Cochrane Singapore

SINGAPORE CLINICAL RESEARCH INSTITUTE

SCRI academy

2.1: Regression models for Meta-analysis

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Cochrane Workshop on Network Meta-Analysis

Outline

- Regression analysis
  - person-level (clinical trial)
  - trial level (meta-analysis)
- Meta-regression model with no predictors
- Meta-regression with predictors

Regression analysis

- A method of analysis that models the quantitative relationship between one **dependent variable (DV)** and one or more **independent variables (IV)**

- From this statistical model we can measure:
  - the **effect of the IVs** on the DV
  - measure the **average value of the DV** given the values of the IVs

In analysis of a clinical trial

- Variables are **person-level** characteristics
- **DV** = clinical outcome (response) in a patient
  - E.g. change in BP (mm Hg), response to Rx (yes/no)

- **IV** = predictors of the **average** response
  - **P** characteristics e.g. age, disease severity, sex etc
  - **I**ntervention characteristics e.g. Rx assigned

In a meta-analysis of trials

- Variables are **study-level** characteristics
- **DV** = treatment effect (contrast)
  - E.g. mean difference, log RR, log OR etc
- **IV** = modifiers of the treatment effect
  - **average P** characteristics e.g. age, disease severity etc
  - **I**ntervention characteristics e.g. dose of Rx
- Model is called a **meta**-regression, to signify an ecologic level analysis

Outline

- Regression analysis

- Meta-regression model with no predictors
  - fixed-effect pooling
  - random-effects pooling

- Meta-regression with predictors

No predictors (IV)model …

- Model: $Y_i = \mu + \varepsilon_i$, i indexes a particular study

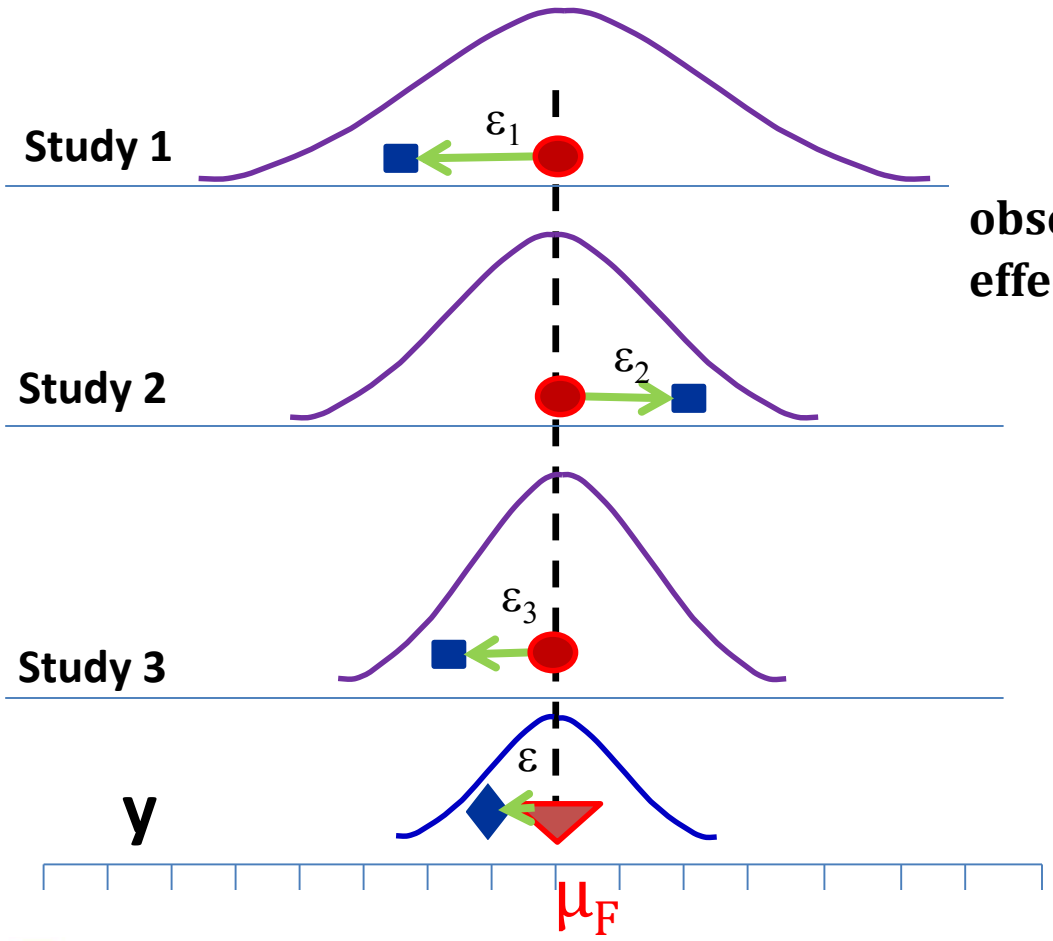
DV **intercept** residual random error

  - written in "prediction" form: $\bar{y} = \mu$
  - intercept value predicts the population mean DV

- Application to standard meta-analysis:
  - fixed-effect (FE) pooling model
  - random-effects (RE) pooling model

Fixed-effect (FE) model

Amoxicillin for acute sinus infection in adults



$$y_i = \mu_F + \varepsilon_i$$

$\varepsilon_i \sim N(0, \sigma_i^2)$
σ_i = Rx-effect variability in studies with **identical PICO** to & **sample size** of study i

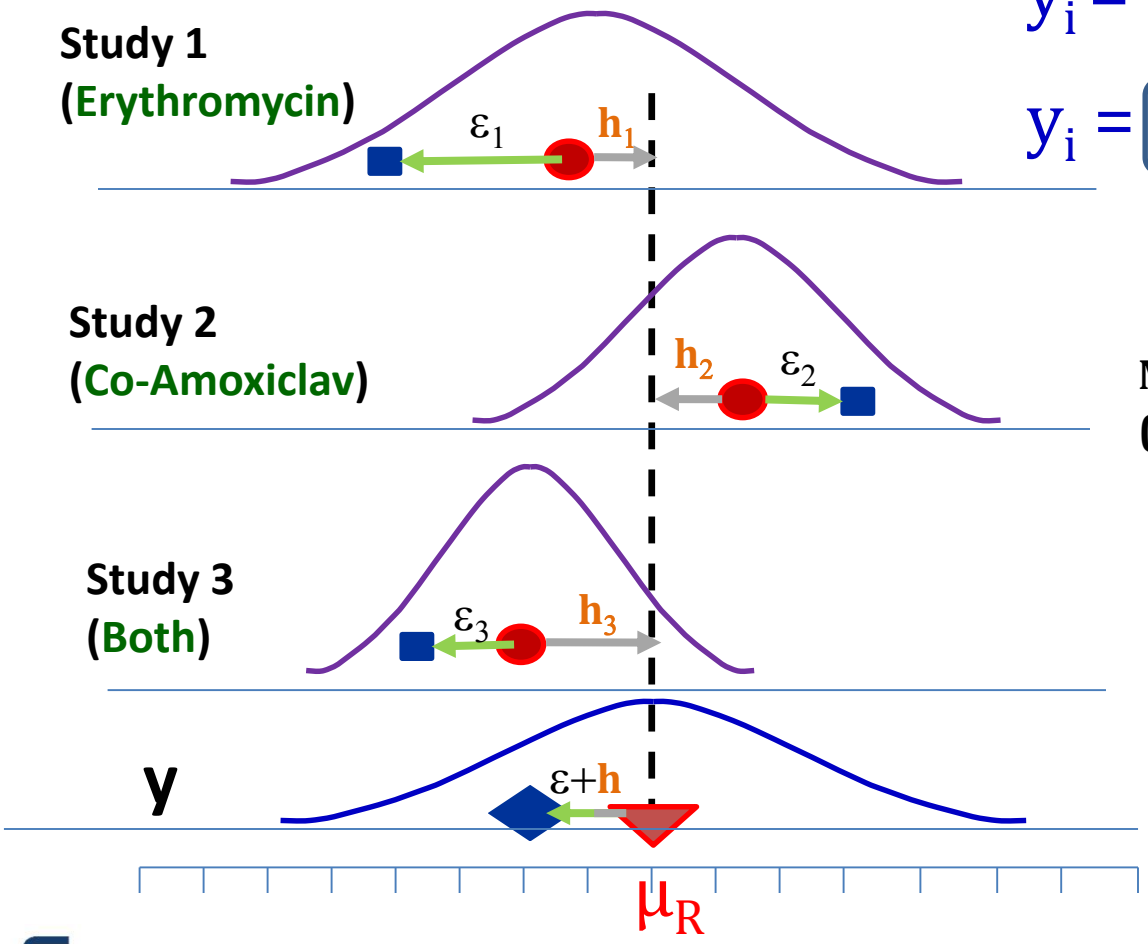
observed Rx effect in study i

the one true effect (fixed-effect mean)

$$y_3 \sim N(\mu_F, \sigma_3^2)$$

distribution of Rx effects in studies with sample size of Study 3

Random-effects (RE) model



True Rx effect of study i

$y_i = \delta_i + \varepsilon_i$

$\varepsilon_i \sim N(0, \sigma_i^2)$

$h_i \sim N(0, \tau^2)$

$y_i = \mu_R + h_i + \varepsilon_i$

Between-study effects variability

Mean of the true study Rx effects (random-effects mean)

$y_i|\delta_i \sim N(\delta_i, \sigma_i^2)$

distribution of Rx effects of type i studies (δ_i)

where $\delta_i \sim N(\mu_R, \tau^2)$

distribution of the true Rx effects

Outline

- Regression analysis
- Meta-regression model with no predictors
- Meta-regression with predictors
  - accounting for systematic between-study differences in SMA
  - extension to NMA

Meta-regression with predictors – heterogeneity in SMA

- The premise of RE pooling is that there are systematic differences between-studies which causes the between-study variance component (τ^2)

- The rationale of meta-regression with predictors is to explicitly account for these (suspected)causes, hence reducing the size of τ^2
  - realistically we can never be sure of completely eliminating τ^2, so we still have a residual of it in the model which makes it (still)a RE model

Meta-regression with predictors – heterogeneity in SMA

- Models with one or more study-level predictors (**IV**s):

- $Y_i = \mu_R + \beta_1 \mathbf{X_1} + \beta_2 \mathbf{X_2} + \cdots + h_i + \varepsilon_i$

  $\mathbf{X_1}$: average age of patients

  $\mathbf{X_2}$: dose of Intervention

- The predictors' are (treatment)effect-modifiers and their coefficients (β_i) estimate the change in treatment effect per unit change in predictor value

RE meta-regression model with predictors

- **Model:** $y_i|\delta_i \sim N(\delta_i, \sigma_i^2)$ where $\delta_i \sim N(\mu_0 + \sum_j \beta_j x_{ij}, \tau^2)$

$$y_i = \mu_0 + \sum_j \beta_j x_{ij} + h_i + \varepsilon_i$$

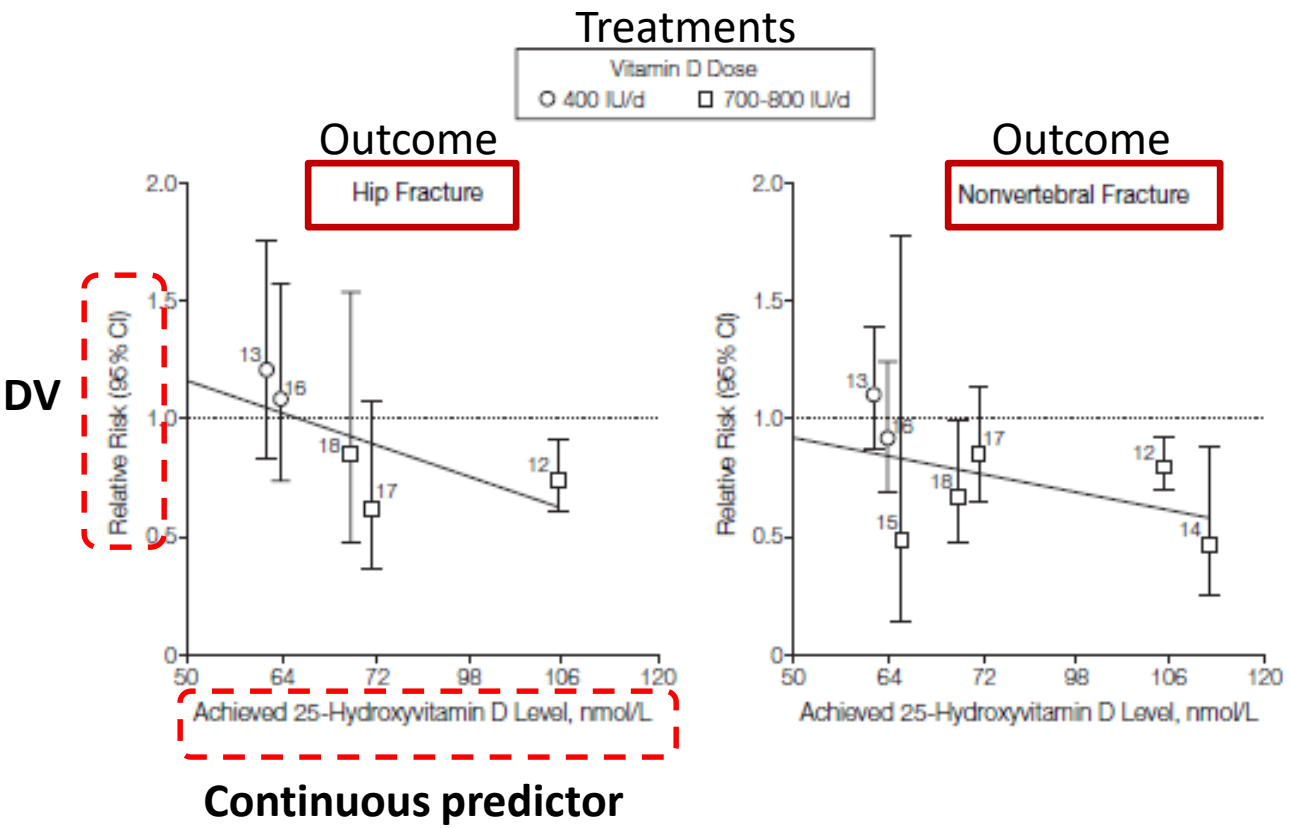
$h_i \sim N(0, \tau^2)$

$\varepsilon_i \sim N(0, \sigma_i^2)$

- The difference among study-effects has a systematic (non-random) component that varies with the predictor values **AND** a random component (h_i)
  - –reporting a pooled (across studies)mean in this perspective is less sensible, instead report the study-specific means i.e. the δ_i ($= \mu_0 + \Sigma\beta_j x_{ij}$)

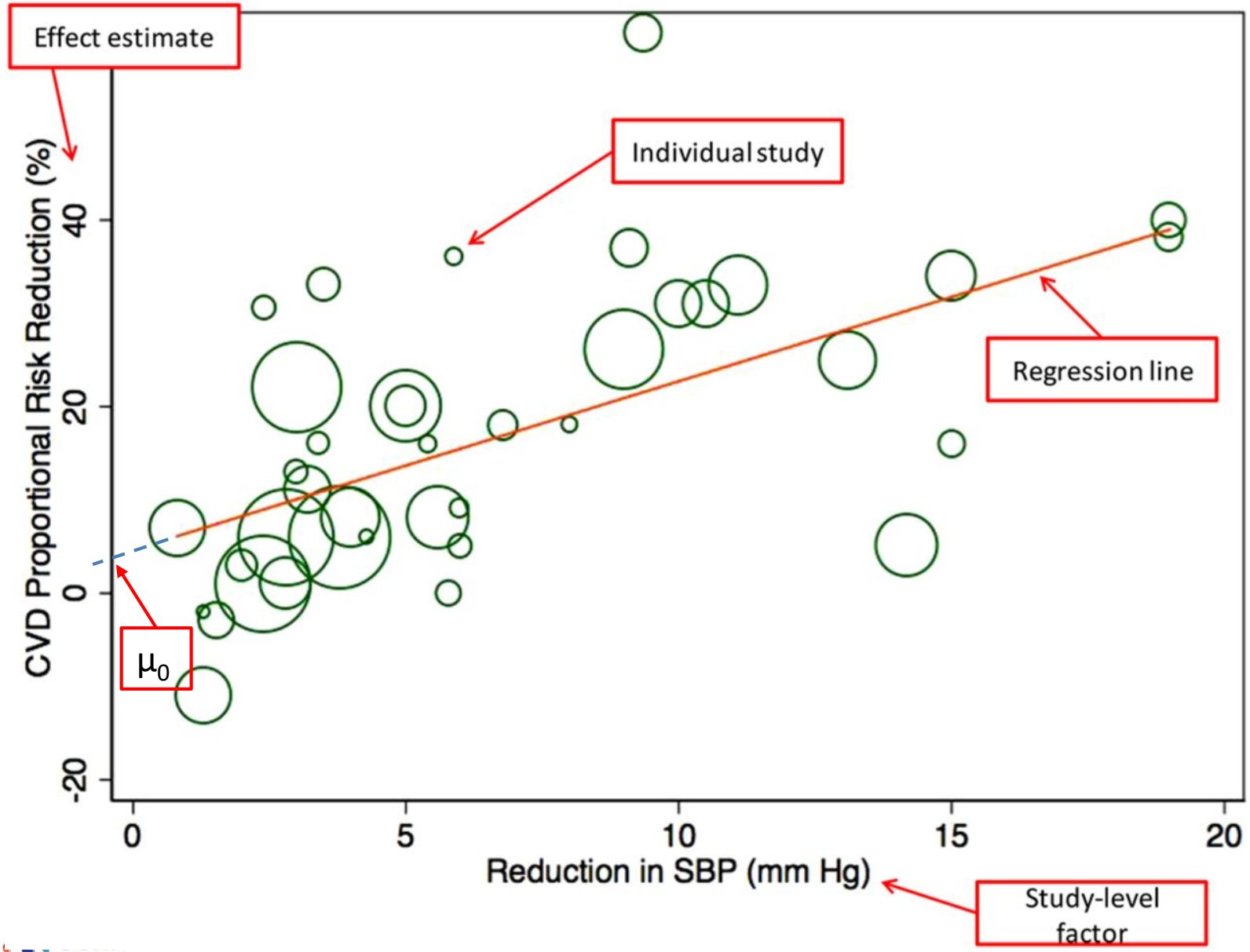
One predictor for RR of fracture – 25-HVD plasma levels

Fracture Prevention With Vitamin D Supplementation: A Meta-analysis of Randomized Controlled Trials, Bischoff-Ferrari et al, JAMA, 2005



$$\text{Model: } \log RR = \mu_R + \beta_1[\text{25-HVD}]$$

Meta-regression (bubble) plot



No-predictor meta-regression for NMA (design-by-treatment interaction model)

$$y_{di}^{AJ} = \boldsymbol{\delta^{AJ}} + \boldsymbol{h_{di}^{AJ}} + \omega_d^{AJ} + \varepsilon_{di}^{AJ}, \qquad J = B, C, \ldots$$

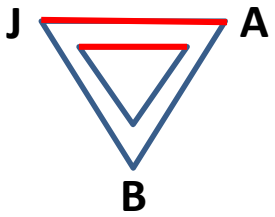
d represents the study design (2- or multi-arm with specific interventions)

i represents i th study in the d th design

$\boldsymbol{\delta^{AJ}}$ represents the (pooled) **treatment effect** J vs A

$\boldsymbol{h_{di}^{AJ}}$ represents **heterogeneity** in the J–A effects among studies of the same design i.e. the usual between-study heterogeneity of an SMA

Three 2-arm **JA** RCTs
Design i=1



Two 3-arm **JAB** RCTs
Design i=2

Design-by-treatment interaction model cont'd …

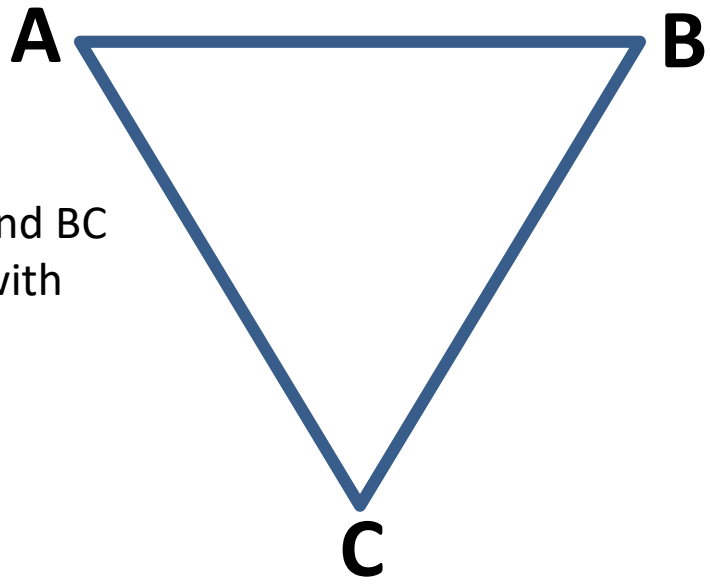
$$y_{di}^{AJ} = \delta^{AJ} + h_{di}^{AJ} + \boldsymbol{\omega_d^{AJ}} + \varepsilon_{di}^{AJ}, \qquad J = B, C, \ldots$$

$\boldsymbol{\omega_d^{AJ}}$ represents **inconsistency** in the J–A effects (both loop & design consistency of closed loops)

ε_{di}^{AJ} is the residual error term

Correlation of effect estimates from multi-arm studies

- When there are more than two arms in a study there will be correlated treatment effect estimates due to sharing of the same arms for different estimates



Effects AB, AC and BC are correlated with each other

Multi-variate modeling strategy

- To account for the correlation effects from multi-arm studies a multi-variate modeling approach is adopted
- With T different treatment arms, all studies are conceived as T-arm studies with missing information on the arms that were not included in the actual study
- The Rx effect parameter becomes a T-1 vector of independent contrasts
  - with 3 different interventions (A,B,C) tested in four 2-arm studies …

Multi-variate model, assuming equal between-study variances for all contrasts

2 independent contrast parameters – with T treatments only T-1 contrasts are independent

4 studies

$$\begin{pmatrix} y_{1,1} \\ y_{2,1} \\ y_{3,1} \\ y_{4,1} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} h_{1,1} \\ h_{2,1} \\ h_{3,1} \\ h_{4,1} \end{pmatrix} + \begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \end{pmatrix}$$

Between-study variation (RE model), assuming equal variances

$$\begin{pmatrix} h_{1,1} \\ h_{2,1} \\ h_{3,1} \\ h_{4,1} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau^2 & 0 & 0 & 0 \\ 0 & \tau^2 & 0 & 0 \\ 0 & 0 & \tau^2 & 0 \\ 0 & 0 & 0 & \tau^2 \end{pmatrix} \right)$$

With one 3-arm study …

Study #4 has 3-arms

$$\begin{pmatrix} y_{1,1} \\ y_{2,1} \\ y_{3,1} \\ y_{4,1} \\ y_{4,2} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} h_{1,1} \\ h_{2,1} \\ h_{3,1} \\ h_{4,1} \\ h_{4,2} \end{pmatrix} + \begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}$$

Between-study variation (RE model) accounting for correlation in the multi-arm study

$$\begin{pmatrix} h_{1,1} \\ h_{2,1} \\ h_{3,1} \\ h_{4,1} \\ h_{4,2} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau^2 & 0 & 0 & 0 & 0 \\ 0 & \tau^2 & 0 & 0 & 0 \\ 0 & 0 & \tau^2 & 0 & 0 \\ 0 & 0 & 0 & \tau^2 & \frac{\tau^2}{2} \\ 0 & 0 & 0 & \frac{\tau^2}{2} & \tau^2 \end{pmatrix} \right)$$

With one 3-arm study …

Study #4 has 3-arms

$$\begin{pmatrix} y_{1,1} \\ y_{2,1} \\ y_{3,1} \\ y_{4,1} \\ y_{4,2} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ -1 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix} + \begin{pmatrix} h_{1,1} \\ h_{2,1} \\ h_{3,1} \\ h_{4,1} \\ h_{4,2} \end{pmatrix} + \begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix}$$

Within-study variation (RE model) accounting for correlation in the multi-arm study

$$\begin{pmatrix} \varepsilon_{1,1} \\ \varepsilon_{2,1} \\ \varepsilon_{3,1} \\ \varepsilon_{4,1} \\ \varepsilon_{4,2} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma^2 & 0 & 0 & 0 & 0 \\ 0 & \sigma^2 & 0 & 0 & 0 \\ 0 & 0 & \sigma^2 & 0 & 0 \\ 0 & 0 & 0 & \sigma^2 & \frac{\sigma^2}{2} \\ 0 & 0 & 0 & \frac{\sigma^2}{2} & \sigma^2 \end{pmatrix} \right)$$

Meta-regression with predictors for NMA

- "Contrast-based" models with additional predictors

$$y_{di}^{AJ} = \delta^{AJ} + h_{di}^{AJ} + \omega_d^{AJ} + \beta_n X_n + \varepsilon_{di}^{AJ}, \qquad J = B, C, \ldots$$

- $X_1, X_2, \ldots, X_n$ are the study-level factors
- $\beta_1, \beta_2, \ldots, \beta_n$ are the change in treatment effect between unit level changes of predictor

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Thank you!

Questions & comments welcome!

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