University of Ioannina

School of Medicine

ΙΑΤΡΙΚΗ ΣΧΟΛΗ
ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ

Addressing continuous missing outcomes in pairwise and network meta-analysis

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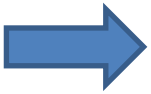
Why missing data matter

- Missing outcome data are common in RCT's
- In mental health, the dropout rate may exceed 50%.
- Loss in power and precision
- Any analysis must make an untestable assumption about missing data
  - wrong assumptions  biased estimates
- Some popular techniques for missing data get biased standard errors.
  - resulting in wrong p-values and confidence intervals

Reasons why data are missing

- Missing At Random (MAR)

The probability that data are missing

  - may depend on the values of the observed data
  - does not depend on the values of the missing data (conditional on the values of the observed data)

- Missing Not At Random (MNAR) or Informatively Missing (IM)

The probability that data are missing

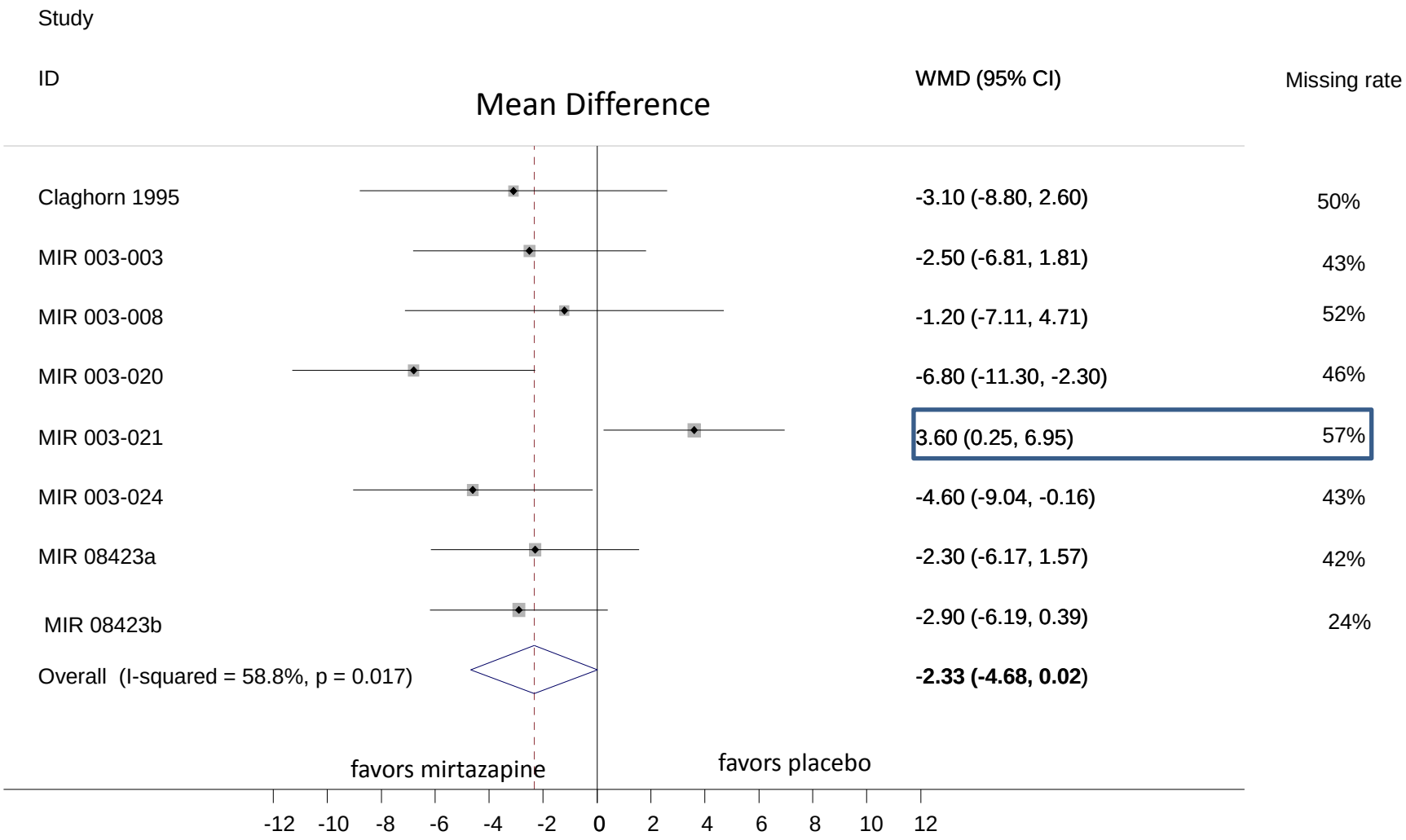
- may depend on unobserved data
- may depend on the actual missing outcome

- The widely used approach is to assume that missing data are MAR conditional on the treatment received. This justifies a complete case (CC) analysis (unbiased results with lower precision)
- **We consider a single quantitative(continuous) outcome measured at one time point without considering any covariates**

Mirtazapine meta-analysis: mean change in HAMD21 scores, standard deviations, and numbers of completers and non-completers for the mirtazapine and placebo arms.

Study	Placebo				Mirtazapine			
	x_{iC}^{obs}	sd_{iC}^{obs}	n_{iC}	m_{iC}	x_{iT}^{obs}	sd_{iT}^{obs}	n_{iT}	m_{iT}
Claghorn 1995	-11.4	10.2	19	26	-14.5	8.8	26	19
MIR 003-003	-11.5	8.3	24	21	-14	7.3	27	18
MIR 003-008	-11.4	8	17	13	-12.6	8	12	18
MIR 003-020	-6.2	6.5	24	19	-13	9	23	21
MIR 003-021	-17.4	5.3	21	29	-13.8	5.9	22	28
MIR 003-024	-11.1	9.9	27	23	-15.7	6.7	30	20
MIR 84023a	-11.9	8.6	33	24	-14.2	7.6	35	25
MIR 84023b	-11.8	8.3	48	18	-14.7	8.4	51	13

Random effect meta-analysis of mean change in HAMD21 score. Mirtazapine vs placebo. Complete case analysis

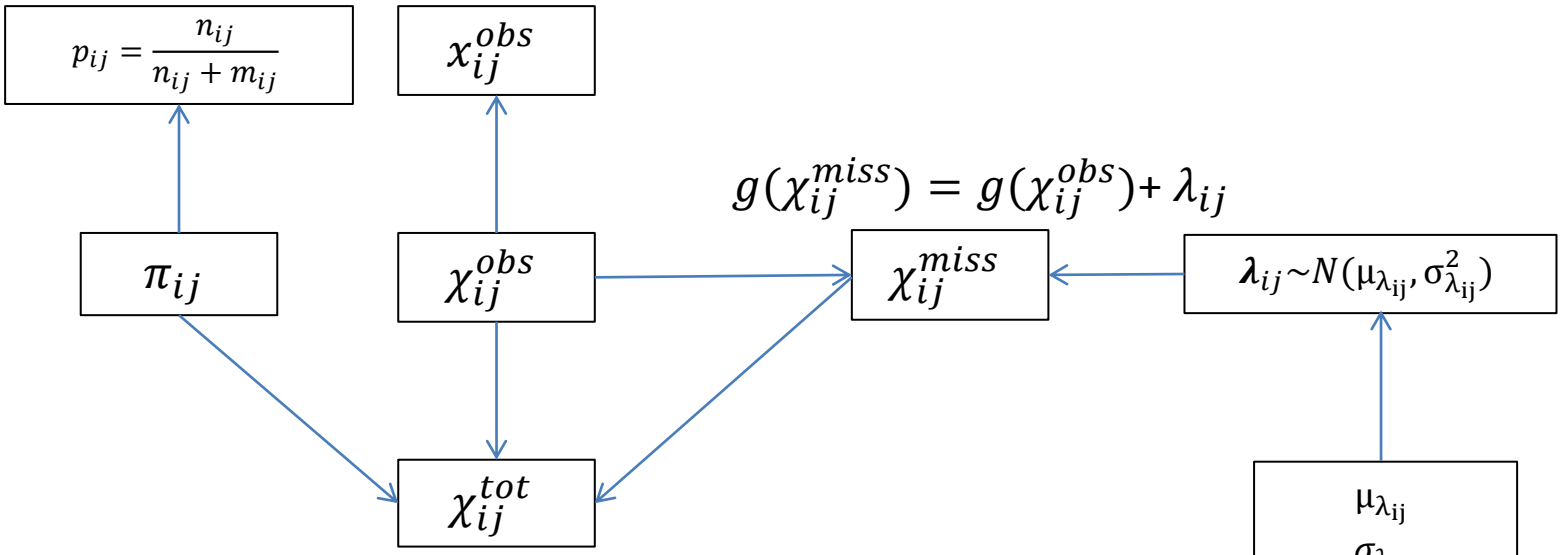


Our proposal for continuous missing outcomes Two-stage method

- We develop a two-stage method that models departures from MAR
- 1st stage: estimate effect sizes β_i and its variance $var(\beta_i)$ in each study i.
  - increase uncertainty to effect sizes to account for the fact that missing data are imputed rather than observed.
  - downweight studies with large missing rates

- 2nd stage: Pool adjusted effect sizes

Model for arm j of study i pattern mixture model



$$\chi_{ij}^{tot} = p_{ij}\chi_{ij}^{obs} + (1 - p_{ij})\chi_{ij}^{miss}$$

$$\chi_{ij}^{tot} = p_{ij}\chi_{ij}^{obs} + (1 - p_{ij})g^{-1}\left((\lambda_{ij} + g(\chi_{ij}^{obs})\right)$$

studies i, arms j

Parameters for Informative Missingness λ Difference of Means(IMDoM) or Ratio of Means (IMRoM)

- IM is quantified as a contrast between the unobserved mean value in the missing data and the mean value in the observed data

$$\lambda_{ij} = g(\chi_{ij}^{miss}) - g(\chi_{ij}^{obs})$$

1. If g is the identity function (IMDoM)

$$\lambda_{ij} = \chi_{ij}^{miss} - \chi_{ij}^{obs}$$

2. If g is the ln function (IMRoM)

$$\lambda_{ij} = \ln\left(\chi_{ij}^{miss}\right) - \ln(\chi_{ij}^{obs})$$

Assumptions about the missingness parameter

- Missing at random (MAR) $\lambda_{ij} = 0$
- Free λ_{ij}: $\boldsymbol{\lambda}_{ij} \sim N(\mu_{\lambda_{ij}}, \sigma^2_{\lambda_{ij}})$
- Study specific λ: $\lambda_i \sim N\left(\mu_{\lambda_i}, \sigma^2_{\lambda_i}\right)$
- Correlated λ's:

$$\begin{pmatrix} \lambda_{iC} \\ \lambda_{iT} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{\lambda_{iC}} \\ \mu_{\lambda_{iT}} \end{pmatrix}, \begin{pmatrix} \sigma^2_{\lambda_{iC}} & \rho_\lambda \sigma_{\lambda_{iC}} \sigma_{\lambda_{iT}} \\ \rho_\lambda \sigma_{\lambda_{iC}} \sigma_{\lambda_{iT}} & \sigma^2_{\lambda_{iT}} \end{pmatrix} \right)$$

Adjusted effect sizes

$$\beta_i = f\left(x_{iT}^{tot}\right) - f\left(x_{iC}^{tot}\right)$$

1. $f(u_i) = u_i$: Mean Difference (MD)

2. $f(u_i) = \ln u_i$: Logarithm of the ratio of means (ln RoM)

3. $f(u_i) = u_i / S_i$: Standardized Mean Difference (SMD) where S_i is the pooled standard deviation

Estimating $E(\beta_i)$ and $var(\beta_i)$ Taylor series approximation

$$\beta_i = f\left(x_{iT}^{tot}\right) - f\left(x_{iC}^{tot}\right)$$

$$\chi_{ij}^{tot} = \pi_{ij}\chi_{ij}^{obs} + \left(1 - \pi_{ij}\right)g^{-1}\left(\left(\lambda_{ij} + g\left(\chi_{ij}^{obs}\right)\right)\right)$$

- $E(\beta_i)$ is straightforward calculated, e.g. if f and g are identity functions (MD and IMDoM)

$$E(\beta_i) = (1 - p_{iT})\mu_{\lambda_{iT}} + \mathrm{x}_{iT}^{\mathrm{obs}} - (1 - p_{iC})\mu_{\lambda_{iC}} - \mathrm{x}_{iC}^{\mathrm{obs}}$$

$$var(\beta_i) \approx \sum_{j=C,T}\left[\frac{p_{ij}\left(1 - p_{ij}\right)}{n_{ij} + m_{ij}}\left(\mu_{\lambda_{ij}}^2 + \sigma_{\lambda_{ij}}^2\right) + \frac{s_{ij}^2}{n_{ij}} + \sigma_{\lambda_{ij}}^2\left(1 - p_{ij}\right)^2\right] - 2\rho_{\lambda_i}\sigma_{\lambda_{iC}}\sigma_{\lambda_{iT}}(1 - p_{iT})(1 - p_{iC})$$

Estimating $E(\beta_i)$ and $var(\beta_i)$ Monte Carlo Method

- Repeat B times, $b = 1, \dots, B$
- draw $\left(\chi_{ij}^{obs}\right)^b \sim N\left(x_{ij}^{obs}, \frac{s_{ij}^2}{n_{ij}}\right)$
- draw $\lambda_{ij}^b \sim N\left(\mu_{\lambda_{ij}}, \sigma_{\lambda_{ij}}^2\right)$
- set $\left(\chi_{ij}^{miss}\right)^b = \lambda_{ij}^b + \left(\chi_{ij}^{obs}\right)^b$ for IMDoM or
  $\left(\chi_{ij}^{miss}\right)^b = e^{\lambda_{ij}^b}\left(\chi_{ij}^{obs}\right)^b$ for IMRoM
- draw $\pi_{ij}^b \sim N\left(p_{ij}, \frac{p_{ij}(1-p_{ij})}{n_{ij}}\right) T(0,1)$
- compute $\left(\chi_{ij}^{tot}\right)^b = \pi_{ij}^b\left(\chi_{ij}^{obs}\right)^b + (1-\pi_{ij}^b)\left(\chi_{ij}^{miss}\right)^b$
- Compute $E(\beta_i)$ and $var(\beta_i)$

Mirtazapine meta-analysis: mean change in HAMD21 scores, standard deviations, and numbers of completers and non-completers for the mirtazapine and placebo arms.

Study	Placebo				Mirtazapine			
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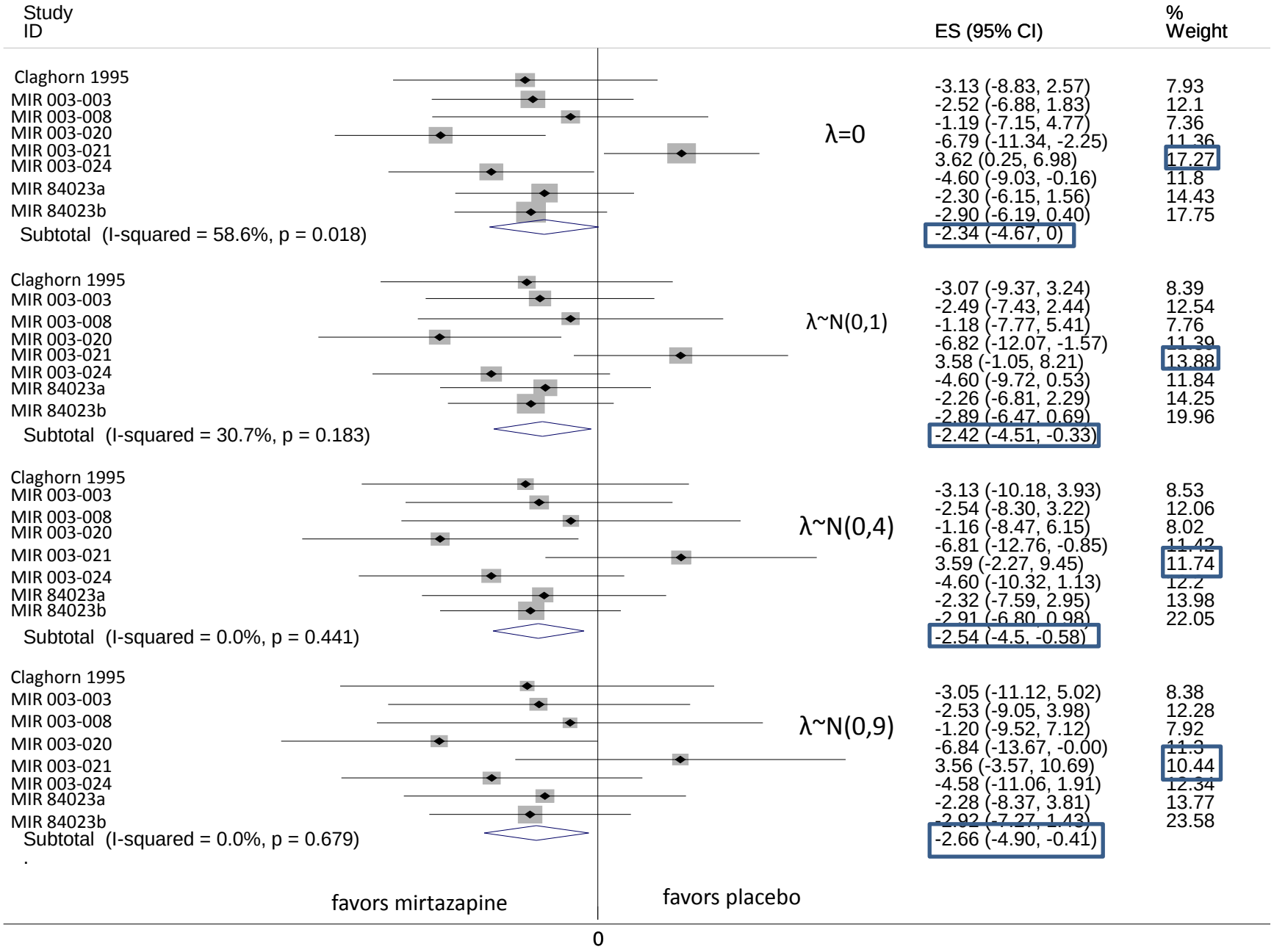
Study ID
ES (95% CI)
% Weight
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
λ=0
-3.13 (-8.83, 2.57) 7.93
-2.52 (-6.88, 1.83) 12.1
-1.19 (-7.15, 4.77) 7.36
-6.79 (-11.34, -2.25) 11.36
3.62 (0.25, 6.98) 17.27
-4.60 (-9.03, -0.16) 11.8
-2.30 (-6.15, 1.56) 14.43
-2.90 (-6.19, 0.40) 17.75
Subtotal (I-squared = 58.6%, p = 0.018)
-2.34 (-4.67, 0)
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
λ~N(0,1)
-3.07 (-9.37, 3.24) 8.39
-2.49 (-7.43, 2.44) 12.54
-1.18 (-7.77, 5.41) 7.76
-6.82 (-12.07, -1.57) 11.39
3.58 (-1.05, 8.21) 13.88
-4.60 (-9.72, 0.53) 11.84
-2.26 (-6.81, 2.29) 14.25
-2.89 (-6.47, 0.69) 19.96
Subtotal (I-squared = 30.7%, p = 0.183)
-2.42 (-4.51, -0.33)
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
λ~N(0,4)
-3.13 (-10.18, 3.93) 8.53
-2.54 (-8.30, 3.22) 12.06
-1.16 (-8.47, 6.15) 8.02
-6.81 (-12.76, -0.85) 11.42
3.59 (-2.27, 9.45) 11.74
-4.60 (-10.32, 1.13) 12.2
-2.32 (-7.59, 2.95) 13.98
-2.91 (-6.80, 0.98) 22.05
Subtotal (I-squared = 0.0%, p = 0.441)
-2.54 (-4.5, -0.58)
Claghorn 1995
MIR 003-003
MIR 003-008
MIR 003-020
MIR 003-021
MIR 003-024
MIR 84023a
MIR 84023b
λ~N(0,9)
-3.05 (-11.12, 5.02) 8.38
-2.53 (-9.05, 3.98) 12.28
-1.20 (-9.52, 7.12) 7.92
-6.84 (-13.67, -0.00) 11.3
3.56 (-3.57, 10.69) 10.44
-4.58 (-11.06, 1.91) 12.34
-2.28 (-8.37, 3.81) 13.77
-2.92 (-7.27, 1.43) 23.58
Subtotal (I-squared = 0.0%, p = 0.679)
-2.66 (-4.90, -0.41)
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favors mirtazapine
favors placebo
0

Conclusions/Future work

- We developed a model that can
  - model departures from MAR (IMDoF,IMRoM) for MD, SMD and RoM
  - downweight studies with lots of missing data
- we need priors for IMDoM/IMRoM or conduct a sensitivity analysis
- there is a trade-off between within-study and between-study variability
- method extended to network meta-analysis allowing for multi-arm studies
- metamiss command in STATA (in collaboration with Anna Chaimani)

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