} \sum_{i=1}^{k} \hat{w}_i \left(\hat{\theta}_i - \hat{\theta}_{RE}\right)^2$$

Comments

We use the meta-analysis model

$$\hat{\theta}_i \sim \mathcal{N}\left(\theta, \tau^2 + \hat{\sigma}^2(\hat{\theta}_i)\right), \; i = 1, 2, \ldots, k,$$

assuming $\tau^2 = 0$ (fixed effect) or $\tau^2 > 0$ (random effects)
and the following assumptions and interpretations (depending on the effect size of interest):

- the analysis is conditionally on the observed $\hat{\sigma}^2(\hat{\theta}_i)$;
- the statistical uncertainty of $\hat{\sigma}^2(\hat{\theta}_i)$ is ignored;
- a possible correlation between $\hat{\theta}_i$ and $\hat{\sigma}^2(\hat{\theta}_i)$ is also ignored;
- estimator $\hat{\theta}_i$ do not have to be unbiased;
- unknown parameters are θ and τ^2.

Example

Results of eight randomized controlled trials comparing the effectiveness of amlodipine and a placebo on work capacity

	Amlodipine 10 mg (E)			Placebo (C)		
Protocol	n_{Ei}	$\bar{y}_{Ei}$	s^2_{Ei}	n_{Ci}	$\bar{y}_{Ci}$	s^2_{Ci}
154	46	0.2316	0.2254	48	-0.0027	0.0007
156	30	0.2811	0.1441	26	0.0270	0.1139
157	75	0.1894	0.1981	72	0.0443	0.4972
162A	12	0.0930	0.1389	12	0.2277	0.0488
163	32	0.1622	0.0961	34	0.0056	0.0955
166	31	0.1837	0.1246	31	0.0943	0.1734
303A	27	0.6612	0.7060	27	-0.0057	0.9891
306	46	0.1366	0.1211	47	-0.0057	0.1291

Example

Let μ_E be the expected value in the amlodipine group and μ_C in the control group. We are interested in $\delta = \mu_E - \mu_C$.
In each study, an estimator of δ_i is given by the difference of means, that is,

$$D_i = \bar{X}_{Ei} - \bar{X}_{Ci},$$

The variance of D_i can be estimated by

$$\widehat{\text{Var}(D_i)} = \frac{S_{Ei}^2}{n_{Ei}} + \frac{S_{Ci}^2}{n_{Ci}}$$

with S_{Ei}^2 und S_{Ci}^2 denoting the sample variances in the respective groups and n_{Ei} and n_{Ci} the respective sample sizes.

Meta-Analysis in R

Given values of D_i and $\widehat{\text{Var}}(D_i)$, we can easily use the function `metagen` in the R Paket *meta* to perform a meta-analyis.

General call of the function:

`metagen(TE, seTE, sm=""),`

with `TE` the vector of effect sizes, `seTE` the vector of standard errors, and `sm=""` a character string indicating underlying summary measure, e.g.,`"MD"` for the difference of means.

Example (Output slightly modified)

```
       MD             95%-CI %W(fixed) %W(random)
1  0.2343 [ 0.0969; 0.3717]     21.22      17.47
2  0.2541 [ 0.0663; 0.4419]     11.35      12.74
3  0.1451 [-0.0464; 0.3366]     10.92      12.45
4 -0.1347 [-0.3798; 0.1104]      6.67       9.04
5  0.1566 [ 0.0072; 0.3060]     17.94      16.21
6  0.0894 [-0.1028; 0.2816]     10.85      12.40
7  0.6669 [ 0.1758; 1.1580]      1.66       2.90
8  0.1423 [-0.0015; 0.2861]     19.39      16.79

                         MD           95%-CI      z  p-value
Fixed effect model   0.1619 [0.0986; 0.2252] 5.0134 < 0.0001
Random effects model 0.1589 [0.0710; 0.2467] 3.5443   0.0004
Quantifying heterogeneity:
tau^2 = 0.0066; H = 1.33 [1; 2]; I^2 = 43.2% [0%; 74.9%]
Test of heterogeneity:       Q d.f.  p-value
                         12.33    7   0.0902
```


Example (Output modified)

Hartung-Knapp-Sidik-Jonkman-Interval

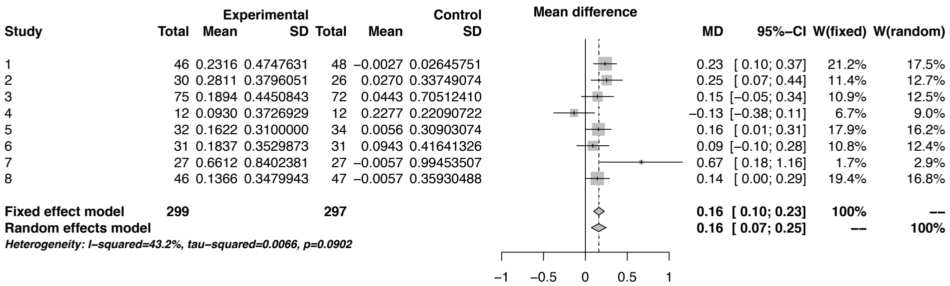
`metagen(TE, seTE,sm="", hakn=TRUE)`

```
                         MD           95%-CI    z|t  p-value
Fixed effect model   0.1619 [0.0986; 0.2252] 5.0134 < 0.0001
Random effects model 0.1589 [0.0387; 0.2791] 3.1257   0.0167

*** Heterogeneity statistics erased ***

Details on meta-analytical method:
- Inverse variance method
- DerSimonian-Laird estimator for tau^2
- Hartung-Knapp adjustment for random effects model
```

Forest Plot




```
forest(meta-object)
```