Quantifying the robustness of primary analysis results: A case study on missing outcome data in pairwise and network meta-analysis§

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Sensitivity Analysis (SA)

- Integral part of the systematic reviews.
- Explore the sensitivity of primary analysis results to different re-analyses of the same dataset or part thereof.
- Popular in the analysis of missing participant outcome data (MOD)
  - Do different reasons for MOD affect the primary analysis results?

Patsopoulos et al. (2008); National Research Council (2010)

SA to address MOD in meta-analyses

- Most systematic reviews addressing MOD **do not** perform SA.
- Those few systematic reviews conducting SA:
  - consider a few clinically implausible scenarios for MOD;
  - do not provide a definition of similar results;
  - emphasise changes in the statistical significance (for significance level 5%) of the summary results.
- Conclusions are sensitive to the selected significance level!

Spineli et al. (2015); Kahale et al. (2018); Spineli et al. (2018)

Proposed framework for SA

- **Progressively stringent** yet clinically relevant scenarios for the MOD mechanism.
- **Objective measure of 'divergence'** of each re-analysis from the primary analysis results.
- **Objective definition of** a total **minimally accepted 'divergence'** between the primary analysis and all re-analysis results for a comparison.
- **Comprehensive illustration** of the summary **results under all different scenarios**.

Informative Missingness Parameter

- Measure the departure from the MAR assumption via a pattern-mixture model:

Informative Missingness Odds Ratio (IMOR)

$$\frac{\text{odds of event given MOD}}{\text{odds of event given completers}}$$

Informative Missingness Difference of Means (IMDoM)

Mean outcome given MOD – Mean outcome given completers

MAR assumption: IMOR = 1 and IMDoM = 0

White et al. (2008); Mavridis et al. (2015)

Clinically plausible scenarios (1)

Defined for an intervention arm

Progressively stringent scenarios

log IMOR: $-ln(3), -ln(2),$ **0**, $ln(2)$, and $ln(3)$

IMDoM: $-2, -1,$ **0**, 1, and 2

MAR assumption

Mavridis et al. (2015); Turner et al. (2015); Spineli (2019a)

Clinically plausible scenarios (2)

5 assumed values → **5^2** possible pairs of values

… for a pairwise meta-analysis or a star-shaped network

Scenario	log IMOR		IMDoM	
	Active	Control	Active	Control
1	$-ln(3)$	$-ln(3)$	-2	-2
2	$-ln(3)$	$-ln(2)$	-2	-1
…	…	…	…	…
13 (MAR)	$\boldsymbol{ln(1)}$	$\boldsymbol{ln(1)}$	**0**	**0**
…	…	…	…	…
24	$ln(3)$	$ln(2)$	2	1
25	$ln(3)$	$ln(3)$	2	2

Clinically plausible scenarios (3)

5 assumed values → **5^2** possible pairs of values

… for a complex network of four interventions

log IMOR (similarly for IMDoM)

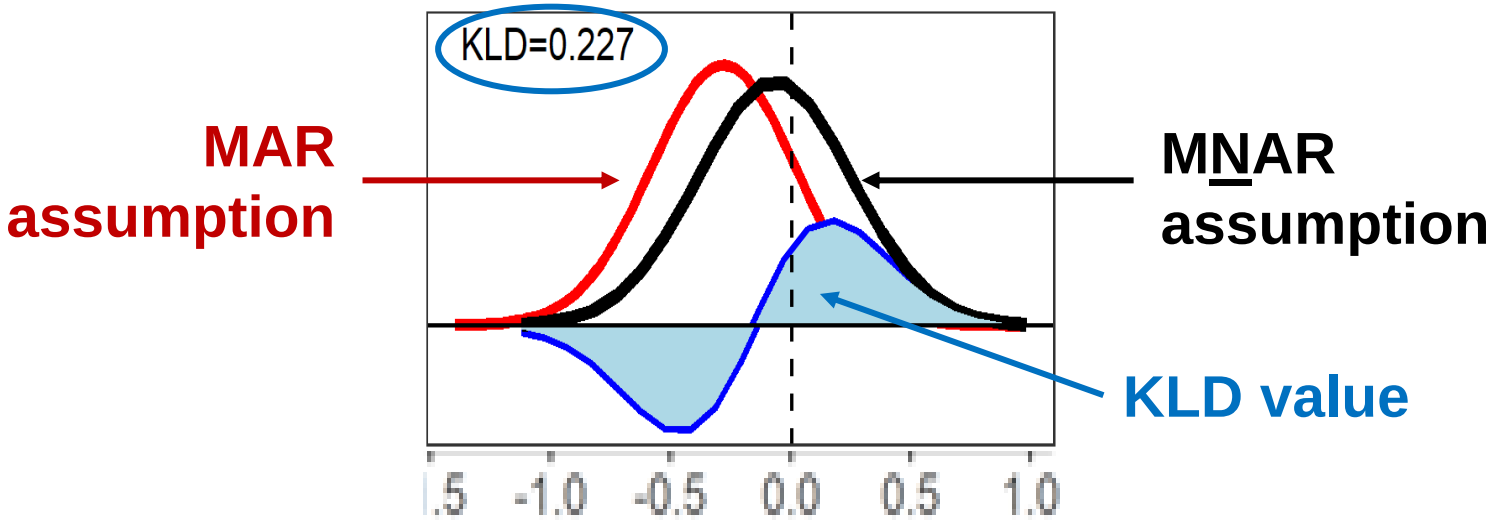
Scenario	A	B	C	D (ref.)
1	$-ln(3)$	$-ln(3)$	$-ln(3)$	$-ln(3)$
2	$-ln(3)$	$-ln(3)$	$-ln(3)$	$-ln(2)$
…	…	…	…	…
13 (MAR)	$\boldsymbol{ln(1)}$	$\boldsymbol{ln(1)}$	$\boldsymbol{ln(1)}$	$\boldsymbol{ln(1)}$
…	…	…	…	…
24	$ln(3)$	$ln(3)$	$ln(3)$	$ln(2)$
25	$ln(3)$	$ln(3)$	$ln(3)$	$ln(3)$

Spineli (2019b)

The Kullback–Leibler divergence (KLD)

How much two probability distributions differ from each other?

(e.g., normal posterior distribution of log OR under MAR and MNAR assumptions)



Kullback & Leibler (1951)

The robustness index (RI)

- **24 informative scenarios**

versus

MAR assumption

⇨ **24 KLD values**

➢ What is the ***total divergence*** from the primary analysis (MAR)?

$$RI = \sqrt{\sum_{i \in S} {D_{13,i}}^2}$$

$$S = \{1, 2, \dots, 12, 14, \dots, 25\}$$

- Pairwise meta-analysis ⇨ **One** RI
- NMA with T interventions ⇨ $\binom{T}{2}$ RIs

The threshold of robustness (1)

- No universally accepted definition of similar results.

Proposed intuitive rule

Low divergence → **RI < 1** SD of low heterogeneity

Substantial divergence → **RI ≥ 1** SD of low heterogeneity

Low statistical heterogeneity*

Scale	Prior	Median	95% interval
log OR	log-normal	0.08	0.003 – 2.18
SMD	log-t (5 df)	0.03	0.0002 – 5.16

*Empirically-based prior for τ^2 in a general health-care setting

Turner et al. (2015); Rhodes et al. (2015)

The threshold of robustness (2)

Decision rule in NMA

Robustness in the network

low divergence in **all** possible comparisons

$(RI < \sqrt{median})$

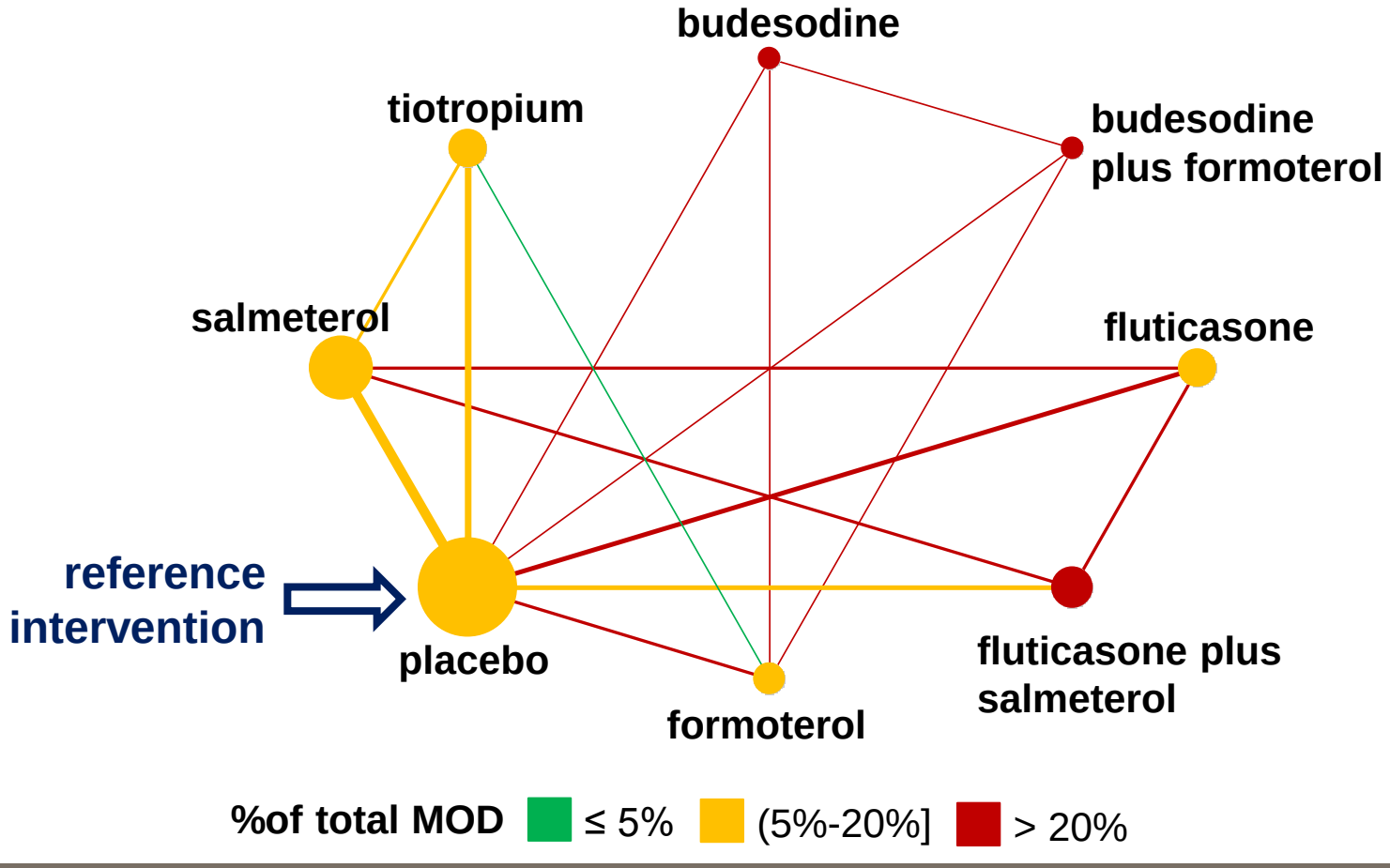
Lack of robustness in the network

substantial divergence in **at least one** possible comparison

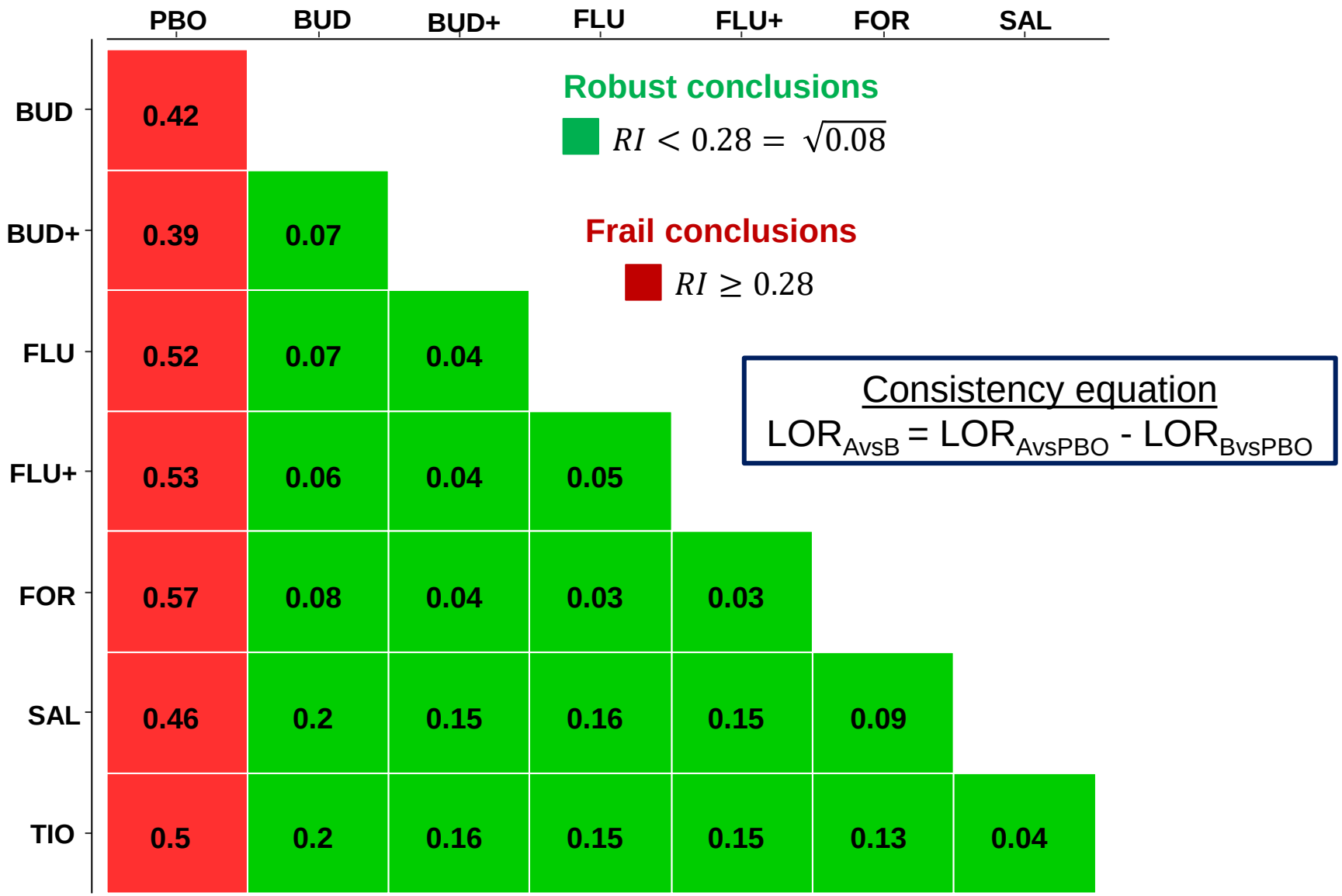
$(RI \geq \sqrt{median})$

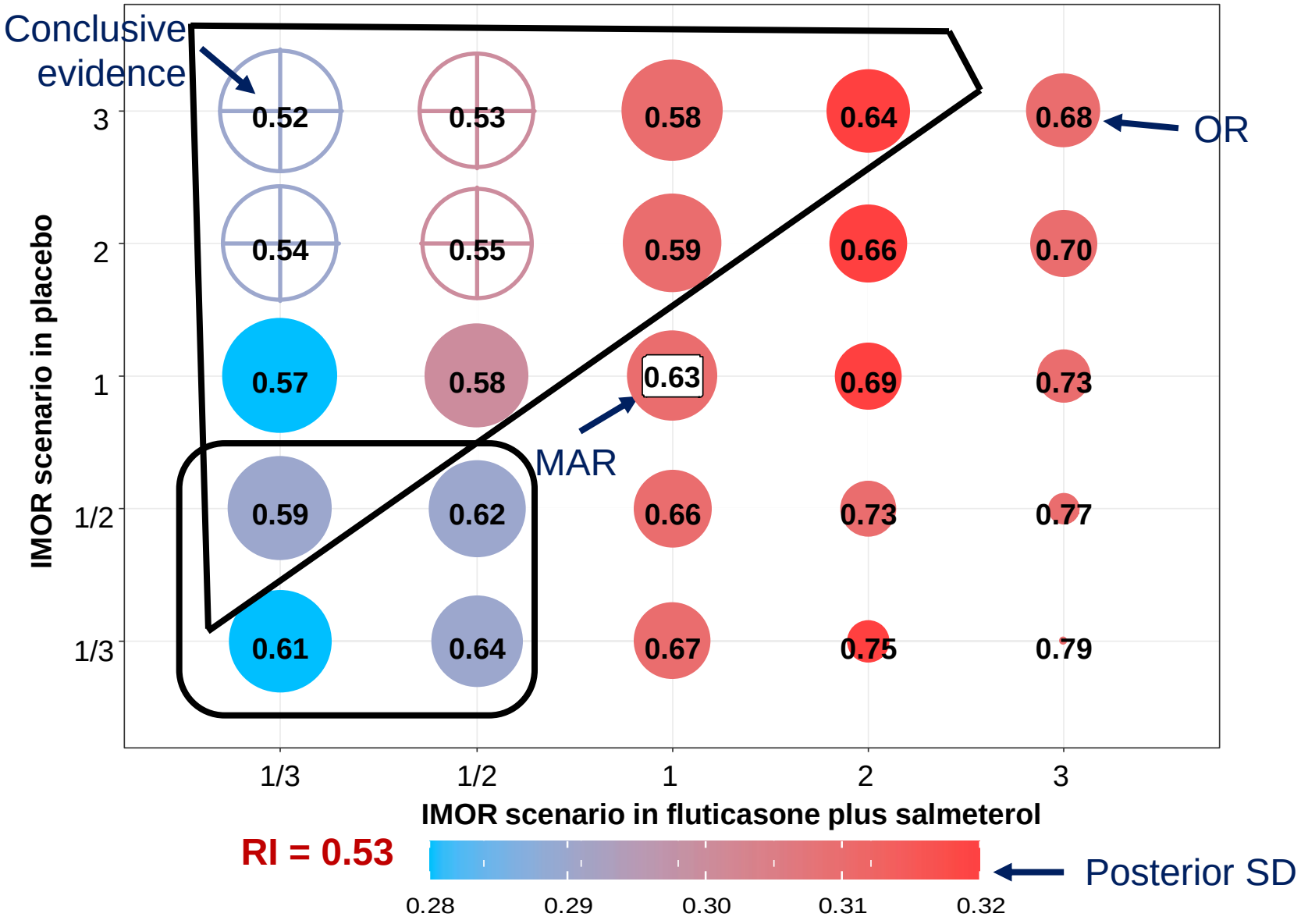
Illustrative example (1)

- Exacerbation (yes/no) of chronic obstructive pulmonary disease



Baker et al. (2009)


PBO
BUD
BUD+
FLU
FLU+
FOR
SAL
BUD
BUD+
FLU
FLU+
FOR
SAL
TIO
0.42
0.39
0.07
0.52
0.07
0.04
0.53
0.06
0.04
0.05
0.57
0.08
0.04
0.03
0.03
0.46
0.2
0.15
0.16
0.15
0.09
0.5
0.2
0.16
0.15
0.15
0.13
0.04
Robust conclusions
$RI < 0.28 = \sqrt{0.08}$
Frail conclusions
$RI \geq 0.28$
Consistency equation
$LOR_{AvsB} = LOR_{AvsPBO} - LOR_{BvsPBO}$


Conclusive evidence
OR
MAR
IMOR scenario in placebo
IMOR scenario in fluticasone plus salmeterol
3
2
1
1/2
1/3
0.52
0.53
0.58
0.64
0.68
0.54
0.55
0.59
0.66
0.70
0.57
0.58
0.63
0.69
0.73
0.59
0.62
0.66
0.73
0.77
0.61
0.64
0.67
0.75
0.79
RI = 0.53
Posterior SD
0.28
0.29
0.30
0.31
0.32

Discussion points

- The RI is useful to broader set of sensitivity analyses.
  - Comparing different priors for the heterogeneity parameter.
- The researchers can increase or decrease the RI threshold.
  - Decrease for HTAs; increase for ‘exploratory’ reviews.
- The RI thresholds are not tailored to the research question.
  - Expert opinion to define similarity in treatment effects.
- The scenarios are based on relevant empirical studies.
  - Ideally, define the scenarios with an expert assistance.

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Thank you for your attention!

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