Agreement of treatment effects from non-randomized studies using causal modelling and randomized trials: a meta-epidemiological study

Hannah EWALD*[1,2]; Aviv LADANIE[1,2]; Kimberly A. MC CORD[1,2]; Heiner C. BUCHER[1,2]; John P.A. IOANNIDIS[3-7]; Lars G. HEMKENS[1,2]

*Hannah.Ewald@usb.ch [1] Basel Institute for Clinical Epidemiology and Biostatistics (ceb), University Hospital Basel, University of Basel, Basel, Switzerland [2] Swiss Tropical and Public Health Institute, Basel, Switzerland [3] Stanford Prevention Research Center, Department of Medicine, Stanford University School of Medicine, Stanford, USA [4] Meta-Research Innovation Center at Stanford (METRICS), Stanford School of Medicine, Palo Alto, USA [5] Department of Health Research and Policy, Stanford University School of Medicine, Stanford, USA [6] Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, USA [7] Department of Statistics, Stanford University School of Humanities and Sciences, Stanford, USA

What is the agreement of treatment effects from non-randomized studies using causal modelling and from RCTs investigating the same clinical question?

ELIGIBILITY

1. Non-randomized studies using marginal structural models providing an effect estimate on any healthcare outcome

2. RCTs on the same clinical question published before or after the non-randomized study

ANALYSES

- Comparison of the direction of treatment effects, effect sizes, and confidence intervals

- Absolute deviation between study designs

- ROR: summary of ORs of treatment effects from RCTs divided by MSM-study effect estimates

- Combined the RORs of all clinical questions using random-effects meta-analysis

- Meta-regression was used to assess whether the agreement between study designs is associated with previous knowledge of RCT-effects.
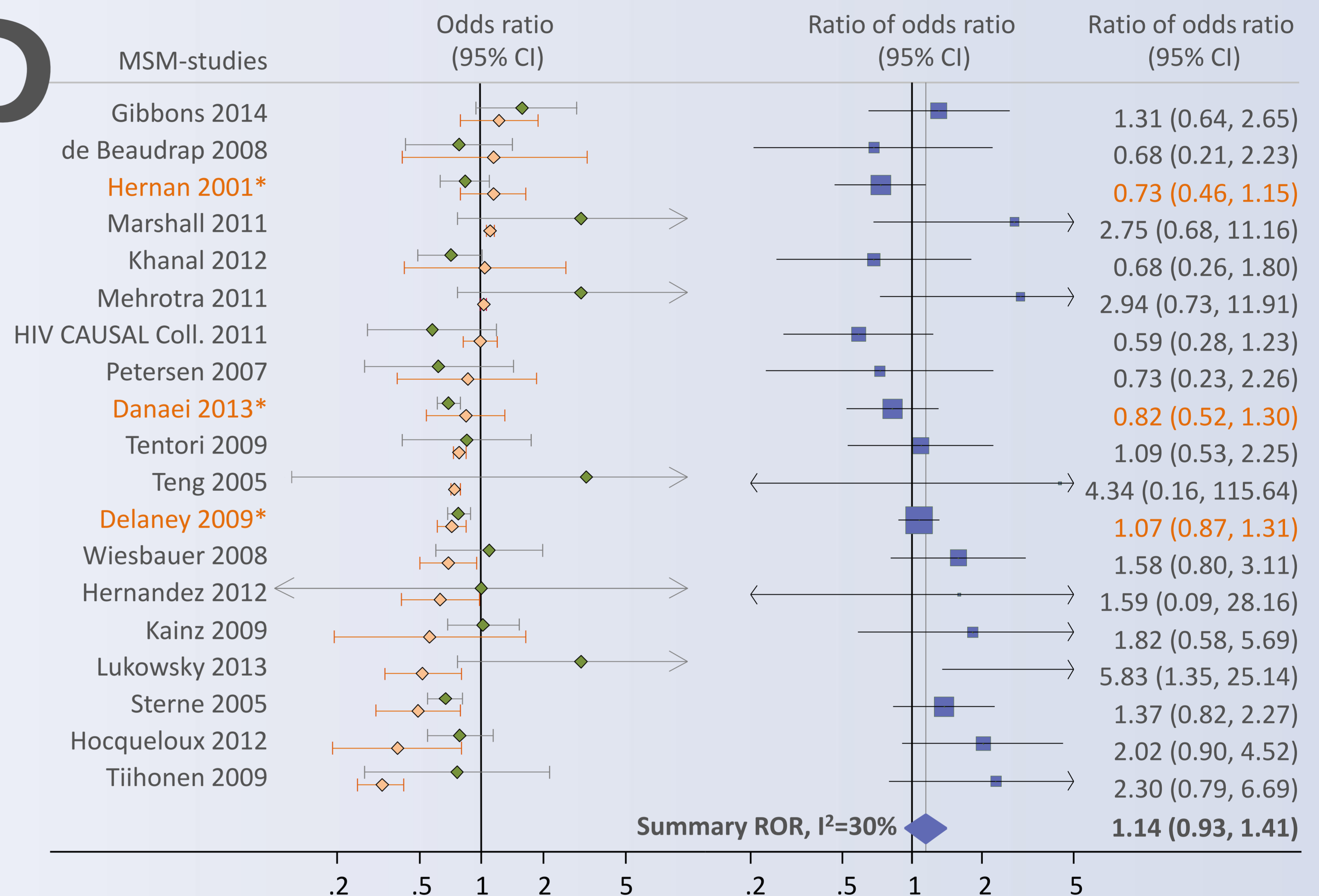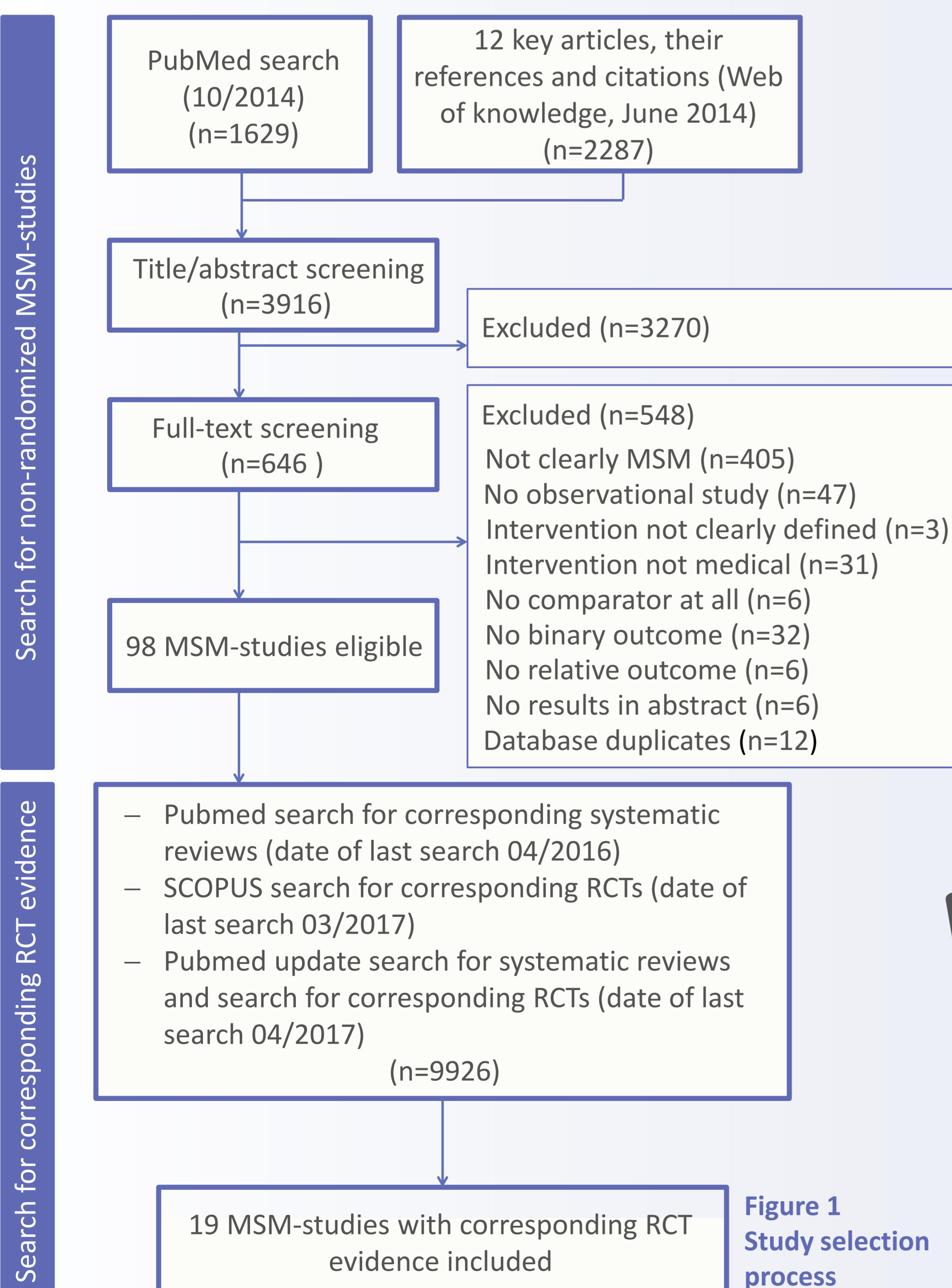
Search for non-randomized MSM-studies

PubMed search (10/2014) (n=1629)

12 key articles, their references and citations (Web of knowledge, June 2014) (n=2287)

Title/abstract screening (n=3916)

Excluded (n=3270)

Full-text screening (n=646)

Excluded (n=548)
Not clearly MSM (n=405)
No observational study (n=47)
Intervention not clearly defined (n=3)
Intervention not medical (n=31)
No comparator at all (n=6)
No binary outcome (n=32)
No relative outcome (n=6)
No results in abstract (n=6)
Database duplicates (n=12)

98 MSM-studies eligible

Search for corresponding RCT evidence

- Pubmed search for corresponding systematic reviews (date of last search 04/2016)
- SCOPUS search for corresponding RCTs (date of last search 03/2017)
- Pubmed update search for systematic reviews and search for corresponding RCTs (date of last search 04/2017)
(n=9926)

19 MSM-studies with corresponding RCT evidence included

Figure 1 Study selection process

Figure 2: Treatment effects estimated with non-randomized studies using marginal structural models and RCTs. **Left panel:** effect estimates (diamonds) and 95% confidence intervals (CIs) of 19 clinical questions reported in MSM-studies (lower graphs, orange) and in RCTs (upper graphs, green). **Right panel:** ratio of odds ratios (blue squares; lines: 95% CIs); combined summary ROR (diamond, random-effects meta-analysis). Values > 1 indicate more favorable results for the experimental treatment by non-randomized studies using causal modelling.

* Studies focussing on statistical methodology

RESULTS

- 19 non-randomized studies with 1,039,570 patients and 141 corresponding RCTs with 120,669 patients were included

- 124/141 RCTs (88%) were published before the non-randomized study

- 3/19 studies focused on statistical methodology, 16 on clinical decision making.

- 37% of non-randomized studies had opposite directions of effect estimates than RCTs (8/19 clinical questions)

- 47% of of non-randomized studies' 95% confidence intervals did not include the RCT estimate (9/19 clinical questions)

- Non-randomised study effects deviated systematically by 1.29-fold (summary absolute deviation OR 1.29; 1.12 to 1.48)

- Overall, causal modelling studies tended to show more favorable results for the experimental treatment (sROR 1.14; 0.93 to 1.41), in particular when excluding studies focussing on statistical methodology (16 studies, sROR 1.34; 1.03 to 1.75), and when more RCTs were previously published (p=0.037).

CONCLUSION AND TAKE HOME MESSAGE

- Treatment effects from non-randomized studies using causal modelling often deviate from RCTs on the same research question and may show stronger effects for experimental treatments.

- Remain cautious when using non-randomized "real world" evidence to guide your health care decisions – even when causal modelling techniques were applied and especially when no evidence from RCTs exists.

ABBREVIATIONS

MSM-Studies: non-randomized studies using marginal structural models; RCT: randomized controlled trial; ROR: ratio of odds ratios (ratio of outcome effects reported in non-randomized studies versus randomized trial evidence); sROR summary ratio of odds ratios