Comparison of Bayesian modeling strategies to handle missing binary outcome data in *network meta-analysis*: an empirical study

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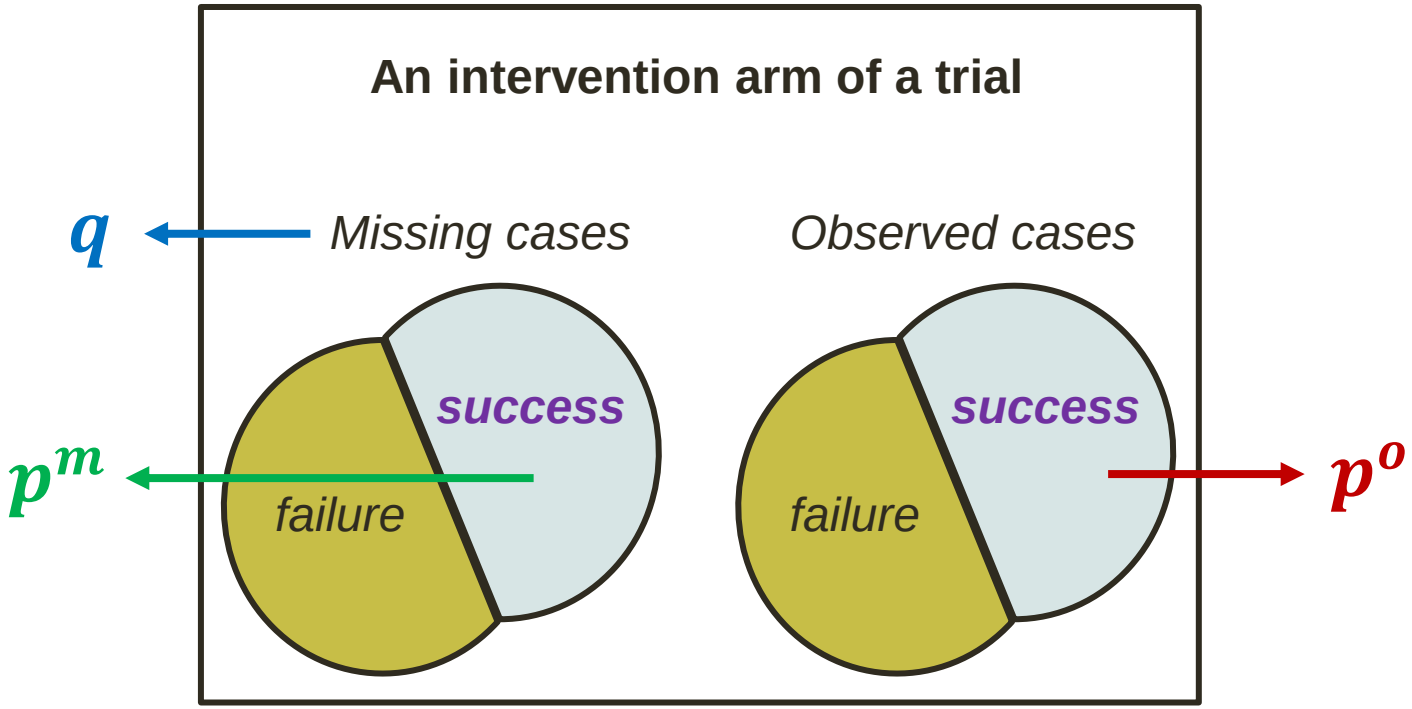
Missingness models considered (1)

Pattern-mixture model



$$p = p^o \cdot (1 - q) + p^m \cdot q$$

Missingness parameter considered (1)

Pattern-mixture model

$$IMOR = \frac{p^m/(1-p^m)}{p^o/(1-p^o)}$$

'Odds of an event being missing to odds of an event being observed'

$$log(IMOR) = \delta_{ik} \sim N(\Delta_{ik}, \sigma_{ik}^2)$$

arm k of trial i

Δ	interpretation
Δ > 0	more likely that a missing case to be an event
Δ < 0	less likely that a missing case to be an event
Δ = 0	Missing at random (on average)

$$\sigma_{ik}^2 = \sigma^2 = 1$$

White IR, Higgins JP, Wood AM. Allowing for uncertainty due to missing data in meta-analysis--part 1: two-stage methods. Stat Med 2008;27:711-727

Prior structures of logIMOR (1)

Identical structure

… log IMORs are considered identical depending on further assumptions on whether missingness mechanisms are:

- **common in the whole network**
- **intervention-related**
- **trial-related**

Assumption	Prior specification
Common-within-network	$\delta_{ik} = \delta,\ \delta \sim N(0,1)$
Intervention-specific	$\delta_{ik} = \delta_{t_{ik}},\ \delta_{t_{ik}} \sim N(\Delta_{t_{ik}}, 1)$
Trial-specific	$\delta_{ik} = \delta_i,\ \delta_i \sim N(0,1)$

Turner NL, Dias S, Ades AE, Welton NJ. A Bayesian framework to account for uncertainty due to missing binary outcome data in pairwise meta-analysis. Stat Med 2015;34:2062-80

Missingness scenarios

$$\delta_{t_{ik}} \sim \mathbf{N}\left(\boldsymbol{\Delta_{t_{ik}}}, \mathbf{1}\right)$$

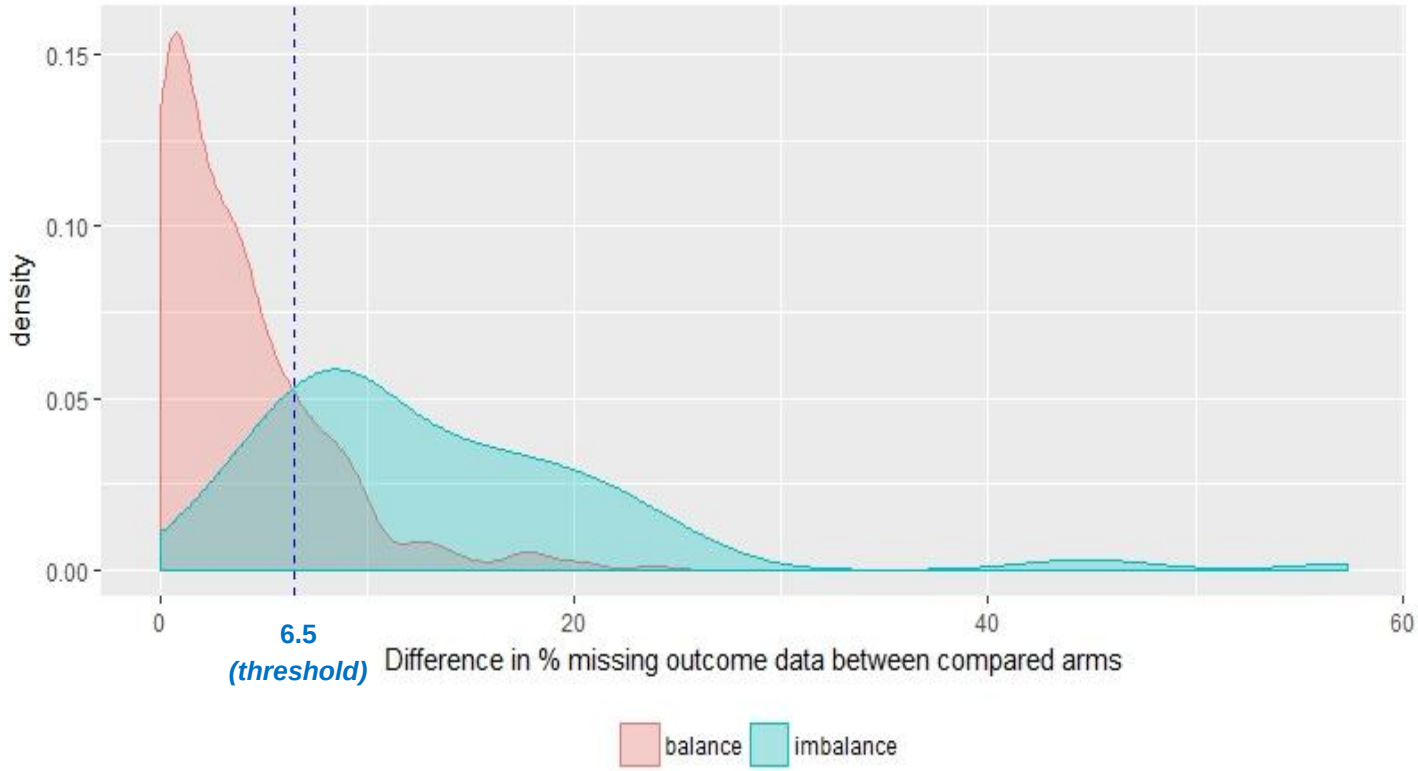
Scenario	Interpretation	Abbrev.
$e^{\Delta_{ik}} = 1$	Missing at random more likely	**MAR**
$e^{\Delta_{t_{ik}}} = 2$	More missing are events	**MME**
$e^{\Delta_{t_{ik}}} = 1/2$	More missing are non-events	**MMNE**
$e^{\Delta_{t_{ik}}} = 2$ & $e^{\Delta_R} = 1/2$	**MME** for non-references; **MMNE** for reference	**BC**
$e^{\Delta_{t_{ik}}} = 1/2$ & $e^{\Delta_R} = 2$	**MMNE** for non-references; **MME** for reference	**WC**

Spineli LM, Higgins JP, Cipriani A, Leucht S, Salanti G. Evaluating the impact of imputations for missing participant outcome data in a network meta-analysis. Clin Trials 2013;10:378-88

Prevalence and balance of MOD (1)

Balance vs. Imbalance in the compared arms

Calculate difference in %MOD between compared arms ***within each trial*** :



Prevalence and balance of MOD (2)

Prevalence: low, moderate, large

Use of the *'five to twenty' rule* based on Sackett et al (1997) ***in each network***:

- **low** → median of total %MOD across trials < 5%
- **high** → median of total %MOD across trials > 20%
- **moderate** → otherwise

- **Low** MOD → 12/29 (41%) networks
- **Moderate** and **balance** MOD → 14/29 (48%) networks
- **Moderate** and **imbalance** MOD → 2/29 networks
- **Large and imbalance** MOD → 1/29 networks

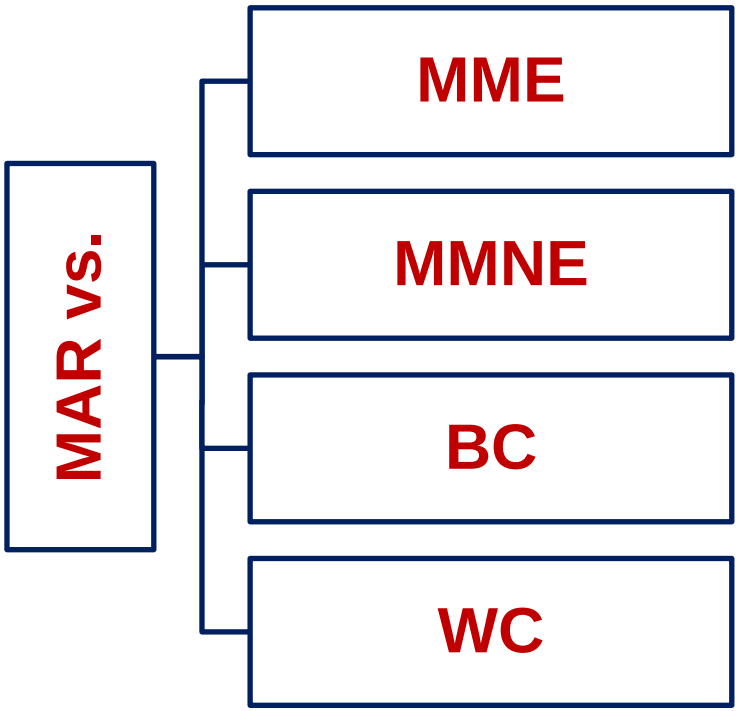
Characterising networks

Sackett DL, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: how to practice and teach EBM. New York: Churchill Livingstone, 1997

Research questions (1)

Agreement between on average MAR and extreme scenarios

- Identical log IMORs with intervention-specific normal prior distribution



$$\delta_{ik} = \delta_{t_{ik}},\ \delta_{t_{ik}} \sim N\left(\boldsymbol{\Delta_{t_{ik}}}, 1\right)$$

Research questions (2)

Agreement between accountability & ignorance of uncertainty due to MOD

- Identical log IMORs with intervention-specific normal prior distribution

$$\delta_{ik} = \delta_{t_{ik}},\ \delta_{t_{ik}} \sim N\left(\boldsymbol{\Delta_{t_{ik}}}, 1\right)$$

- Scenarios considered: MAR, MME, MMNE, BC and WC

uncertainty about the scenario considered	
Accounted for vs.	**ignored**
$\delta_{t_{ik}} \sim N\left(\boldsymbol{\Delta_{t_{ik}}}, 1\right)$	$\delta_{t_{ik}} = \boldsymbol{\Delta_{t_{ik}}}$

Model specification & Presentation of results

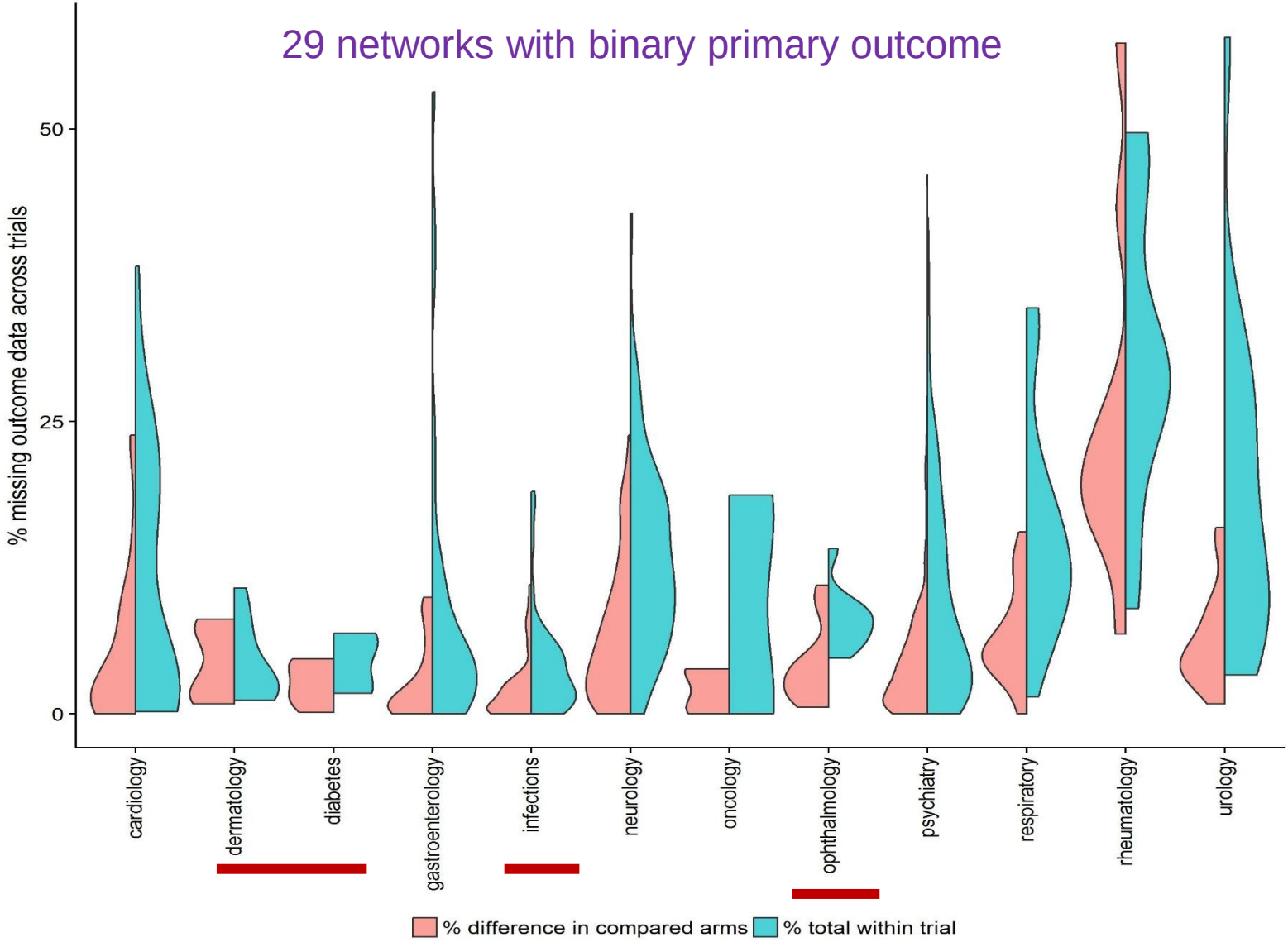
JAGS/R2jags

- Bayesian random-effects NMA model by Dias et al (2013);
- Incorporation of log IMOR as described in Turner et al (2015);
- Initially, GeMTC to obtain *automatically* the nodes to split according to van Valkenhoef et al (2015);
- Then application of the node-splitting model as developed by Dias et al (2010);
- For location parameters use of N(0, 10 000);
- Use of empirical priors on between-trial variance based on Turner et al (2015);
- 3 chains for 10 000 updates and 1 000 burn-in.
- Bland-Altman plots to investigate the agreements in the compared methods


RESULTS

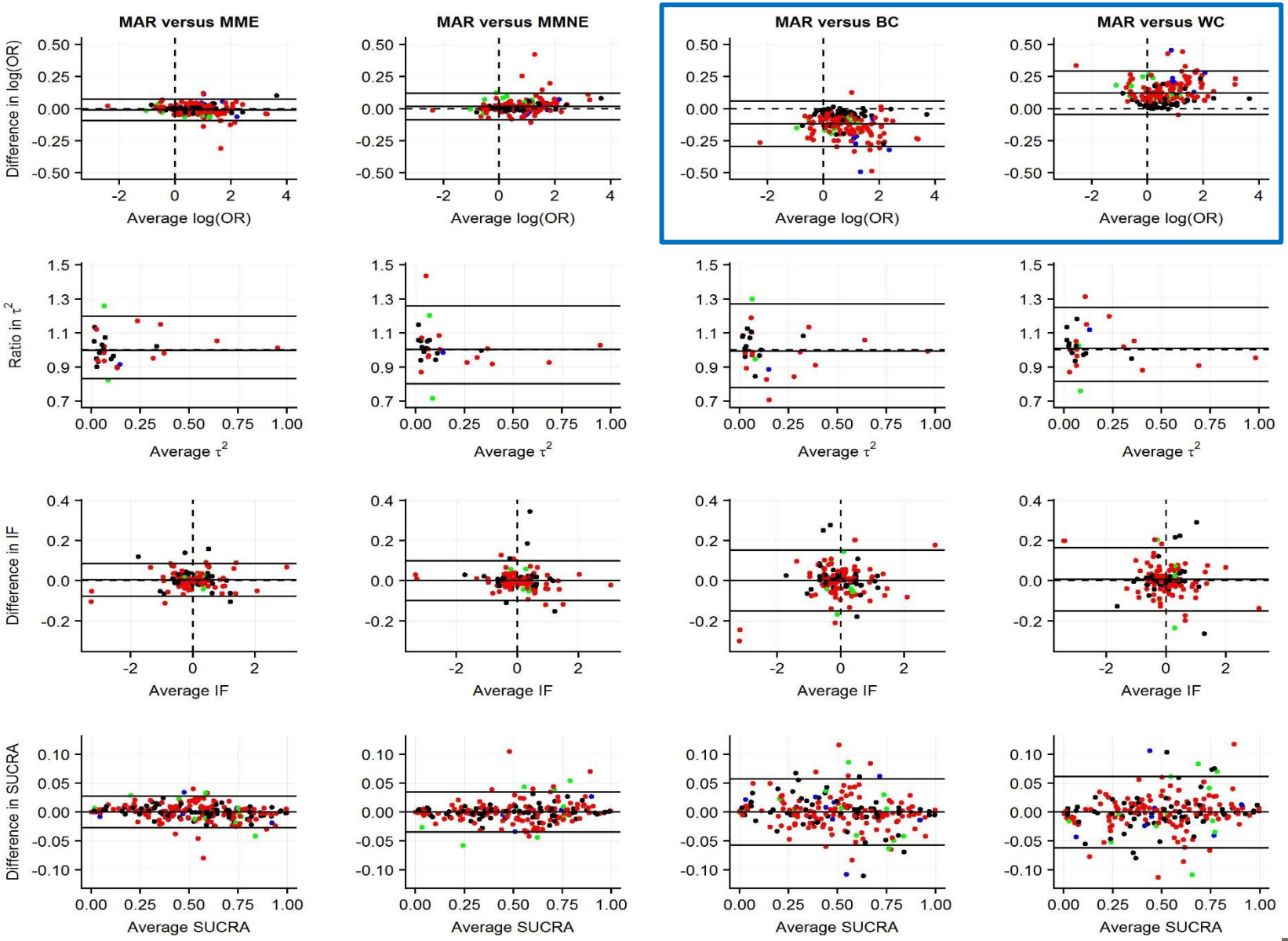
Description of the database used

29 networks with binary primary outcome



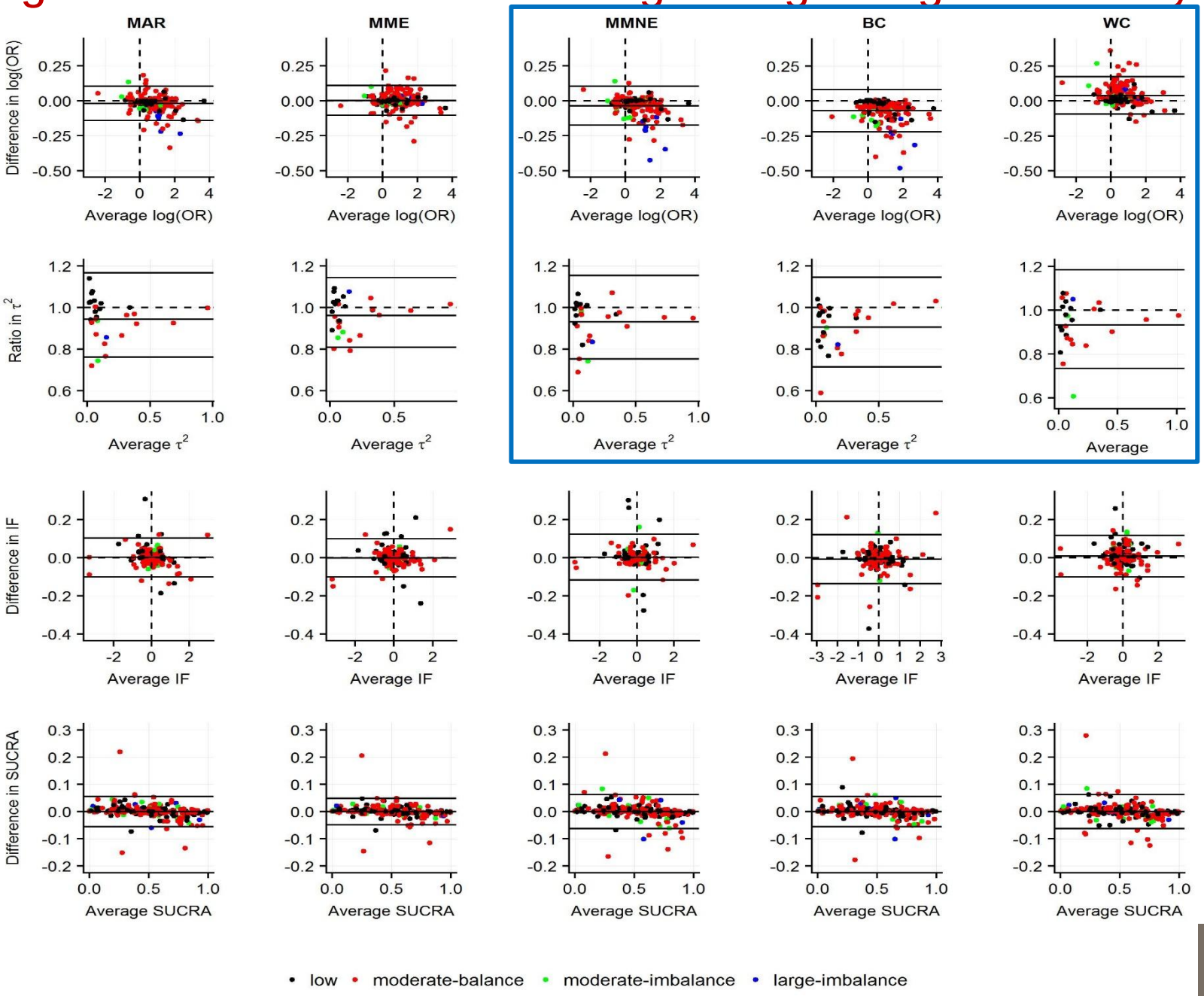
Agreement between on average MAR and extreme scenarios

Posterior mean/median

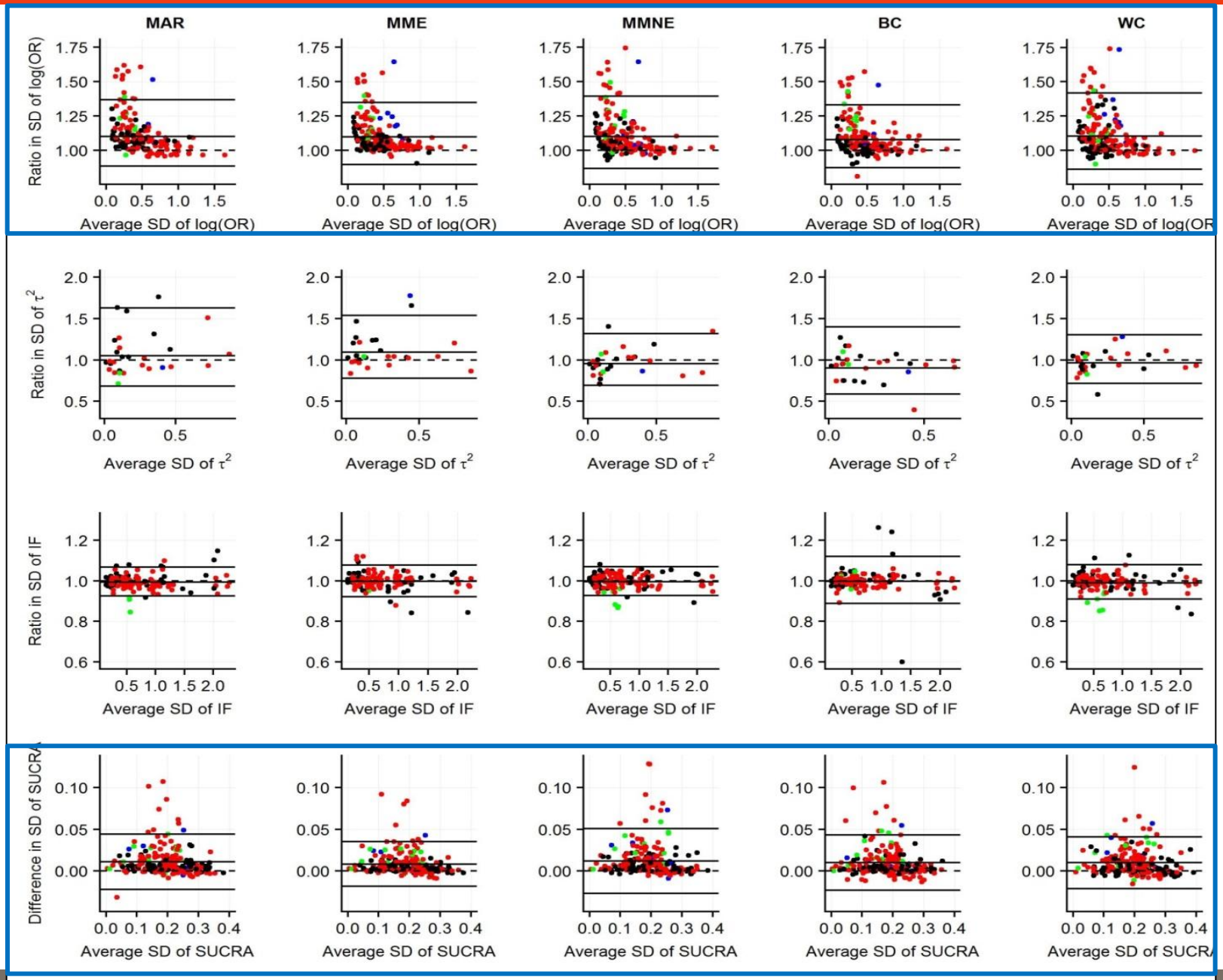


Agreement between accounting and ignoring uncertainty

Posterior mean/median



Posterior standard deviation



Limitations of the study

- Available arm-level data in only 29 (11%) out of 273 NMAs due to severe limitations in the reporting quality of the reviews.
  - *I do not expect that conclusions would differ, if a larger dataset was collected.*
- Good agreement when points were randomly scattered within 2 standard deviations and average bias was close to 0 (for differences) or 1 (for ratios)
  - *These limits might not represent clinically important differences.*
- Prior values for log IMOR were chosen based on recommendations from relevant literature
  - *Ideally, priors should be elicited tailored to condition and interventions considered*.

Take-home messages

1. Use **'on average MAR' for primary analysis** and **assumptions with clinical plausibility as sensitivity analyses**.
2. **Model the missingness mechanism via the IMOR parameter** in order to accommodate the uncertainty about the missingness scenarios considered.
3. **Avoid imputing or excluding MOD before analysis!!!** 💣💣💣

☺ Simulation analysis is ongoing.

Literature mentioned in ‘Model specification’

1. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. Med Decis Making 2013;33:607–617.
2. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JP. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med 2015;34:984-98.
3. van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Res Synth Methods 2016;7:80-93.
4. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010;29:932-44.
5. Turner NL, Dias S, Ades AE, Welton NJ. A Bayesian framework to account for uncertainty due to missing binary outcome data in pairwise meta-analysis. Stat Med 2015;34:2062-80.
6. Plummer M. rjags: Bayesian graphical models using MCMC. R package version 3-10, 2013. URL: http://CRAN.R-project.org/package=rjags.
7. Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. Stat Sci 1992;7:457–511.