A systematic survey shows that reporting and handling of missing outcome data in networks of interventions is poor

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What is already known

Missing outcome data (MOD) in systematic reviews with meta-analysis are **poorly administrated** regarding[1-3]:

- **Reporting** (*e.g. are there MOD in the included trials?)*
- **Handling** (*e.g. how the reviewers addressed MOD?)*
- **Acknowledging** (*MOD implications in the discussion of the results*)

1. **Gamble** C, Hollis S. Uncertainty method improved on best-worst case analysis in a binary meta-analysis. J Clin Epidemiol 2005;58:579–588.
2. **Spineli** LM, Pandis N, Salanti G. Reporting and handling missing outcome data in mental health: A systematic review of cochrane systematic reviews and meta-analyses.Res Synth Methods 2015;6:175–87.
3. **Akl** EA, Carrasco-Labra A, Brignardello-Petersen R, et al. Reporting, handling and assessing the risk of bias associated with missing participant data in systematic reviews: a methodological survey. BMJ Open 2015;5:e009368.

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Overall, **Cochrane and non-Cochrane reviews** are characterized by **inadequacies in reporting and handling MOD**.[1]

1. **Akl** EA, Carrasco-Labra A, Brignardello-Petersen R, et al. Reporting, handling and assessing the risk of bias associated with missing participant data in systematic reviews: a methodological survey. BMJ Open 2015;5:e009368.

What is currently unknown

A similar survey on **systematic reviews with network meta-analysis** (NMA) is missing

Expectations

- **Overall, poor quality** of reporting and addressing MOD in systematic reviews with NMA.

Search strategy

Published databases considered:

- Zarin et al. → **inception – 14/04/2015**; **≥ 4** interventions
- Tan et al.
- Bafeta et al.

  → **1997 – 07/2012**; **≥ 3** interventions

- Nikolakopoulou et al. → **inception – 12/2012**; **≥ 4** interventions

Our own search:

08/2012 – 03/2017; **≥ 3** interventions; using **Petropoulou et al. search strategy** in MEDLINE, EMBASE and the CDSRs.

Eligibility strategy (1)

Following Zarin et al.:

- ✓ Systematic reviews of randomized controlled trials (RCTs);
- ✓ No language restriction;
- ✘ Diagnostic test accuracy studies;
- ✘ Genetic studies;
- ✘ Observational studies;
- ✘ Mixture of RCTs and observational studies;
- ✘ Number of included trials **<** number of interventions.

Eligibility strategy (2)

Our own criteria:

- ✓ At least 3 interventions are investigated;
- ✓ Systematic reviews published from **2009 and onwards**;
  - ❖ *the new Cochrane risk of bias tool was published during 2009*
- ✘ RCTs with non-standard design;
  - ❖ e.g. *quasi, crossover, factorial, cluster, split-mouth.*
- ✘ Commentaries, letters, editorials;
- ✘ Case-series;

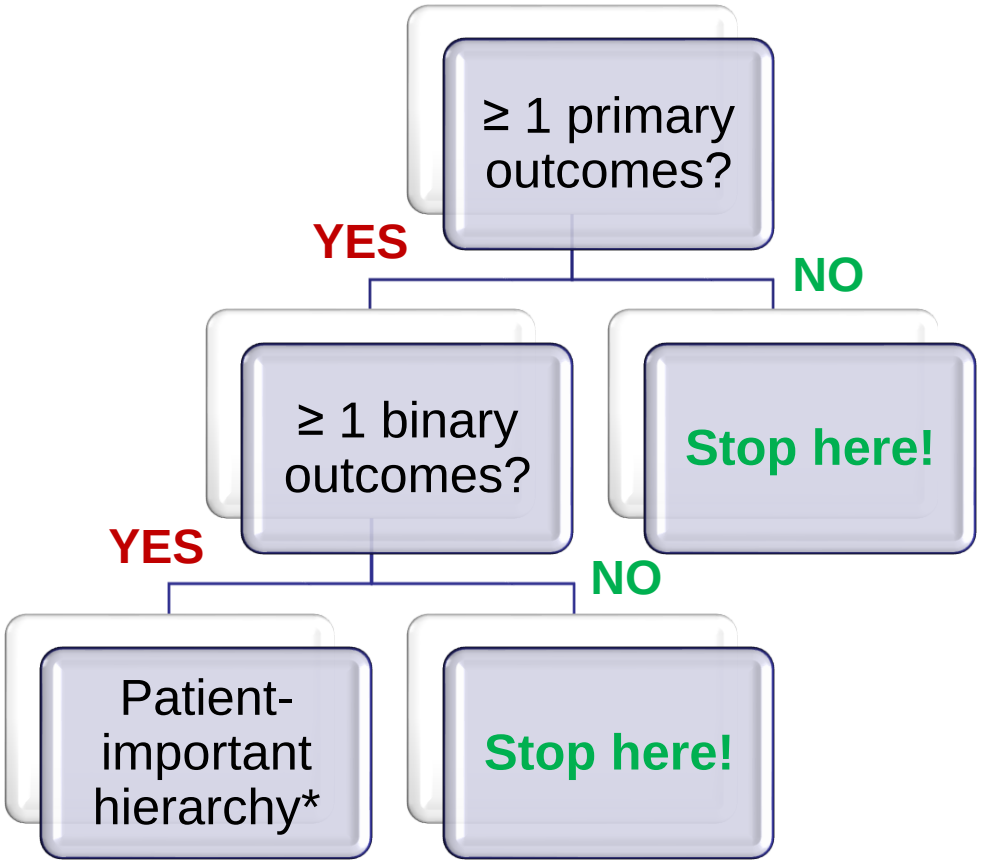
Eligibility strategy (3)

Our own criteria:

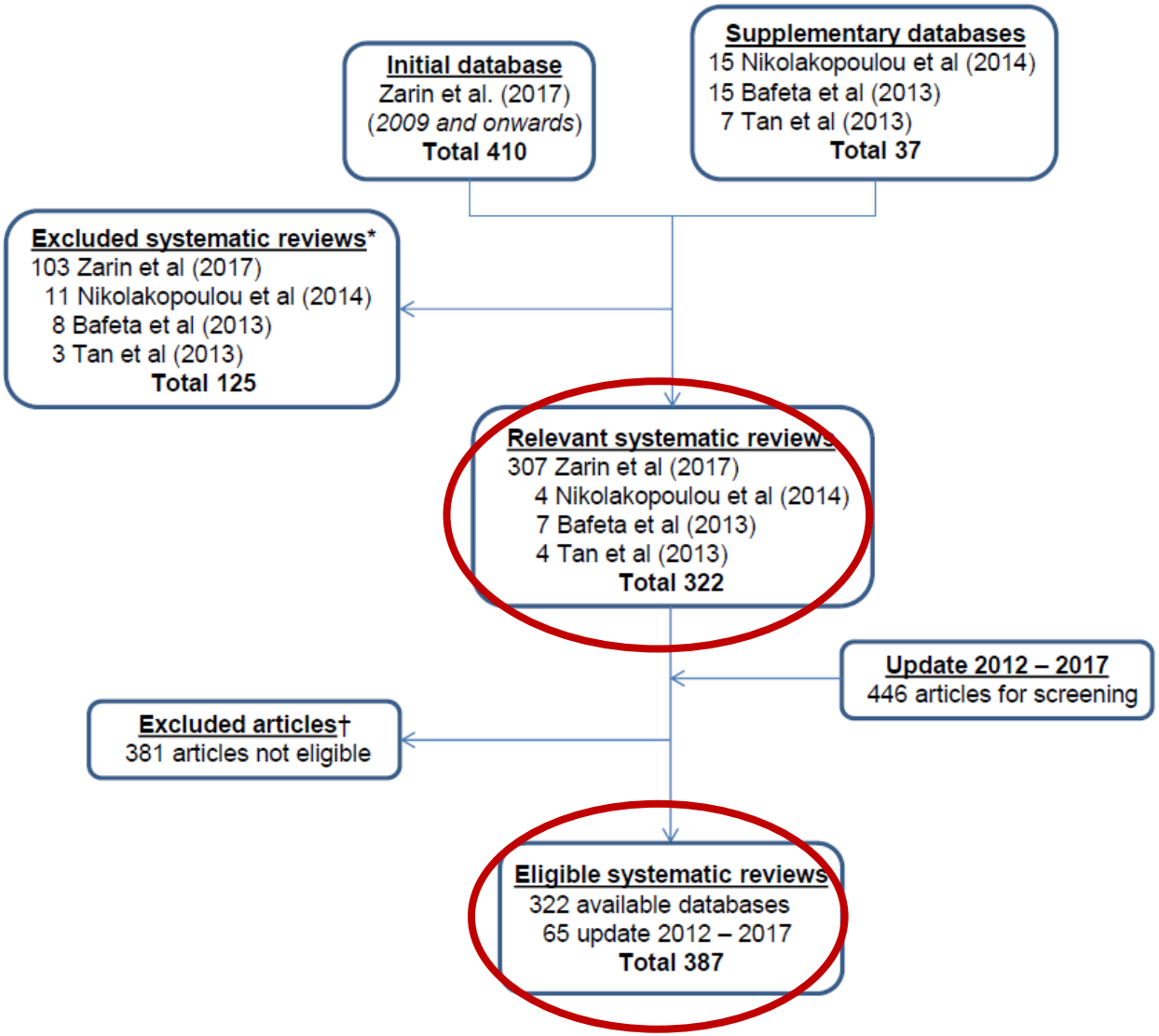
- ✓ At least 3 interventions are investigated;
- ✓ Systematic reviews published from **2009 and onwards**;
  - ❖ *the new Cochrane risk of bias tool was published during 2009*
- ✘ Protocols;
- ✘ Methodological articles relating to NMA;
- ✘ Overviews of systematic reviews;
- ✘ MOD investigated as single primary outcome.

Eligibility strategy (4)

For each eligible Systematic review:



*Akl EA, Kahale LA, Agarwal A, et al. Impact of missing participant data for dichotomous outcomes on pooled effect estimates in systematic reviews: a protocol for a methodological study. Syst Rev 2014;3:137



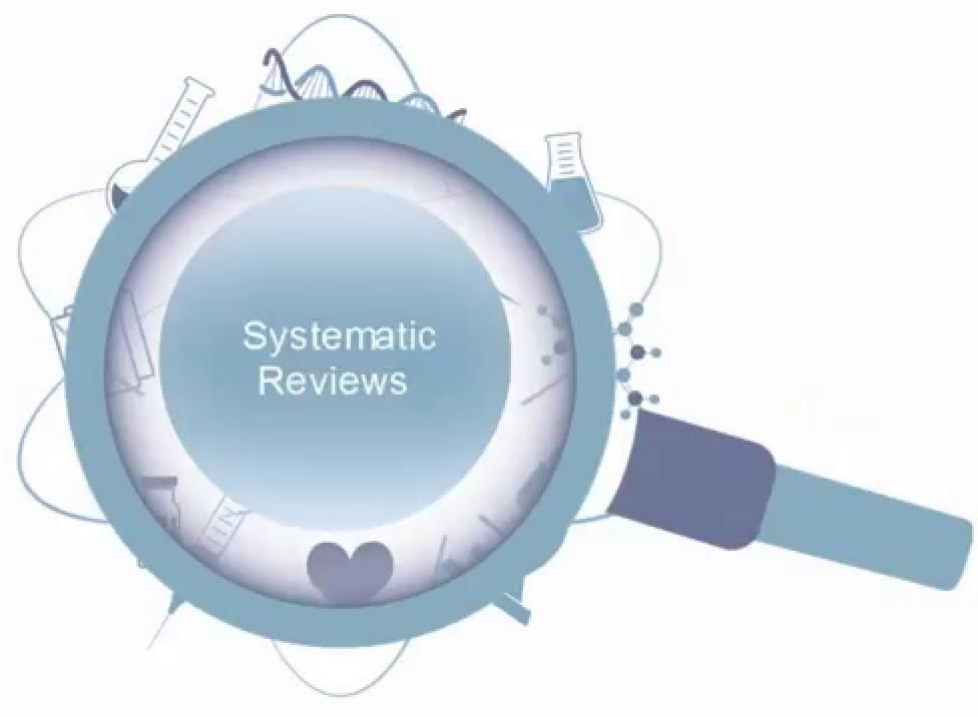
***Reasons for exclusion**

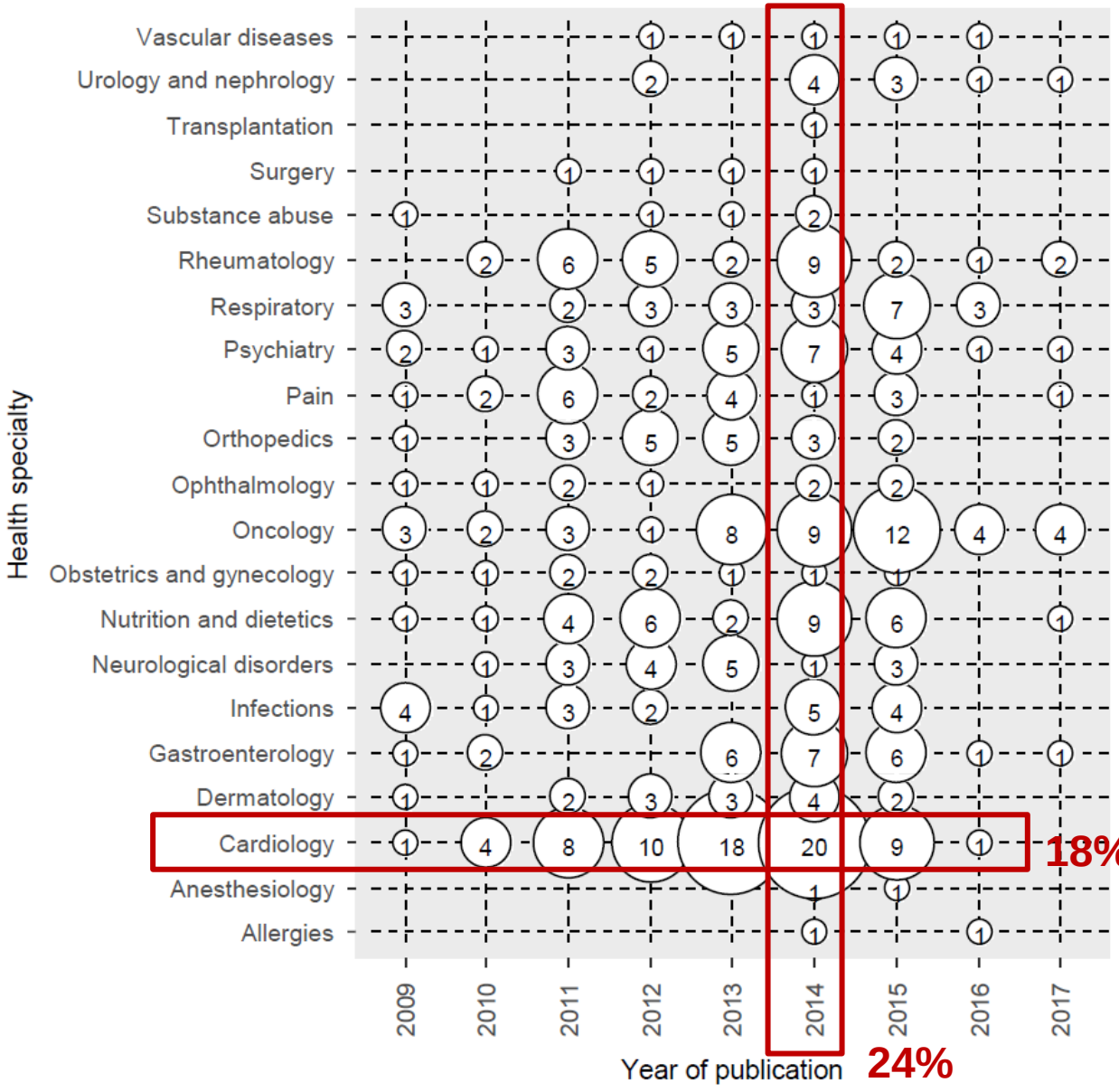
- 3 articles in Chinese
- 1 article in Hungarian
- 9 dropout as the primary outcome
- 3 letter to editor, editorial, commentary
- 6 meta-epidemiological or empirical studies
- 14 methodological articles
- 57 mixture of RCTs with non-standard design
- 16 mixture of RCTs with observational studies
- 6 number of interventions ≥ number of trials
- 6 overviews of systematic reviews
- 1 protocol of systematic review
- 4 published before 2009 (incident in Zarin et al)

†Reasons for exclusion

- 1 article in Russian
- 5 NMA/MA of diagnostic studies
- 2 disconnected network
- 18 letter to editor, editorial, commentaries
- 12 literature reviews on NMA/MA
- 6 meta-epidemiological or empirical studies
- 46 methodological articles on NMA/MA
- 13 mixture of RCTs with non-standard design
- 10 mixture of RCTs with observational studies
- 3 NMA on laboratory or animal studies
- 21 number of interventions ≥ number of trials
- 4 overviews of systematic reviews
- 15 Post-hoc NMA/ITCs from several published MAs or selected clinical trials
- 13 protocol of systematic review
- 3 software reports on NMA
- 4 systematic reviews of observational studies
- 5 systematic reviews on 2 interventions
- 14 tutorials on NMA
- 3 valid NMA was reported not to be feasible
- 137 no systematic reviews
- 46 duplicates

387 selected Systematic Reviews





Non-Cochrane reviews: 98%

Addressing MOD in the PROTOCOL

Protocol availability

- **37 (10%) reviews only**

Strategy for MOD

- **14 (38%) reviews only**

Actually addressed MOD

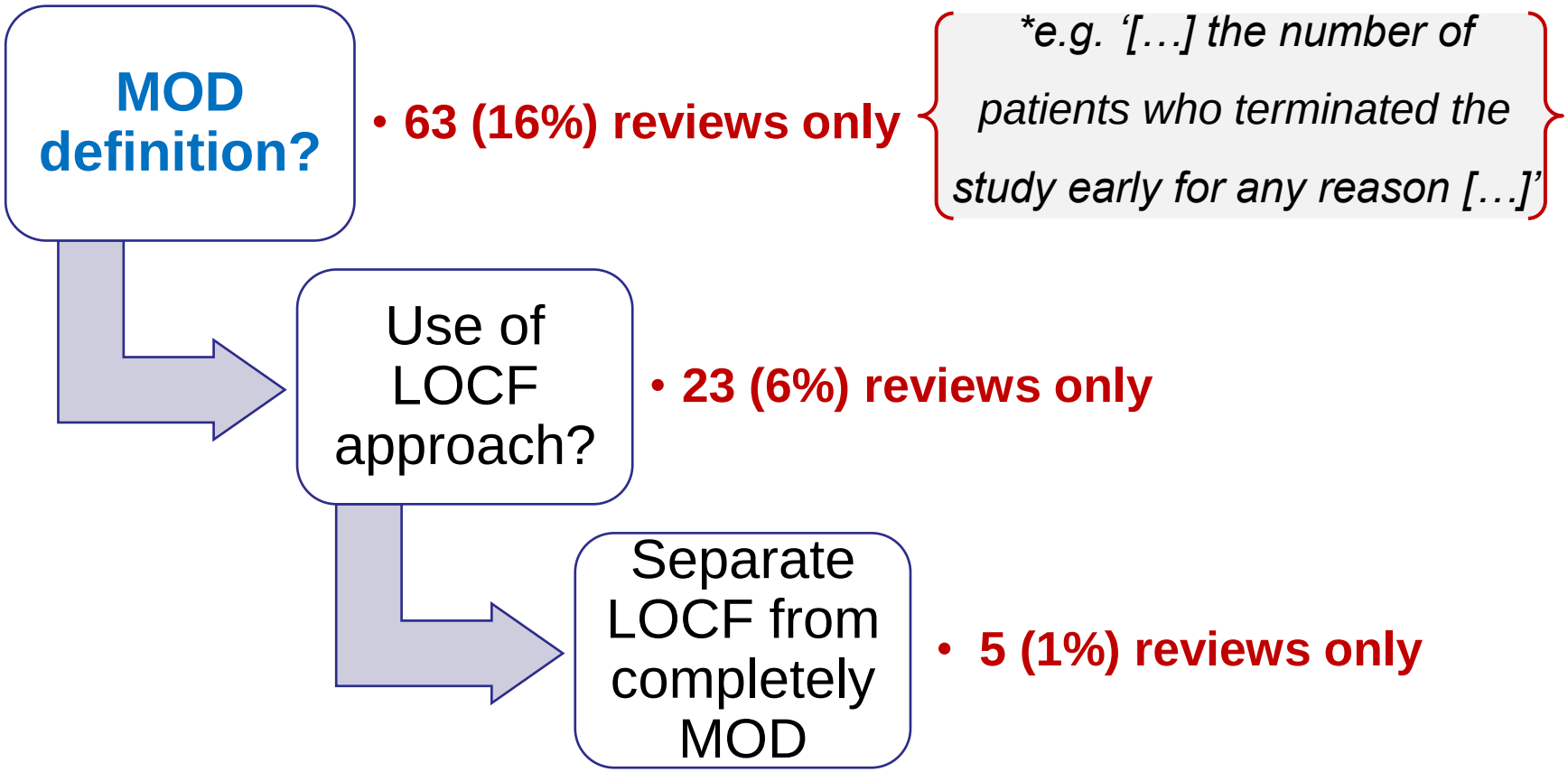
- **12 (86%) reviews only**

24% intention-to-treat

13% MOD as secondary

5% exclude MOD

Addressing MOD in the REVIEW



*Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 generation antidepressants: a multiple-treatments meta-analysis. Lancet 2009;373:746–758.

Addressing MOD in the REVIEW

Explicitly reported **MOD** are **present**

- **273 (70%) reviews**

Addressed MOD with ≥1 strategy

- **153 (56%) reviews only**

71% intention-to-treat

40% MOD as secondary

10% sensitivity analyses

Applied intention-to-treat analysis

- **42%** as reported in trials;
- **28%** applied ITT *de novo*;
- **12%** combination of both.

Addressing MOD in the REVIEW

Assessed attrition bias?

- **198 (51%) reviews**

74% Cochrane RoB tool

34% Jadad scale

10% sensitivity analyses

Justified the risk of bias level

- **18 (9%) reviews only**

Ambiguous assessment of attrition bias (19%)

- **51%** overall score is provided;
- **26%** results on RoB omitted;
- **21%** results on attrition bias omitted.

Addressing MOD in the REVIEW

Implications of MOD?

- **88 (32%) out of 273 reviews**

66% MOD as secondary

18% sensitivity analysis

12% MOD prevalence

Where reported mainly?

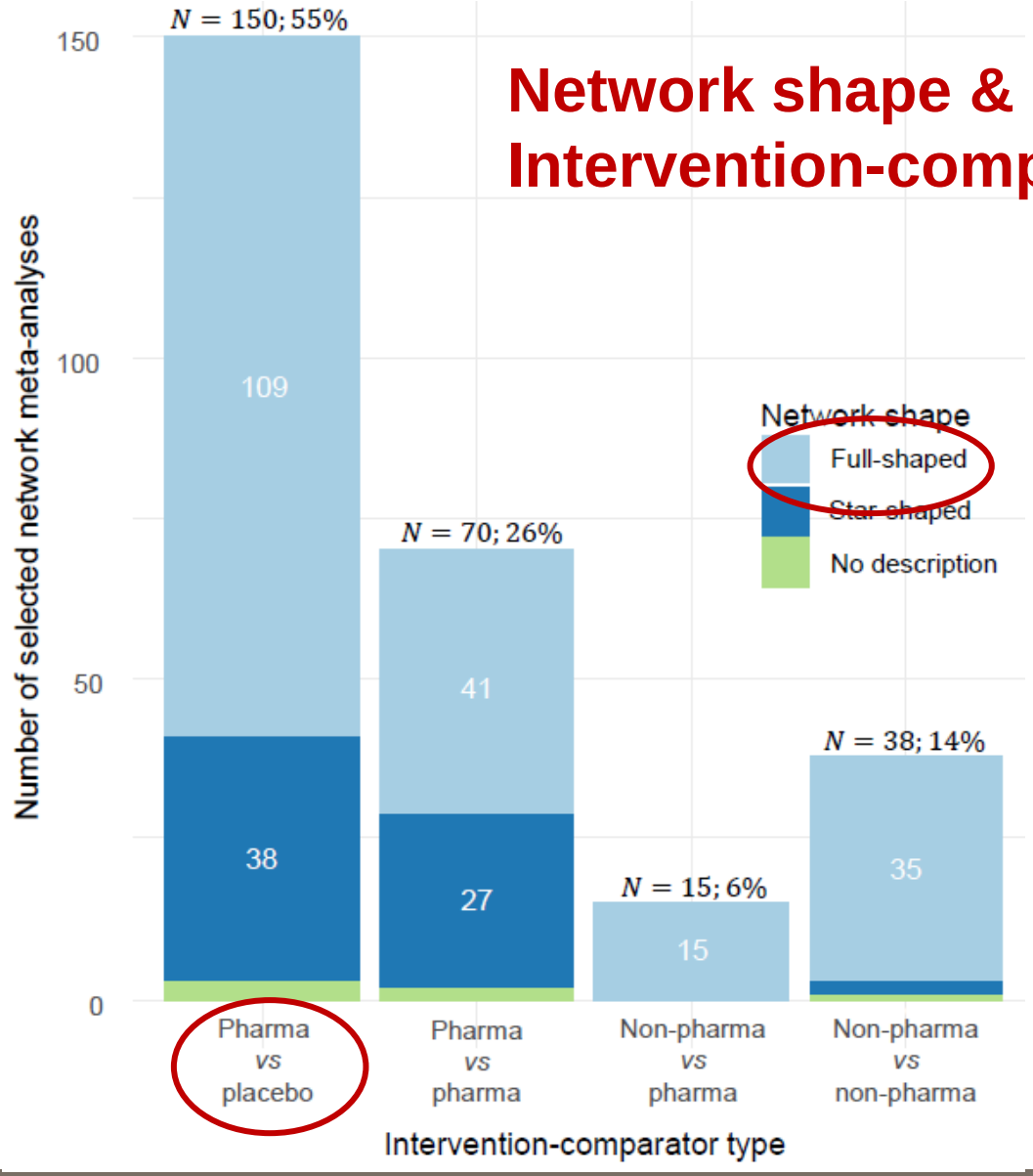
- **74 (84%) in Discussion**
- **46 (52%) in Abstract**

Which NMA components mainly?

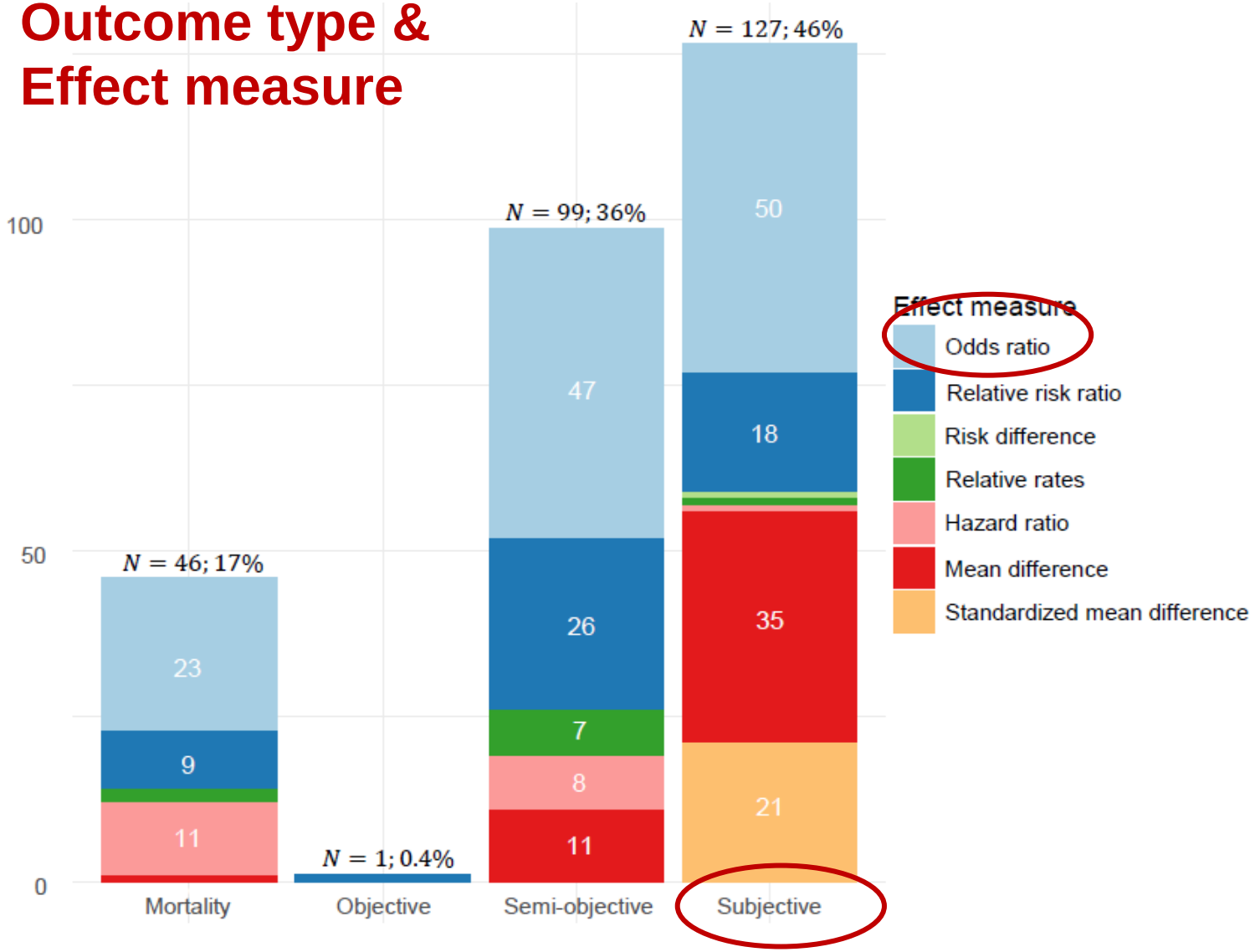
- **84 (95%)** mixed effects;
- **13 (15%)** intervention ranking.

273 NMAs with present MOD

Network shape & Intervention-comparator type



Outcome type & Effect measure



Addressing MOD in the **NMA**

Strategy explicitly reported

- **in 113 (40%) reviews only**
  - ***92% claimed intention-to-treat***

60% as reported in trials

22% exclusion of MOD

17% intention-to-treat

Actual strategy judged

- **agreed with 14 (12%) reviews**
- **able to judge in 95 (35%) reviews**

Intention-to-treat analysis (16; 17%)

- **8** all MOD as non-events;
- **1** all MOD as events;
- **7** no scenario is provided.

Addressing MOD in the **NMA**

Applied sensitivity analysis

- **16 (6%) reviews only**

7 trial exclusion

5 available case analysis

3 imputation

Reported any changes

- **2 reviews only**

‘To carry out a clinically sound analysis, we used a conservative approach and imputed outcomes for the missing participants assuming that they did not respond to treatment’

Justified strategy used in primary & sensitivity analysis

- **12 out of 273** reviews

Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet. 2009;373(9665):746-58.

Strengths

- ✓ **First survey** on reporting and handling MOD in NMA.
- ✓ Systematic reviews from a **wide range of health fields**.
- ✓ **Multitude of sources** = 4 NMA databases + an update.
- ✓ **Comparable results** with our previous work[1].
- ✓ **Comparable results** with work by Akl and colleagues[2].

1. **Spineli** LM, Pandis N, Salanti G. Reporting and handling missing outcome data in mental health: A systematic review of cochrane systematic reviews and meta-analyses.Res Synth Methods 2015;6:175–87.
2. **Akl** EA, Carrasco-Labra A, Brignardello-Petersen R, et al. Reporting, handling and assessing the risk of bias associated with missing participant data in systematic reviews: a methodological survey. BMJ Open 2015;5:e009368.

Limitations

- **Several challenges** stemming from the poor reporting quality:

☹ **Only 21%** of the reviews gave numerical **information on MOD**.

☹ **Implicit information on MOD**; **mostly** via RoB tool.

☹ We might have **underestimated the usage of LOCF**.

☹ We **strived to judge** the actual method applied.

Conclusions - recommendations

- The **quality of reporting and handling MOD** in systematic reviews with NMAs is **particularly inadequate**!
- Reviewers remain **unaware of the presence and importance of MOD** in systematic reviews of multiple interventions.
- Poor handling of MOD attests to **limited knowledge of the reviewers** regarding the existing relevant methodology.
- **Education** amongst reviewers, peer reviewers and journal editors is deemed **necessary**!

References

Zarin W, Veroniki AA, Nincic V, et al. Characteristics and knowledge synthesis approach for 456 network meta-analyses: a scoping review. BMC Med 2017;15:3.

Tan SH, Bujkiewicz S, Sutton A, et al. Presentational approaches used in the UK for reporting evidence synthesis using indirect and mixed treatment comparisons. J Health Serv Res Policy 2013;18:224–32.

Bafeta A, Trinquart L, Seror R, Ravaud P. Analysis of the systematic reviews process in reports of network meta-analyses: methodological systematic review. BMJ 2013;347:f3675.

Nikolakopoulou A, Chaimani A, Veroniki AA, et al. Characteristics of networks of interventions: A description of a database of 186 published networks. PLoS One 2014;9:1–10.

Petropoulou M, Nikolakopoulou A, Veroniki AA, et al. Bibliographic study showed improving statistical methodology of network meta-analyses published between 1999 and 2015. J Clin Epidemiol 2017;82:20–28.

Thank you for your attention!

Examples of systematic reviews with explicit, implicit and unclear judgments

Explicit judgment of the actual method
Available case analysis with or without LOCF
'All analyses were based on the intention-to-treat (ITT) data reported in the manuscripts published for the included RCTs'. By comparing Appendix B (it gives information on randomized and completers sample) with Table 1, totals in latter are smaller in all studies.
Imputation with or without LOCF
'Responders to treatment were calculated on an intention-to-treat basis […] imputed outcomes for the missing participants assuming that they did not respond to treatment'.
Combination of Imputation and Available case analysis
'[…] and results from intention-to-treat (ITT) analyses that included all randomized patients took precedence over results from analyses that excluded patients'. According to Table 1, some trials offered intention-to-treat whereas others either available case analysis or not a clear analysis method.

Examples of systematic reviews with explicit, implicit and unclear judgments

Implicit judgment of the actual method
Available case analysis with or without LOCF
Studies that employed LOCF have been reported in the quality assessment as having done intention-to-treat (see, Appendix 4 and Appendix 3).
Imputation with or without LOCF
Number randomized equals number analyzed but there is no reference to LOCF. All included trials applied intention-to-treat analysis (according to RoB table).
Combination of Imputation and Available case analysis
By comparing Table 1 (number randomized) with Figure 1 (number analyzed), some trials might have applied intention-to-treat analysis (without information on the imputation) and others available case analysis. No information on how trials or the reviewers handled missing outcome data.

Examples of systematic reviews with explicit, implicit and unclear judgments

Unclear judgment of the actual method
There is no information available on the analyzed and randomized sample for each trial as well as no information on how MOD have been handled in each trial. The reviewers don't report how they planned to handle missing outcome data.
The reviewers report that they employed intention-to-treat analysis. Information on randomized sample is provided but there is no information available on analyzed sample to judge whether intention-to-treat analysis is genuine.

Description of intention-to-treat analyses according to reports in reviews

Data extracted as reported in the trials
'Analyses were performed on data that were explicitly reported in the individual papers, with no imputations for data that were not reported. When available, we analysed the ITT population; when this was not possible, we used data from LOCF'.
Intention-to-treat analysis applied de novo
'Responders to treatment were calculated on an ITT basis […] imputed outcomes for the missing participants assuming that they did not respond to treatment'.
Combination of as reported and de novo intention-to-treat analysis
'[…] according to the number of events reported in the original studies or sub-studies ITT analyses. Where studies did not report ITT, we analyzed outcomes as all-patients randomized'.
Unclear classification
'Our analysis was based on intention-to-treat principle.' (No information on whether intention-to-treat is as reported or de novo).