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

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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.

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

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

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)

No comparator at all (n=6)

No binary outcome (n=32)

No results in abstract (n=6)

Database duplicates (n=12)

98 MSM-studies eligible

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

**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 direction of effect estimates than RCTs (8/19 clinical questions)
- 47% 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.

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**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 ratio

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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