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IPD-MA of RCTs: one-stage meta-analysis

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Today

Overview of statistical methods

- Summarizing treatment effect(s)
- Investigating subgroups
- Exploring treatment effect modifiers

Guidance paper

Tutorial

Research Synthesis Methods

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Get real in individual participant data (IPD) meta-analysis: a review of the methodology

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Recall: two-stage meta-analysis

Distinct steps for the analysis of individual trials and the synthesis of corresponding results.

stage 1 • Stratification of *all* model parameters by study (i.e. fixed effects for treatment, study, confounders, interactions, etc.)

corrects for confounding on the study level but in one stage model this needs to be specifically done

stage 2 • Meta-analysis is based on estimates of treatment effect and may assume a fixed or a random treatment effect

One-stage meta-analysis

as they are grouped in different trials - clustering may occur which is why we have to account for it

Analyze all trials simultaneously by specifying an appropriate statistical model that accounts for clustering of subjects within trials.

When accounting for clustering, these models are also known as:

- Multilevel models
- Hierarchical models
- Mixed effects models
- Random intercept models

apply random parameters for certain variables and fixed effects for certain vairables

One-stage meta-analysis

Simultaneous analysis of trials and evidence synthesis

different, related or identical

- We assume that parameters are somehow related or identical across trials.
  - Fixed effects (stratification; makes no assumptions about how effects differ across trials)
  - Random effects
  - Common effect (same for all trials)

not interpreted as fixed to certain value but fixed to effect to the effects of certain trial

Reduce # unknown parameters (as compared to two-stage MA)

- Different types of effects can be specified for each variable

common effect = estimate one beta parameter
random effect = mean of beta parameters and variance across trials

Clinical example

Meta-analysis of antidepressant trials

- 5 randomized trials
  - Patients diagnosed with major depressive disorder
  - Tricyclic antidepressant (TCA) versus Placebo (Plac)
- Outcome measurements
  - Hamilton Depression (HAMD) score, ranging from 0 to 54
  - Measured at baseline and after 6 weeks

Clinical example

How would you analyze the IPD from the antidepressant trials?

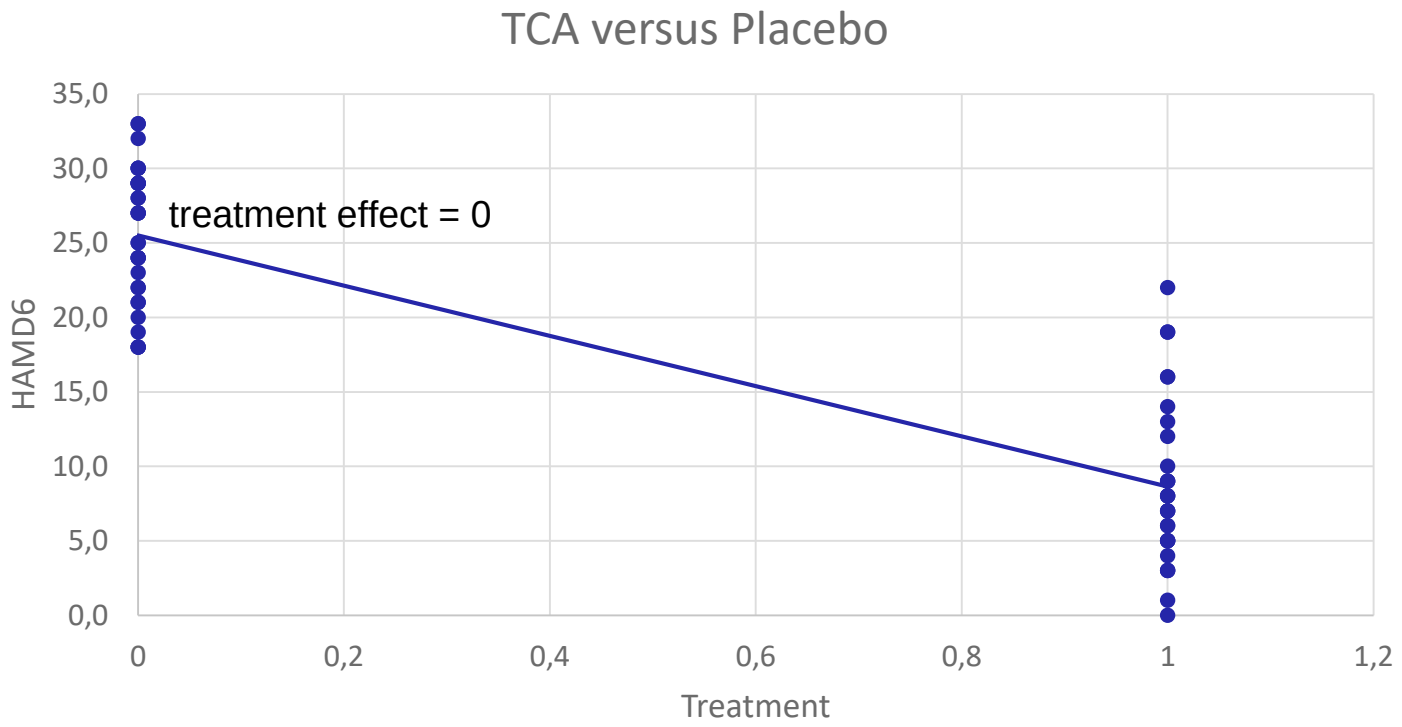
Patient	Study	Treatment	HAMD0	HAMD6
1	1	Placebo	26	15
2	1	TCA	24	18
3	1	Placebo	29	19
…				
439	5	TCA	21	22
440	5	placebo	24	15

Clinical example

Linear regression (clustering ignored)

for baseline variable and for treatment effect -> subject to confounding

$$HAMD6_{ik} = \alpha + \delta\, TREAT_{ik} + \varepsilon_{ik}$$

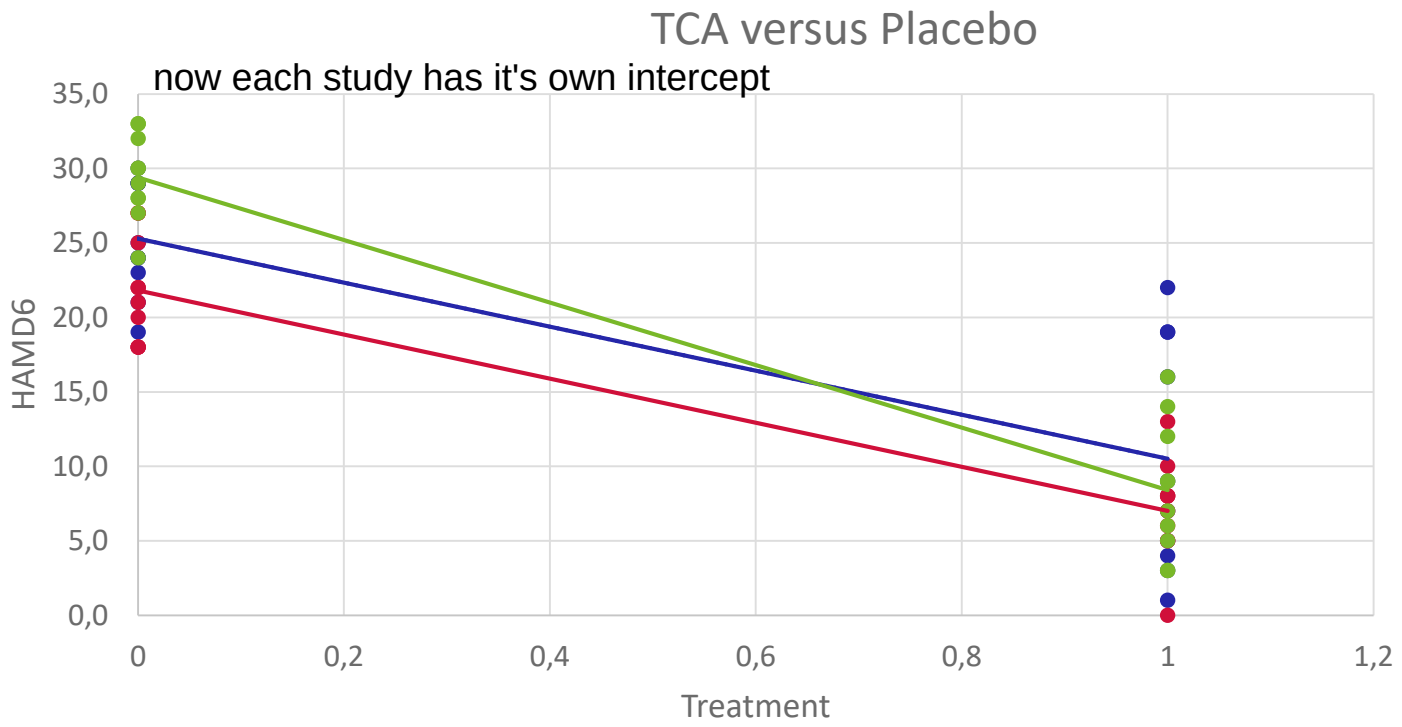


Clinical example

Linear regression accounting for clustering

each study k has it's own delta

$$HAMD6_{ik} = \alpha_k + \delta_k TREAT_{ik} + \varepsilon_{ik}$$



Specifying the statistical model

Implementation of generalized linear *mixed* regression models (GLMM):

$$g\left(E\left(y_{ik}\right)\right) = \alpha_k + \delta_k x_{ik}$$

intercept parameter

y_{ik}: j = subject, k = study

x_{ik}: treatment value for patient i in study k

δ_k: treament effect with k

Where

- Index i denotes the subject and k denotes the study
- $E(y_{ik})$ denotes the expected value of y_{ik}
- α_k denotes the study effect (e.g. baseline risk)
- δ_k represents the relative treatment effect
- $g(\cdot)$ represents the link function

Specifying the statistical model

Implementation of generalized linear *mixed* regression models (GLMM):

$$g\big(E(y_{ik})\big) = \alpha_k + \delta_k x_{ik}$$

Where each δ_k may be taken as

- Fixed effects (estimated separately in each study)
- A common effect (so $\delta_k = \delta$ for all trials)
- Random effects (so δ_k is drawn from a certain, e.g. Normal, distribution)

common to assume fixed effects for the intercept because it removes confounding for the baseline effect

Note: It is common to assume fixed effect**s** for α_k.

Specifying the statistical model

overview for link functions

Common statistical models

- Continuous outcomes
  - Normal distribution with identity link (linear regression)
- Binary outcomes
  - Bernoulli distribution with a logistic link (logistic regression)
- Count data
  - Poisson distribution with a log-link
- Time-to-event data
  - Hierarchical Cox PH model (with strata or frailty terms)
  - Poisson GLMM

Ref: Debray TPA, et al. (2015). Get real in individual participant data (IPD) meta-analysis: a review of the methodology. *Research Synthesis Methods*, (November 2014), n/a–n/a.
Ref: de Jong VMT, Moons KGM, Riley RD, Tudur Smith C, Marson AG, Eijkemans MJC, Debray TPA. Individual participant data meta-analysis of intervention studies with time-to-event outcomes: A review of the methodology and an applied example. Research synthesis methods. 2020 Mar;11(2):148-68.

Clinical example

Calculate mean treatment difference of HAMD score after 6 weeks in each trial:

treatment value is either 0 or 1

outcome $y_{ik} = \alpha_k + \delta_k \, TREAT_{ik} + \varepsilon_{ik}$ residual variance

parameter

$$\varepsilon_{ik} \sim N(0, \sigma_k^2)$$

$$\delta_k \sim N(D, \tau^2)$$

Pooled treatment effect

Random effects for the treatment effect

Clinical example

Mean treatment difference of HAMD score after 6 weeks

shrunk towards the mean because we used normal distribution

Trial	N	δ (1-stage)	δ (2–stage)
1	51	-5.86	-6.93
2	53	0.48	1.80
3	78	-4.34	-4.67
4	63	-3.26	-3.34
5	16	-2.09	-0.97

In one-stage MA, study-specific treatment effects are shrunk towards the overall mean

follows normal distribution with mean 0 and variance

delta k follows normal distribution with mean D and variance tau squared

Comparison	$\widehat{D}$	SE($\widehat{D}$)	$\hat{\tau}^2$
Two-stage	-2.64	1.58	9.51
One-stage	-3.01	1.55	8.35

slightly negative mean effect

similar standard error

smaller within study variance

Extending the model

It is fairly straightforward to extend the statistical model to:

- Correct for baseline imbalance include baseline covarites
- Adjust for prognostic factors
- Explore interaction with trial-level covariates
- Explore interaction with patient-level covariates
- Explore non-linear associations

Investigating effect modification

Statistical model

$$y_{6ik} \sim N\left(\mu_{ik}, \sigma_k^2\right)$$

$$\mu_{ik} = \alpha_k + \delta_k x_{ik} + \gamma_k y_{0ik} + \theta_{AW} x_{ik} y_{0ik}$$

$$\delta_k \sim N(D, \tau^2)$$

Adjust for treatment-covariate interaction

but if done wrongly - bias!

Adjust for baseline imbalance.

including covariate

Note that a common effect is estimated for interaction at the patient level and at the trial level (as mean values of y_{0ik} may vary across trials and be correlated with study-level characteristics such as level of blinding)

=> risk for ecological bias!

Danger of ecological bias

because again mean age might be different in the trials

Treatment effect can be affected by:

- Individual covariate values (e.g. due to effect modification)
- A covariate mean value (e.g. due to study-level confounding)

might be confounded by a third variable

θ_{AW} represents an amalgation of within- and across-trial interactions! mix of both

Ref: Hua H, Burke DL, Crowther MJ, Ensor J, Tudur Smith C, Riley RD. One-stage individual participant data meta-analysis models: estimation of treatment-covariate interactions must avoid ecological bias by separating out within-trial and across-trial information. Statistics in Medicine. 2017;36(5):772–789.

Investigating effect modification

Statistical model

$$y_{6ik} \sim N\left(\mu_{ik}, \sigma_k^2\right)$$

Within-trial interaction

$$\mu_{ik} = \alpha_k + \delta_k x_{ik} + \gamma_k (y_{0ik} - \bar{y}_{0i}) + \theta_W x_{ik} (y_{0ik} - \bar{y}_{0i}) + \theta_A x_{ik} \bar{y}_{0i}$$

$$\delta_k \sim N(D, \tau^2)$$

Across-trial interaction; quantifies the presence of ecological bias.

Centering y_{0ik} about the mean covariate value $\bar{y}_{0i}$ is necessary to separate within-trial interaction from between-trial interaction !

Investigating effect modification

need to split within trial and across trial interactions

Statistical model

$$y_{6ik} \sim N\left(\mu_{ik}, \sigma_k^2\right)$$

subtracting mean value from each persons value

$$\mu_{ik} = \alpha_k + \delta_k x_{ik} + \gamma_k (y_{0ik} - \bar{y}_{0i}) + \theta_W x_{ik} (y_{0ik} - \bar{y}_{0i}) + \theta_A x_{ik} \bar{y}_{0i}$$

same for within trial interaction

$$\delta_k \sim N(D, \tau^2)$$

including mean value for that covariate and adding interaction for it (between study interaction)

If $\theta_k = 0$ and $\theta_A \neq 0$, we have the situation where treatment effects vary according to whether trials included *older* participants ($\bar{y}_{0i}$). However, within trials, there is no relation between participant *age* (y_{0ik}) and treatment effect; the (expected) relative change in HAMD score is the same for all participants.

- Estimates for θ_A can also be obtained from meta-regression
- Estimates for θ_W can also be obtained by pooling of within-trial covariate interactions.
- We can allow for heterogeneity in interaction by replacing θ_W with $\theta_{W,k}$ and assuming random effects for $\theta_{W,k}$

Computer practical

Antibiotics for acute otitis media (AOM): a meta-analysis with individual patient data

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Case study

6 simulated trial datasets that

- Used random allocation of children
- Contain children aged 0-12 years with AOM
- Compare antibiotics with placebo or no treatment
- Assess the presence of an extended course of AOM

Aims of the practicum

- Comparison of one-stage and two-stage meta-analysis methods
- Investigation of treatment-covariate interaction
- Interpretation of meta-analysis results