Comparison of exclusion, imputation and modelling of missing binary outcome data in frequentist network meta-analysis

Chrysostomos Kalyvas[1], Loukia M Spineli[2]

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DFG Deutsche Forschungsgemeinschaft

Hannover Medical School

[1]Department of Health Technology Assessment Statistics, Merck Sharp & Dohme, Brussels, Belgium

[2]Midwifery Research and Education Unit, Hannover Medical School, Hannover, Germany

What is already known

- **Missing outcome data (MOD)** are inevitable in systematic reviews.
- Reviewers tend to handle MOD as **missing at random (MAR)**.
- Available MAR methods:
  - exclusion and ignorance of MOD;
  - exclusion but accountability of MOD;
  - imputation of observed risks;
  - pattern-mixture model.

Exclusion and ignorance of MOD

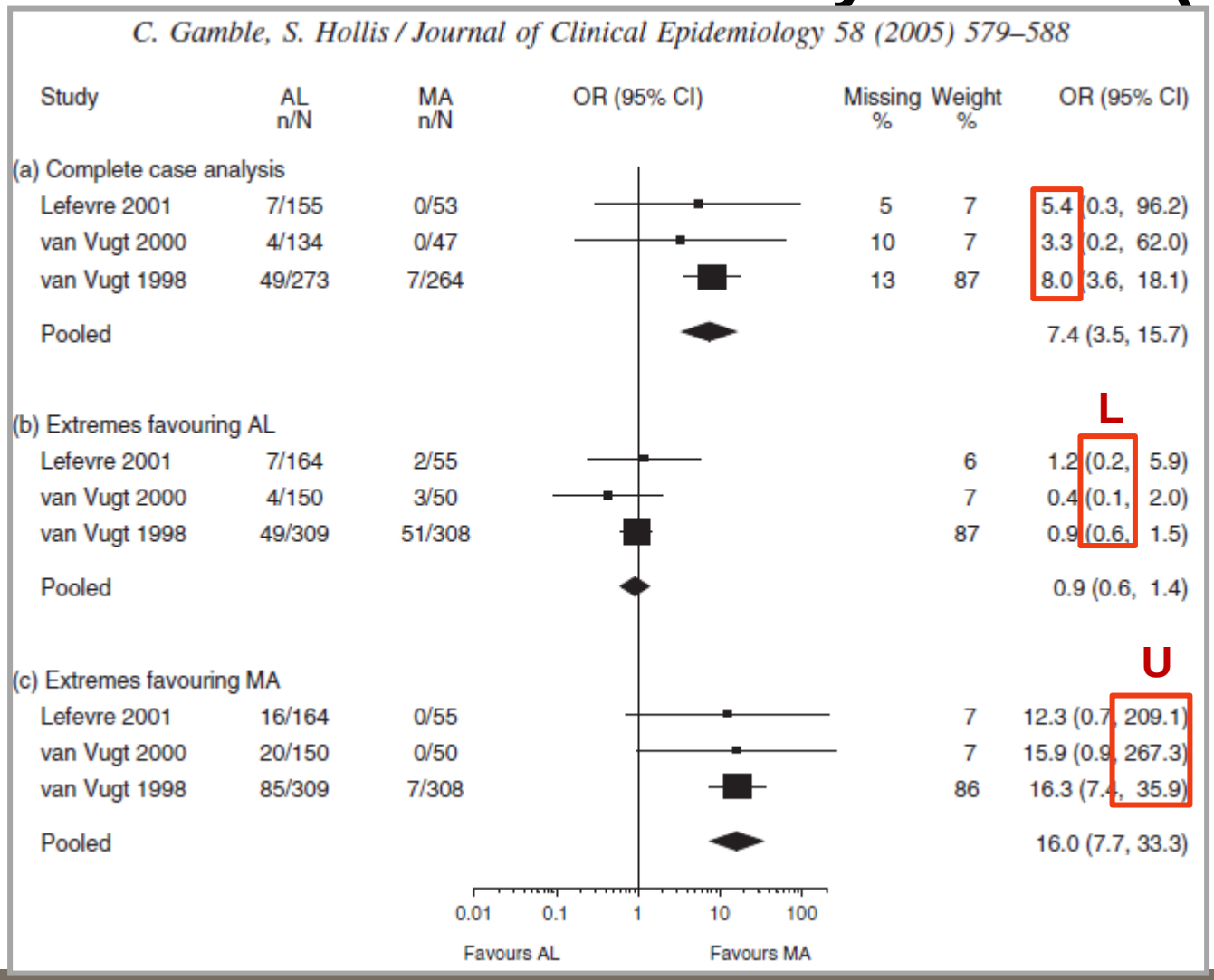
	Completers	MOD
Active	☺☺☺☺☺☺☹ ☺☺☺☺☺☹☹	☹☺☺ ☹☹☹
Placebo	☹☹☹☺☺ ☹☹☹☹☺	☹☹☹☹☹ ☹☹☹☺☺

	Completers
Active	☺☺☺☺☺☺☹ ☺☺☺☺☺☹☹
Placebo	☹☹☹☺☺ ☹☹☹☹☺

Truth	Risk	Risk Ratio
Active	13/20	2.60 (1.14, 5.93)
Placebo	5/20	

Exclusion	Risk	Risk Ratio
Active	11/14	2.62 **(0.98, 7.01)**
Placebo	3/10	

Exclusion but accountability of MOD (1)



Gamble C, Hollis S. Uncertainty method improved on best-worst case analysis in a binary meta-analysis. J Clin Epidemiol. 2005;58(6):579-88.

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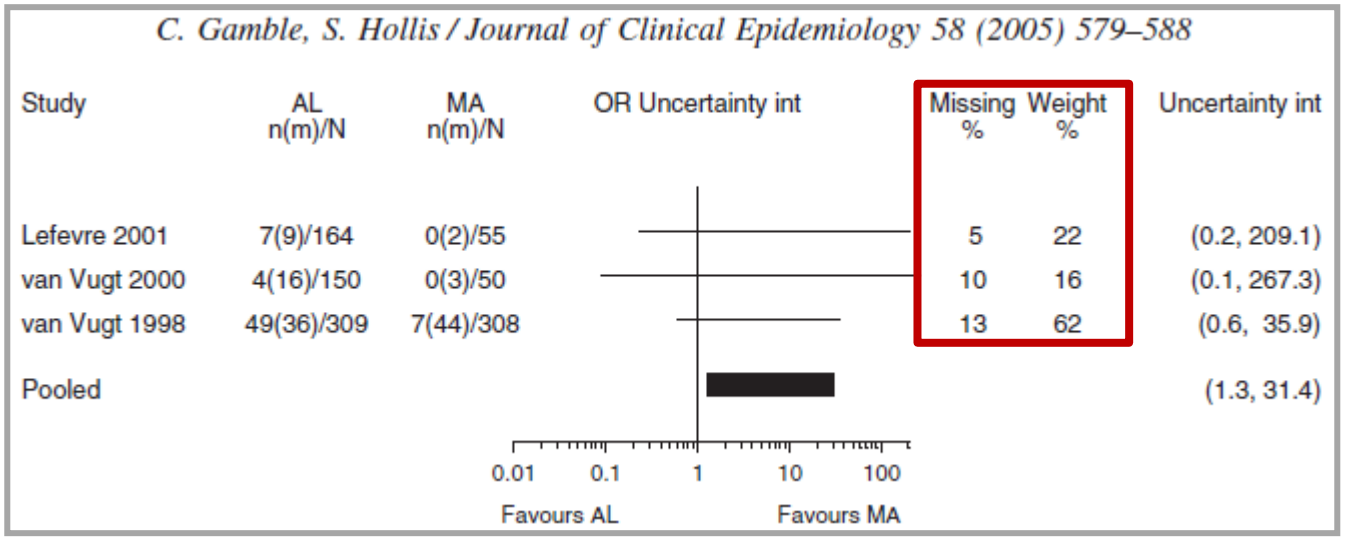
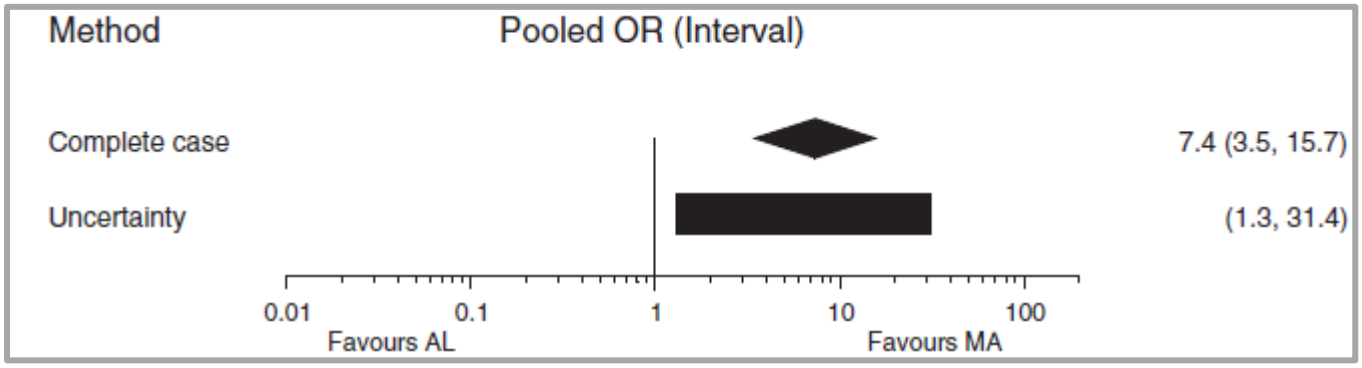
Exclusion but accountability of MOD (2)

within-trial:

$$se(logOR) = \frac{U - L}{2 \cdot 1.96}$$





Gamble C, Hollis S. Uncertainty method improved on best-worst case analysis in a binary meta-analysis. J Clin Epidemiol. 2005;58(6):579-88.

Imputation of observed risks

Truth	Risk	%MOD	Risk Ratio
Active	13/20	**30%**	2.60 (1.14, 5.93)
Placebo	5/20	**50%**	

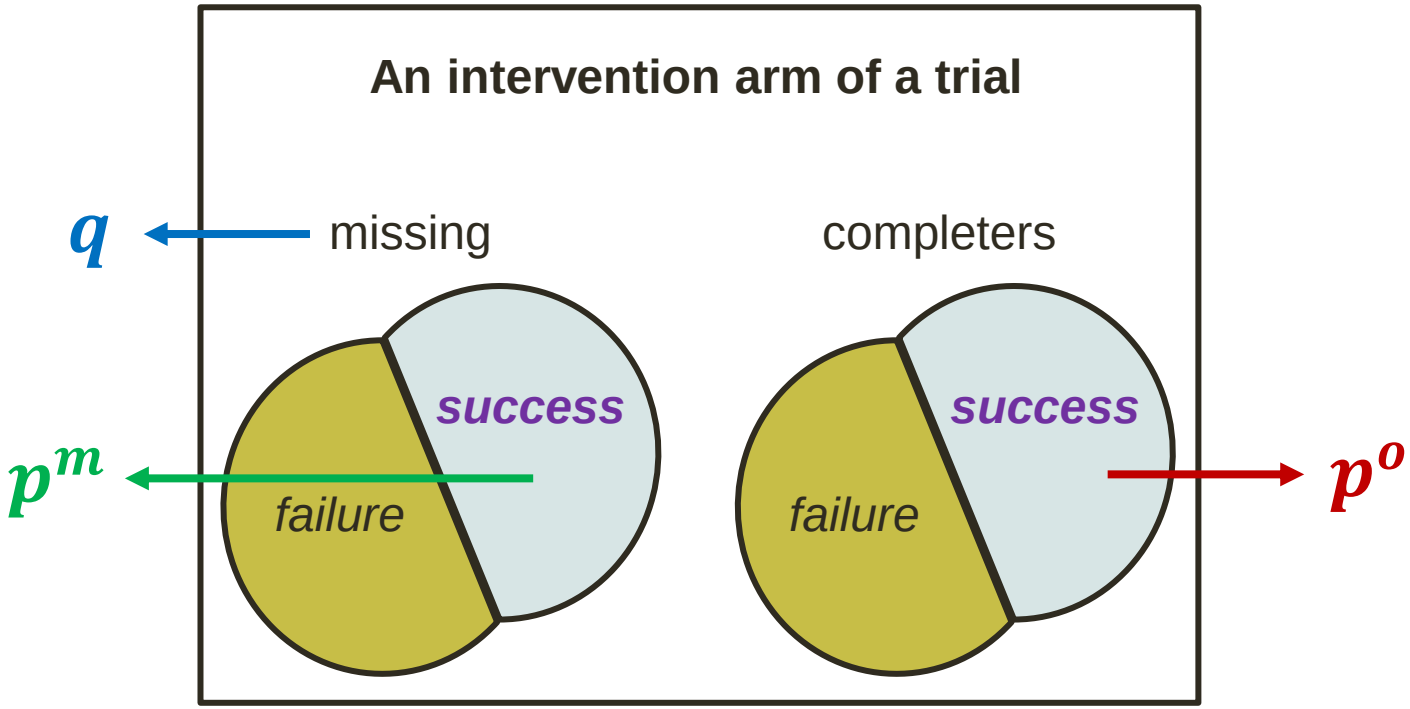
Observed	to impute
$\frac{11}{14} \cdot (1 - \mathbf{0.3})$	$+ \frac{11}{14} \cdot \mathbf{0.3}$
$\frac{3}{10} \cdot (1 - \mathbf{0.5})$	$+ \frac{3}{10} \cdot \mathbf{0.5}$

- **Same RR** with Exclusion (and ignorance of MOD)…
- but **more precise** for maintaining the randomised sample

Imputation	Risk	Risk Ratio
Active	11/14	2.62 **(1.29, 5.31)**
Placebo	3/10	

Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. Clin Trials. 2008;5(3):225-39.

Pattern-mixture model



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

Little RJA. Pattern-mixture models for multivariate incomplete data. Journal of the American Statistical Association 1993; 88:125–134

Informative Missingness Odds Ratio

Under 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'

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

arm k of trial i

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

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(5):711-27.

Pattern-mixture model with IMOR

- Risk ratio (RR) same with Exclusion.
- Variance of RR =

Variance due to sampling error

+

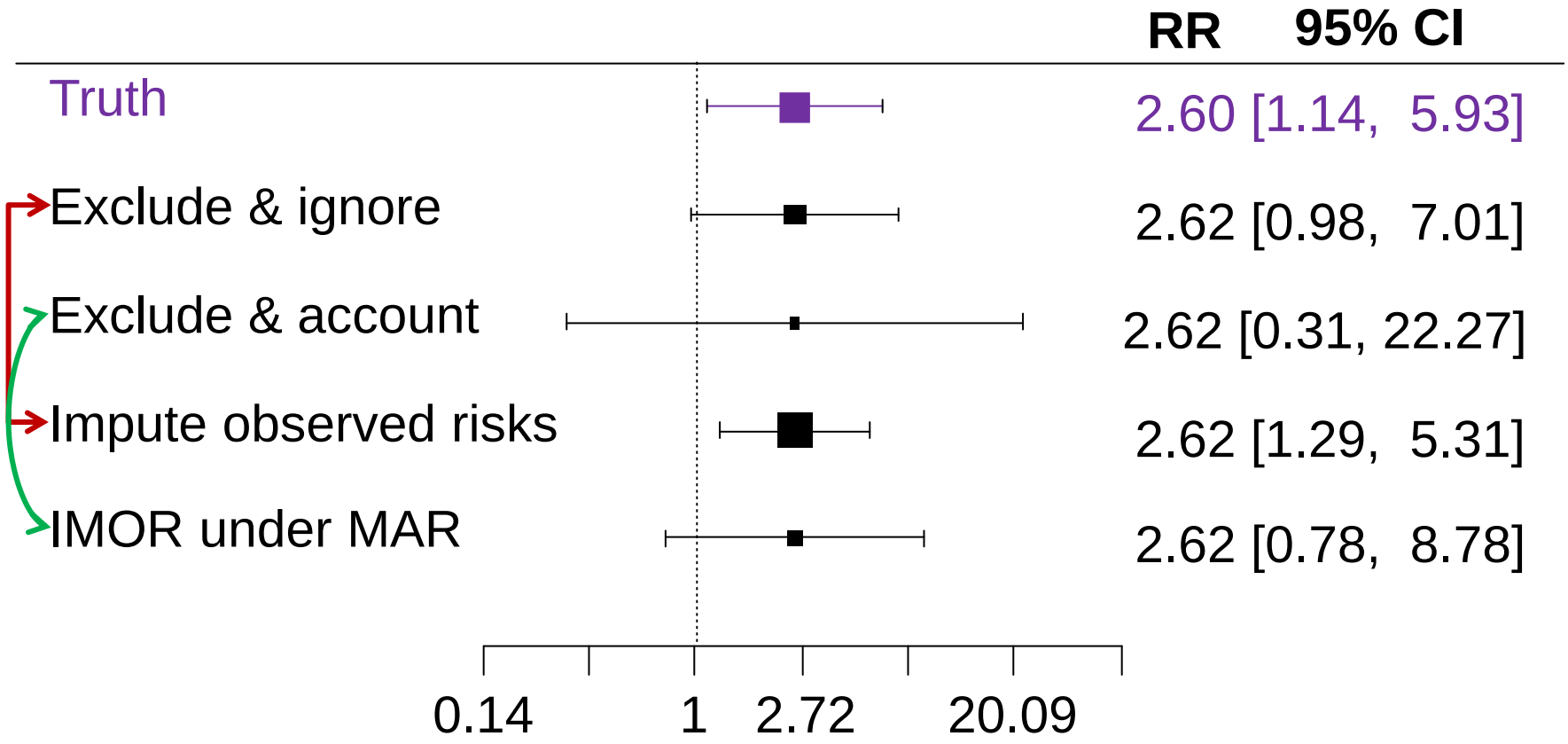
Variance arising from IMOR **| MAR**

↓

IMOR	Risk	Risk Ratio
Active	11/14	2.62 **(0.78, 8.76)**
Placebo	3/10	

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(5):711-27.

Bring all methods together



ignores uncertainty due to MOD

accounts uncertainty due to MOD

Aims of the study

Empirical study

- Agreement of the methods regarding **network meta-analysis (NMA) parameters**:
  - Exclude and ignore MOD
  - Exclude but account MOD
  - Impute observed risks

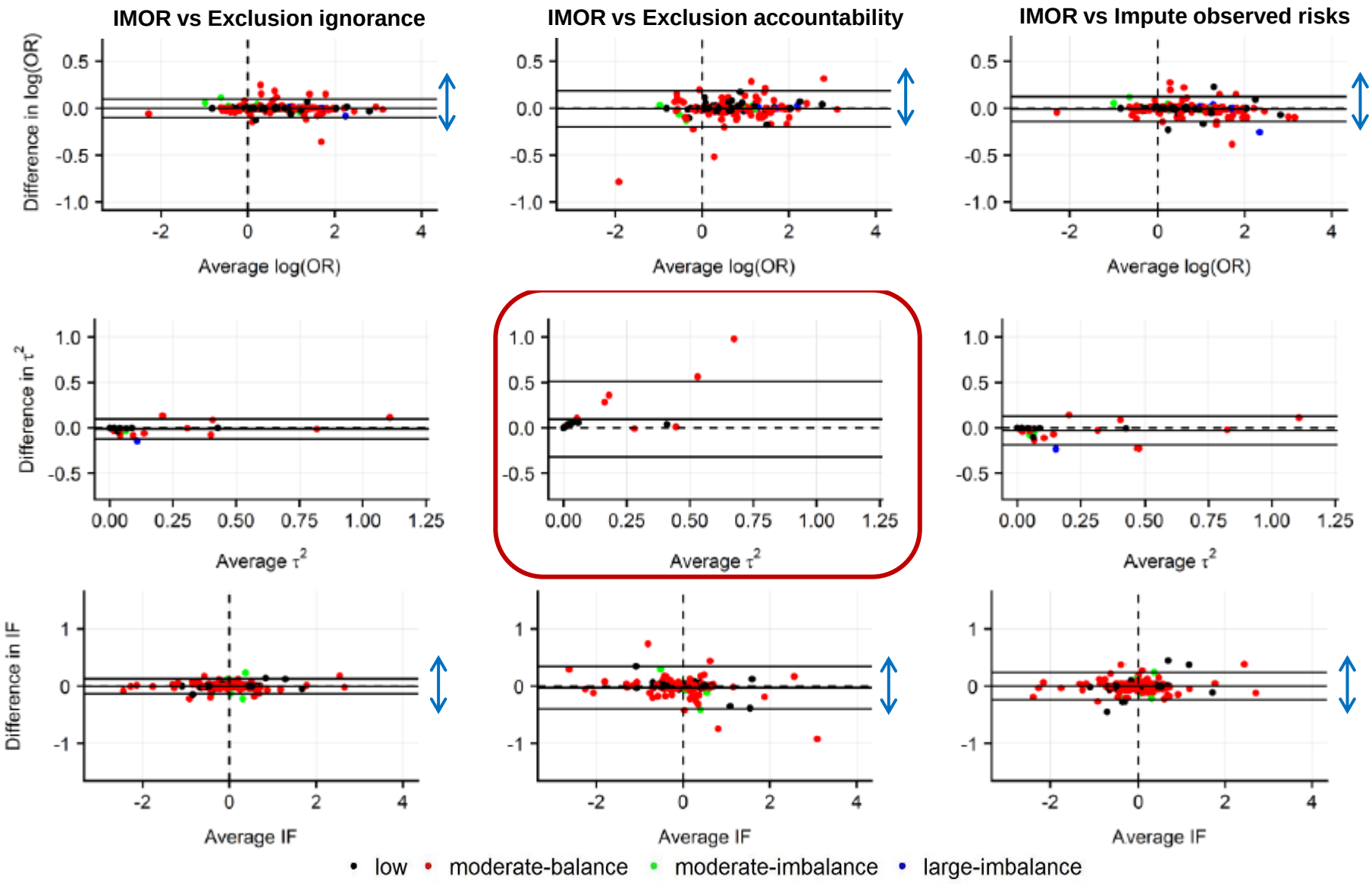
  } vs. IMOR under MAR

Simulation study

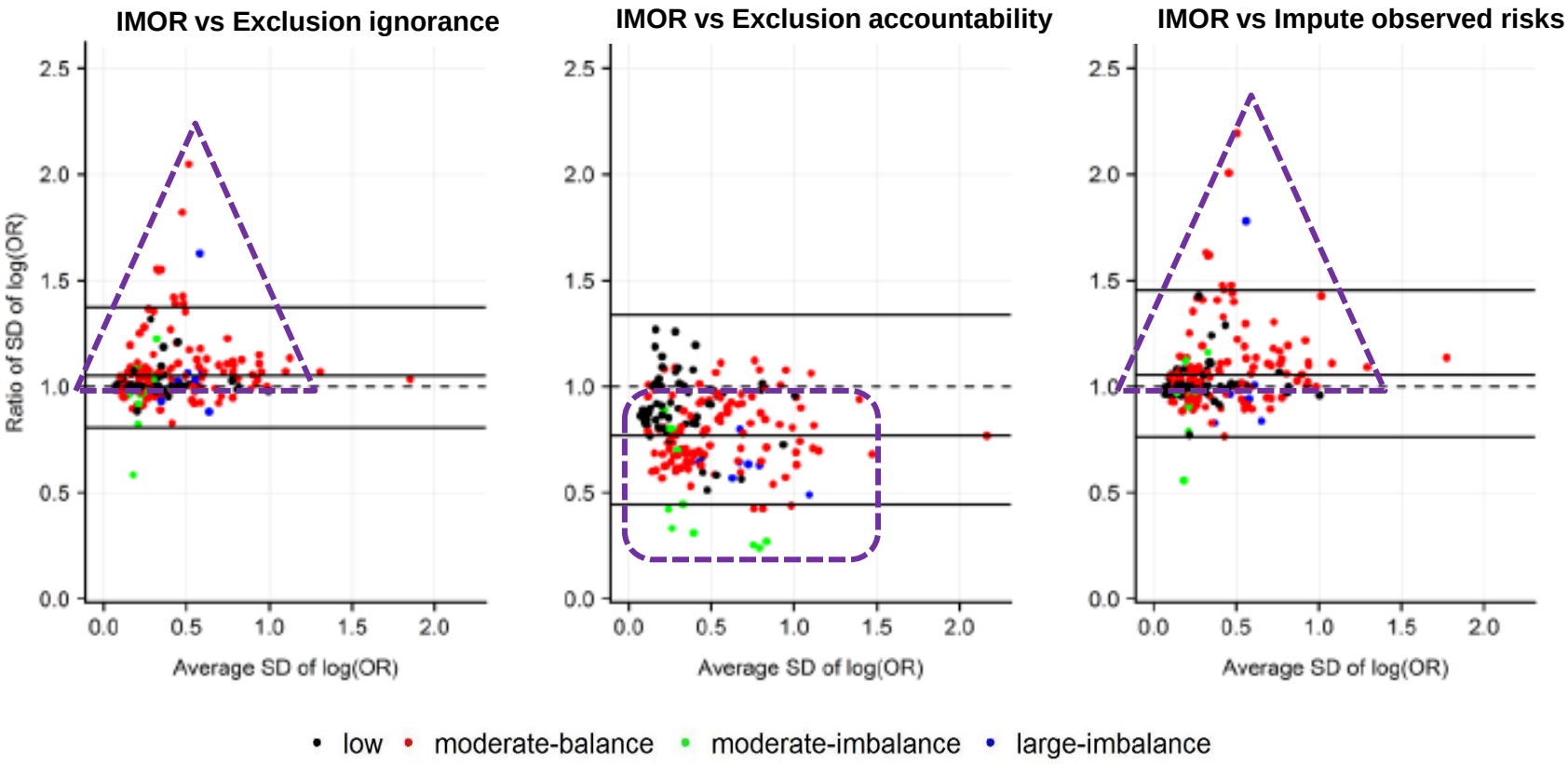
- Performance of methods in terms of:
  - Bias (NMA log odds ratio, τ^2)
  - Coverage (NMA log odds ratio)

Empirical study: Methods used

- Database: 29 networks from various health fields.
- MOD distinction: **low**, **moderate** and **large** w/o balanced arms.
- Bland-Altman scatterplots to assess agreement.
- Random-effects NMA model based on electrical network theory.
- All analyses were ran using the *netmeta* R package.

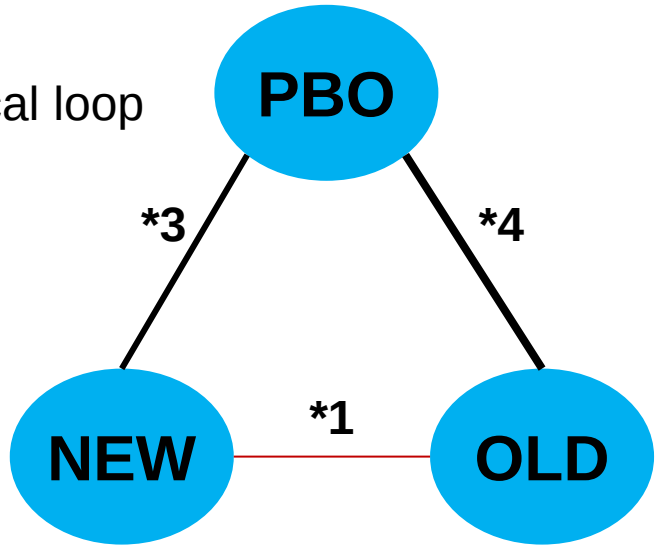

IMOR vs Exclusion ignorance
IMOR vs Exclusion accountability
IMOR vs Impute observed risks
Difference in log(OR)
Average log(OR)
Difference in τ^2
Average τ^2
Difference in IF
Average IF
low
moderate-balance
moderate-imbalance
large-imbalance

Posterior standard deviation of NMA log OR



Simulation study: Methods used

*Typical loop



Scenarios based on 29 networks

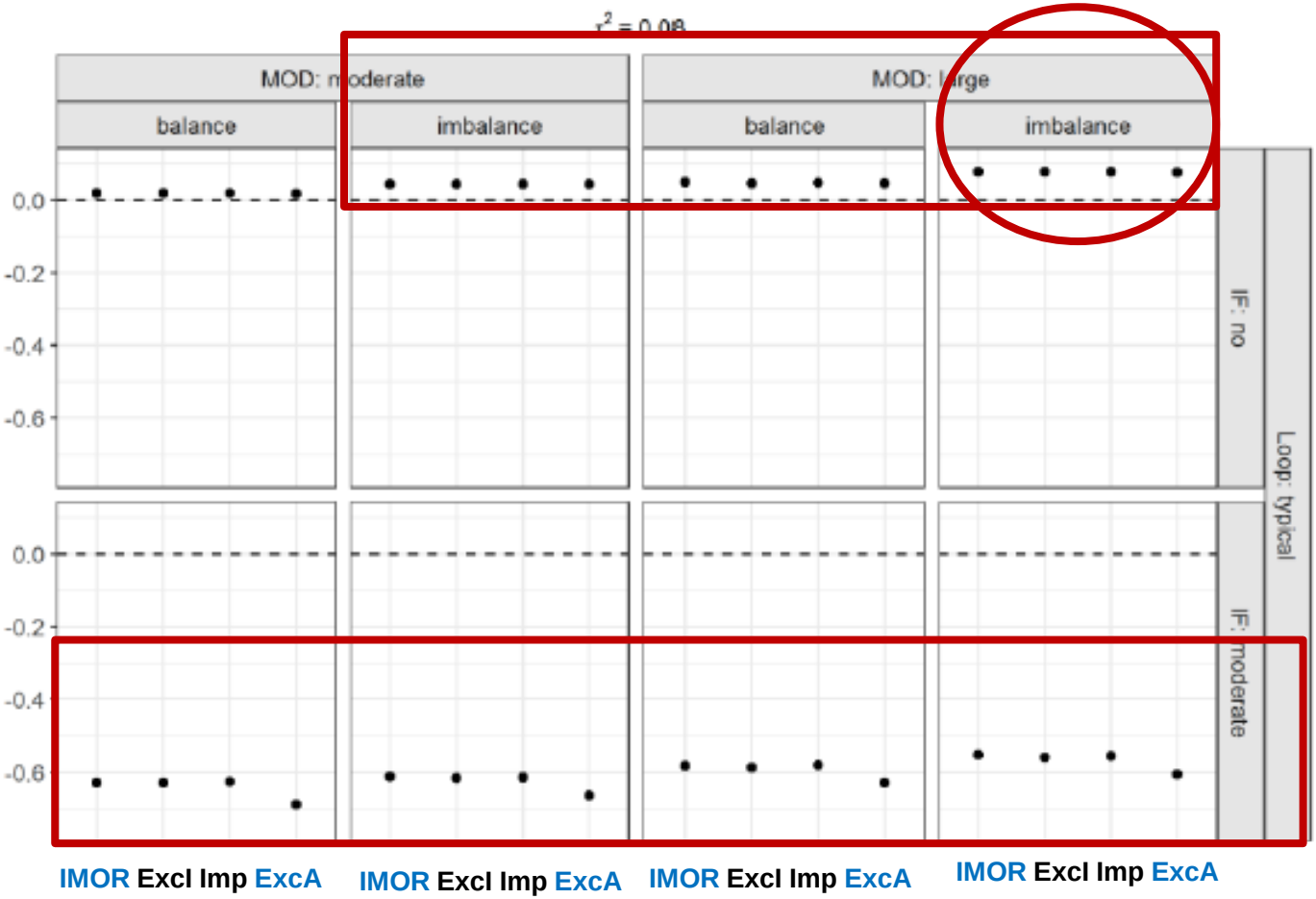
- PBO-ctrl studies have less patients
  - Baseline risk higher in OLD than PBO

- IMOR = 2 for NEW and OLD
- IMOR = 0.5 for PBO

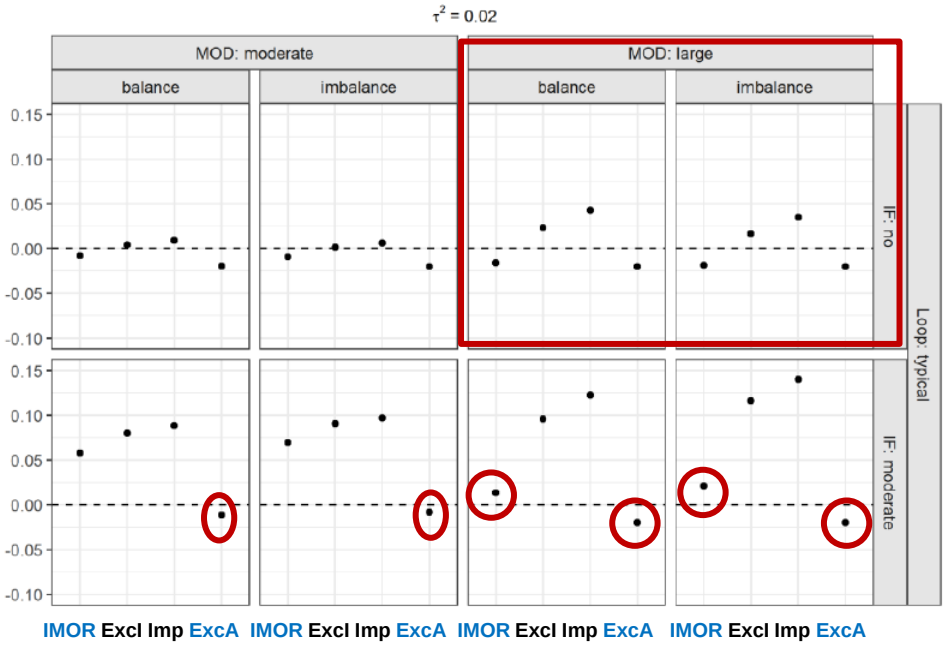
Comparison		Moderate %MOD		Large %MOD	
NEW	PBO	$U(0.05,0.10)$	$U(0.11,0.20)$	$U(0.21,0.30)$	$U(0.31,0.40)$
OLD	PBO				
NEW	OLD				

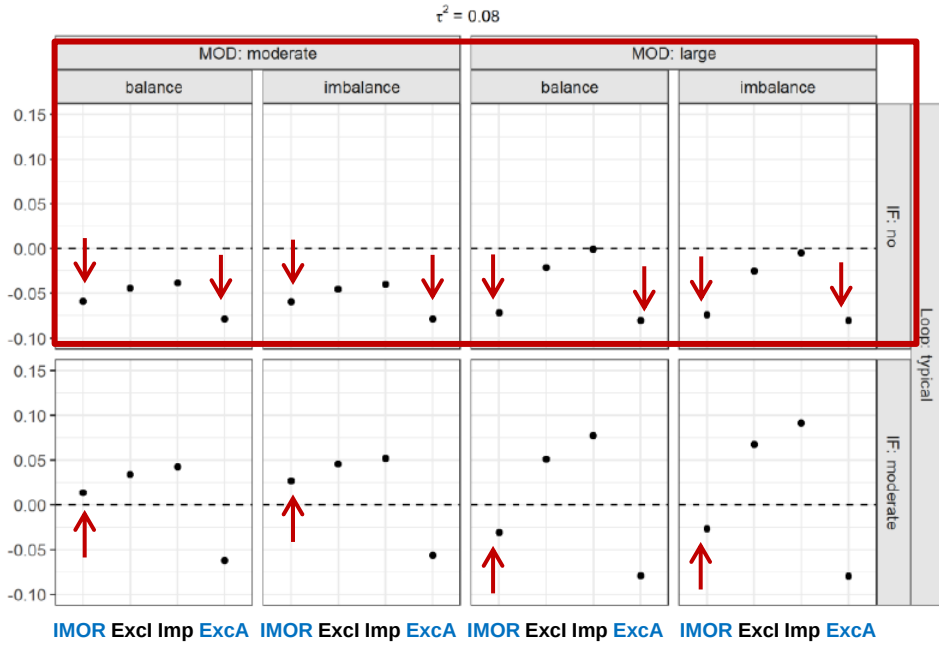
Veroniki AA, Mavridis D, Higgins JPT, Salanti G. Characteristics of a loop of evidence that affect detection and estimation of inconsistency: a simulation study. BMC Med Res Methodol. 2014;14:106.
Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. Stat Med. 2001;20:3875–89.

Mean bias for log OR (new vs. old): substantial τ^2

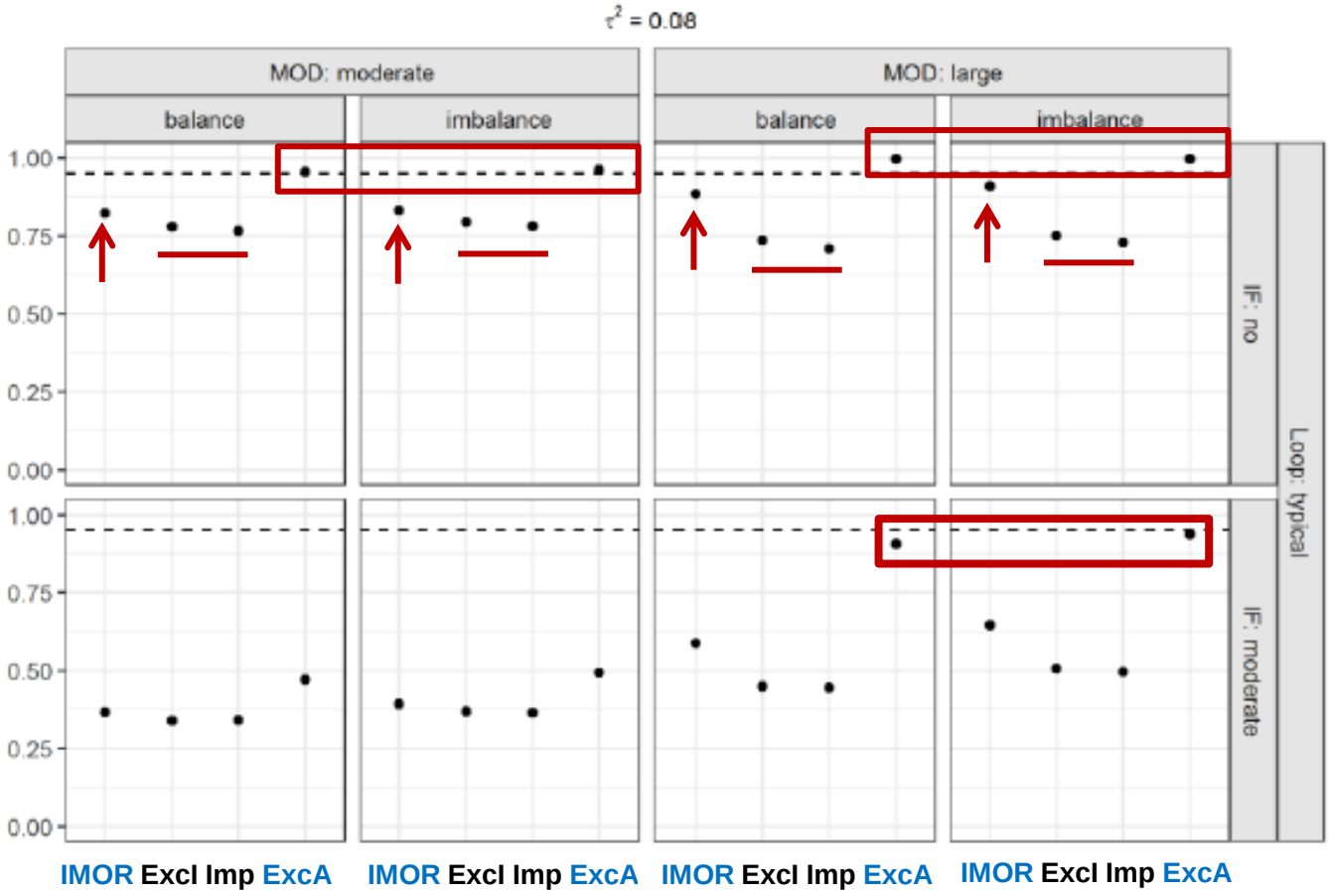


Mean bias for τ^2: typical loop





95% coverage for log OR (new vs. old): substantial τ^2



Take home message

- ✗ Methods that **ignore uncertainty** due to MOD are **simple, but suboptimal** overall.
- ✓ Methods that **account for uncertainty** due to MOD should **be preferred**.
  - ? 'Exclusion with accountability' **shares same shortcoming** with 'Exclusion but ignorance'.
  - ➢ IMOR is computationally intensive but **adjusts results for MOD** while **maintain**ing **randomised sample**.
  - ? Interpret IMOR with **caution** when: **large MOD**, **substantial τ^2** and/or **inconsistency**.

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https://theculturetrip.com/europe/belgium/articles/10-things-to-know-when-traveling-in-brussels-belgium/

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Thank you for your attention!