Treatment effect in meta-analyses: comparison of different strategies for analysis

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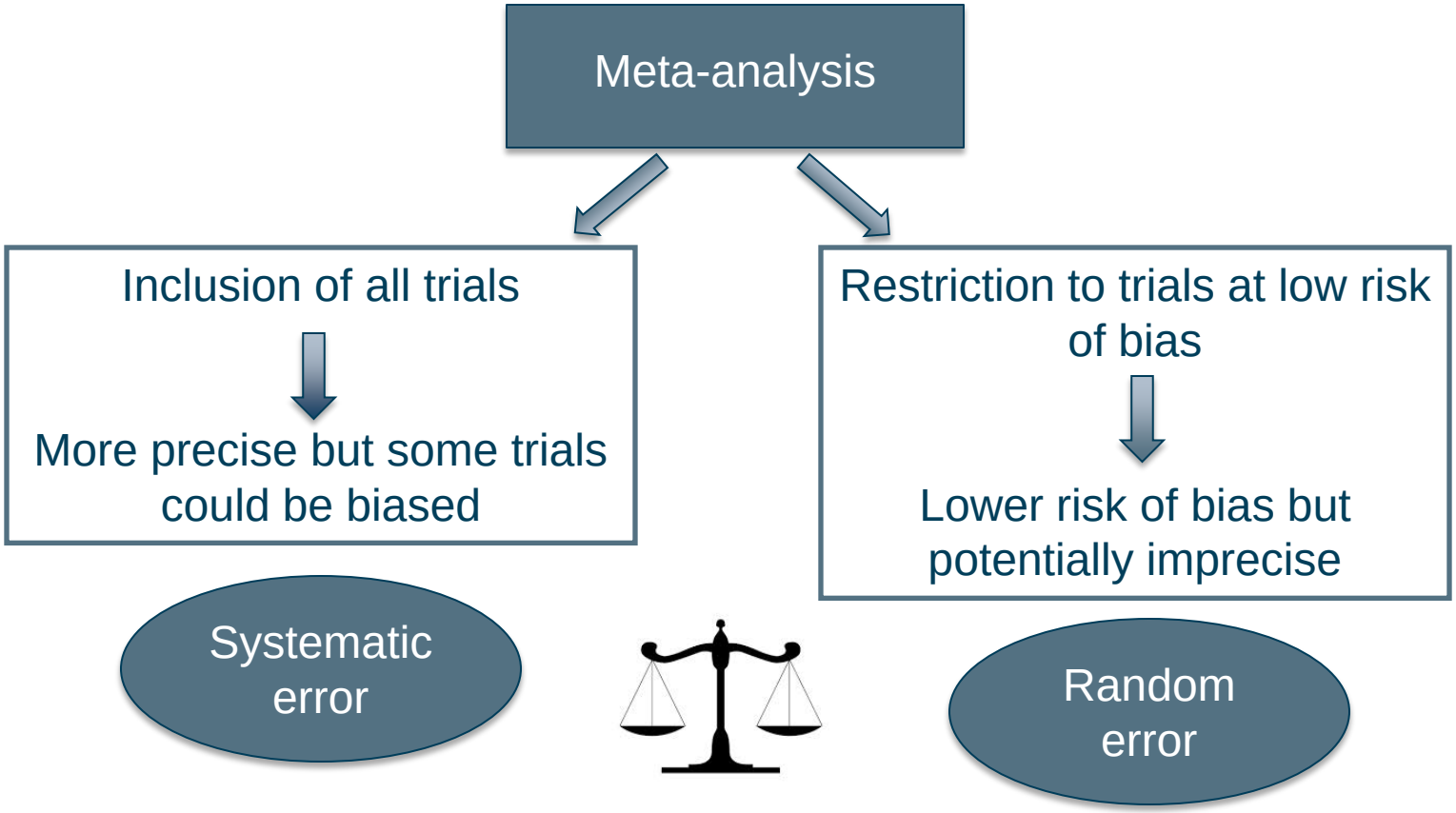
Which trials to combine: a persistent dilemma



Incorporation of risk of bias assessment into meta-analyses

- What is recommended[1]
  - To restrict the primary meta-analysis to trials at low risk of bias
  - To present meta-analyses stratified according to risk of bias
- Less recommended option:
  - To present meta-analysis of all trials while providing a summary of the risk of bias across trials

- What is actually done[2]
  - Cross sectional review
  - 200 SRs published in Jan-March 2012 (100 Cochrane SRs)
  - 11% incorporated the risk of bias assessment into the analysis
    - Sensitivity analysis with exclusion of trials at high or unclear risk of bias

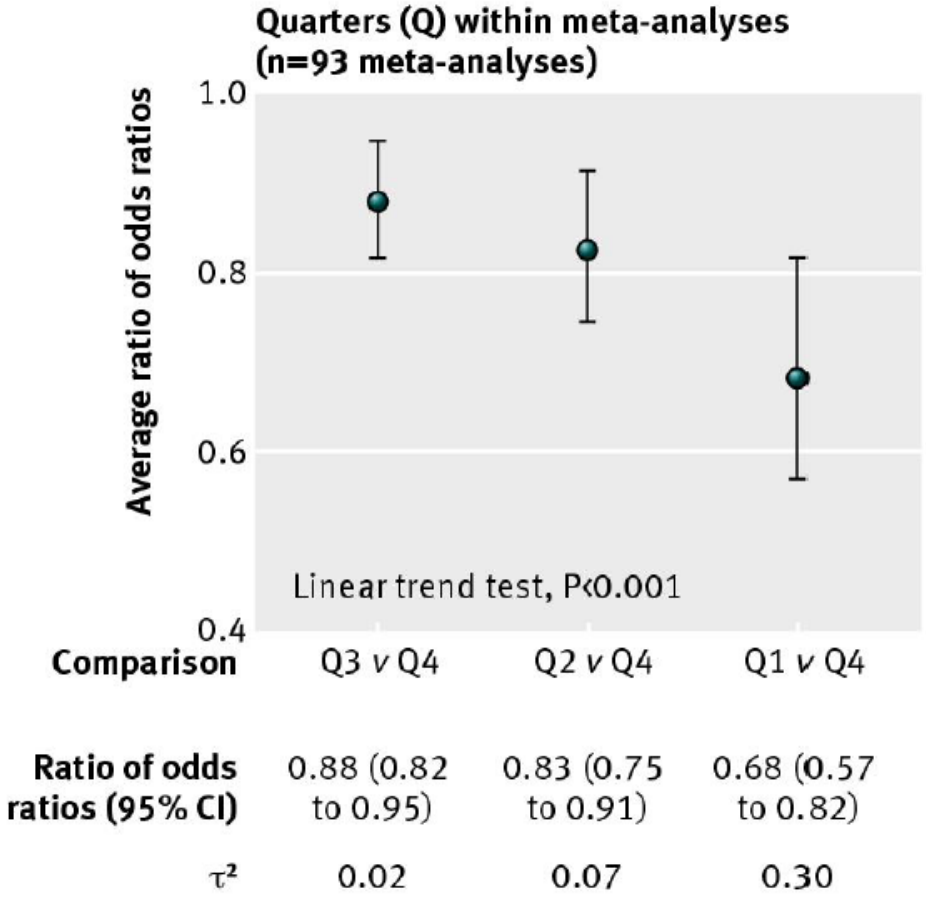
[1] Higgins et al. *BMJ*. 2011

[2] Hopewell et al. *BMJ open*. 2013

Influence of trial sample size on treatment effect within meta-analyses

- Not only « small » trials
- Stronger effects in small to moderate-sized trials may not reflect the true treatment effect

- Should meta-analyses be restricted to the largest trials?
  - 4th quarter of sample size within MAs
  - « Largest » trial

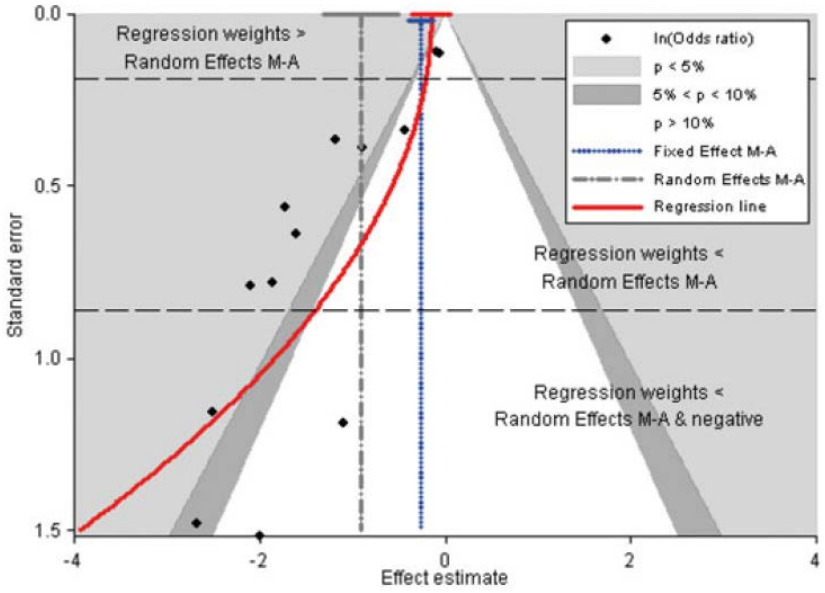


Dechartres et al. *BMJ*. 2013

Interest of recent methods for correcting « small study effect »

- Regression-based methods
  - Described by Rücker et al.[1,2] and Moreno et al.[3]

- « Limit » meta-analysis method
  - Predicted treatment effect for an infinite precision trial (variance or standard error=0)
  - By extrapolation of the regression line (treatment effect ~ variance or standard error)



[1] Rücker al. *Biostatistics*. 2011
[2] Rücker et al. *Biom J*. 2011
[3] Moreno et al. *Stat Med*. 2012

Objectives

- To compare treatment effects obtained from all available evidence (meta-analysis of all trials) to:

- “Best evidence” strategy related to trial sample size and precision:
  - Trial with the most precise treatment effect
  - Meta-analysis restricted to the largest trials (Quarter 4 with 25% of the largest trials)
  - « Limit » meta-analysis method[1]

- “Best evidence” strategy related to risk of bias:
  - Meta-analysis restricted to trials at low risk of bias

[1] Rücker et al. *Biostatistics*. 2011

Data sources

- Combination of data from 2 collections of meta-analyses used for previous meta-epidemiological studies[1,2]:
  - 48 MAs (421 RCTs) for the 1st collection
    - Published in high-impact factor journals in 2008 and 2010
    - Minimum number of trials: 3
  - 45 MAs (314 RCTs) for the 2nd collection
    - Cochrane reviews published in 2011
    - Minimum number of trials: 4
  - Binary outcomes

[1] Dechartres et al. *Ann Intern Med*. 2011
[2] Dechartres et al. *BMJ*. 2013

Data extraction

- General characteristics and results
- Assessment of risk of bias by domains
  - From individual RCT reports (1st collection)
  - From Cochrane reviews (2nd collection)
- Overall risk of bias for a trial

Risk of bias	Interpretation	Within a trial
Low risk of bias	Bias, if present, is unlikely to alter the results seriously	Low risk of bias for all key domains
Unclear risk of bias	A risk of bias that raises some doubt about the results	Low or unclear risk of bias for all key domains
High risk of bias	Bias may alter the results seriously	High risk of bias for one or more key domains

Key domains:
Sequence generation
Allocation concealment
Blinding
Incomplete outcome data

Higgins et al. *BMJ*. 2011

Analysis

- Treatment effect expressed as Odds ratios (ORs)
- Meta-analyses performed with DerSimonian and Laird random-effects model
  - All trials
  - Trials at low overall risk of bias
  - Largest trials (Quarter 4 with 25% of the largest trials)
- « Limit » meta-analysis method (Rücker et al.[1])
  - Expected limit estimate
- Stratification: Objective versus subjective outcomes

[1] Rücker et al. *Biostatistics*. 2011

Classification of outcomes

- Objective outcomes:
  - All-cause mortality
  - Other objectively assessed
    - Pregnancy, live births, laboratory outcomes
  - Objectively measured but potentially influenced by clinicians or patients judgement
    - Hospitalizations, total dropouts or withdrawals, cesarean section, operative or assisted delivery, additional treatments administered
- Subjective outcomes:
  - Clinician-assessed outcomes, symptoms, pain, mental-health outcomes, cause-specific mortality

Savovic et al., *Ann Intern Med*, 2012

Characteristics of the 93 meta-analyses

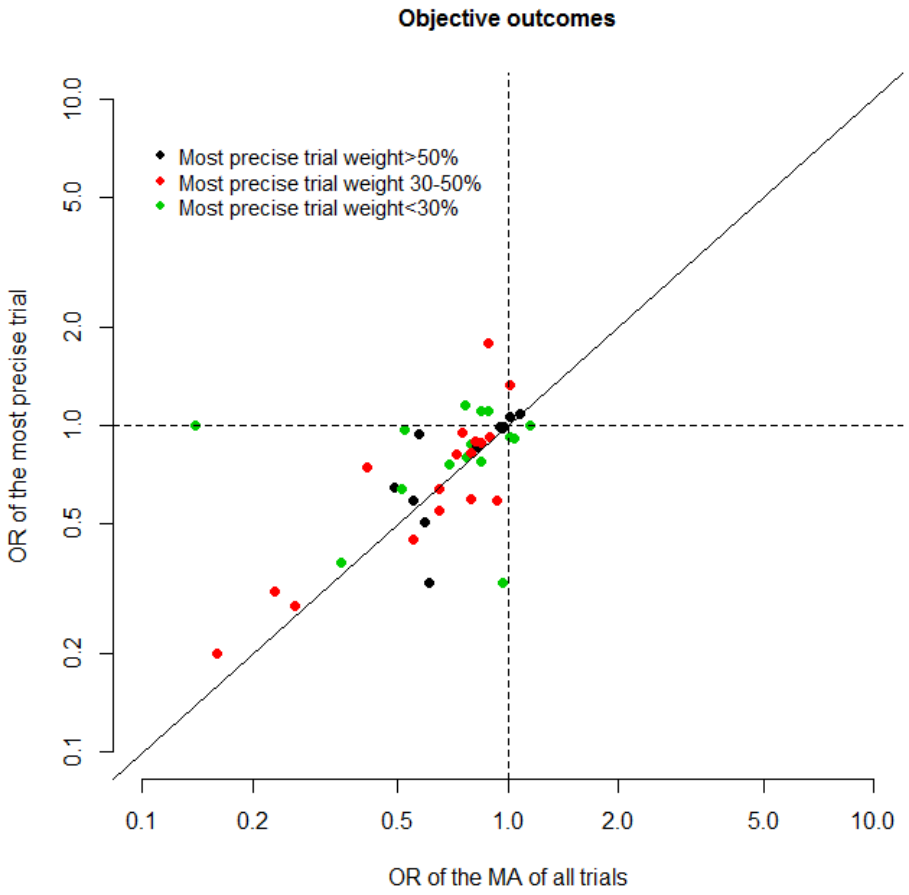
- Nb of trials per meta-analysis:
  - Median 7 (range 3 to 30)
- Treatment effect : 0.10 (0.03-0.35) to 1.59 (1.15-2.20)
  - 48 MAs: statistically significant benefit for the experimental arm
  - 1 MA: statistically significant benefit for the control arm
  - 44 MAs: no statistical difference between experimental and control arms
- Overall risk of bias
  - 47 MAs included at least 1 trial at low overall risk of bias
  - 24 MAs included only 1 trial at low overall risk of bias

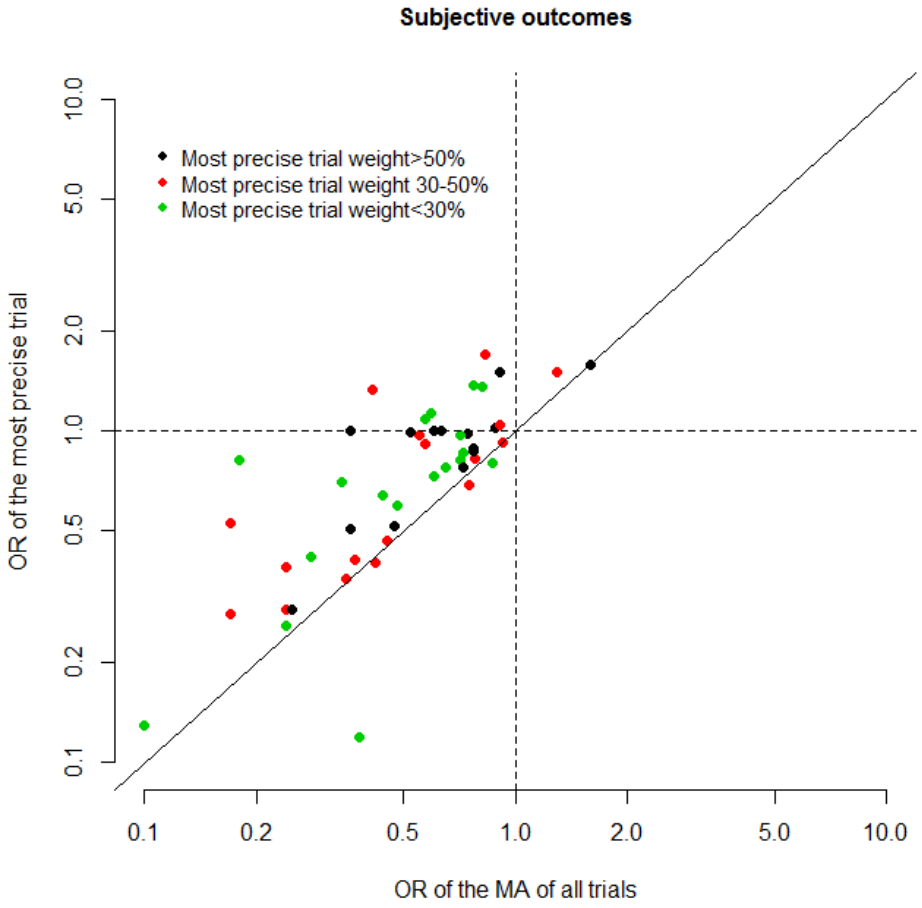
Classification of outcomes

- 43 (46%): objective outcome
  - 31 : all-cause mortality
  - 7 : other objectively assessed
  - 5 : objectively measured but potentially influenced by clinician or patient judgement

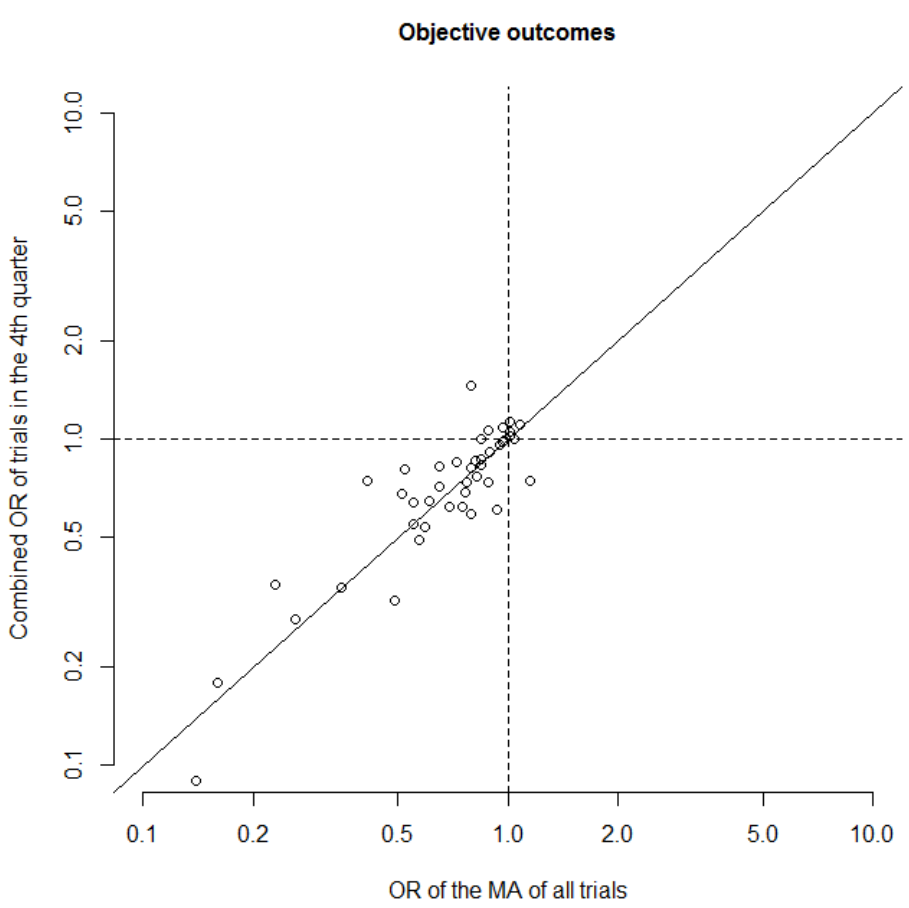
- 50 (54%): subjective outcome

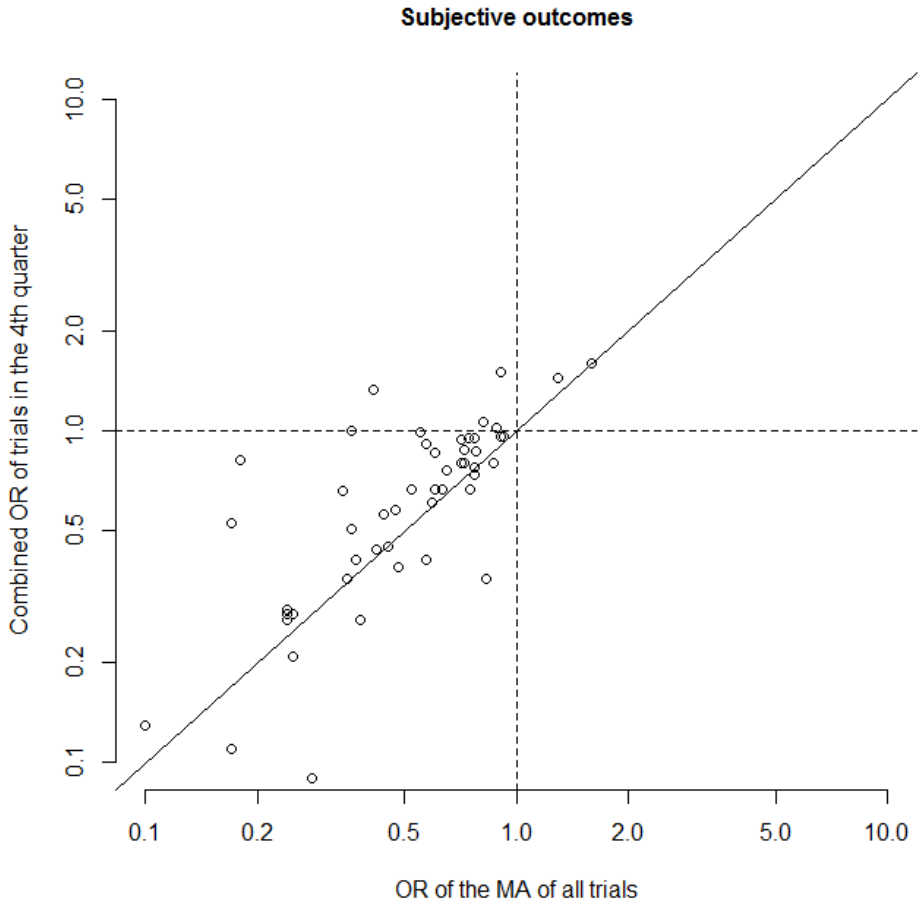
Comparison of treatment effect between the overall MA and the most precise trial



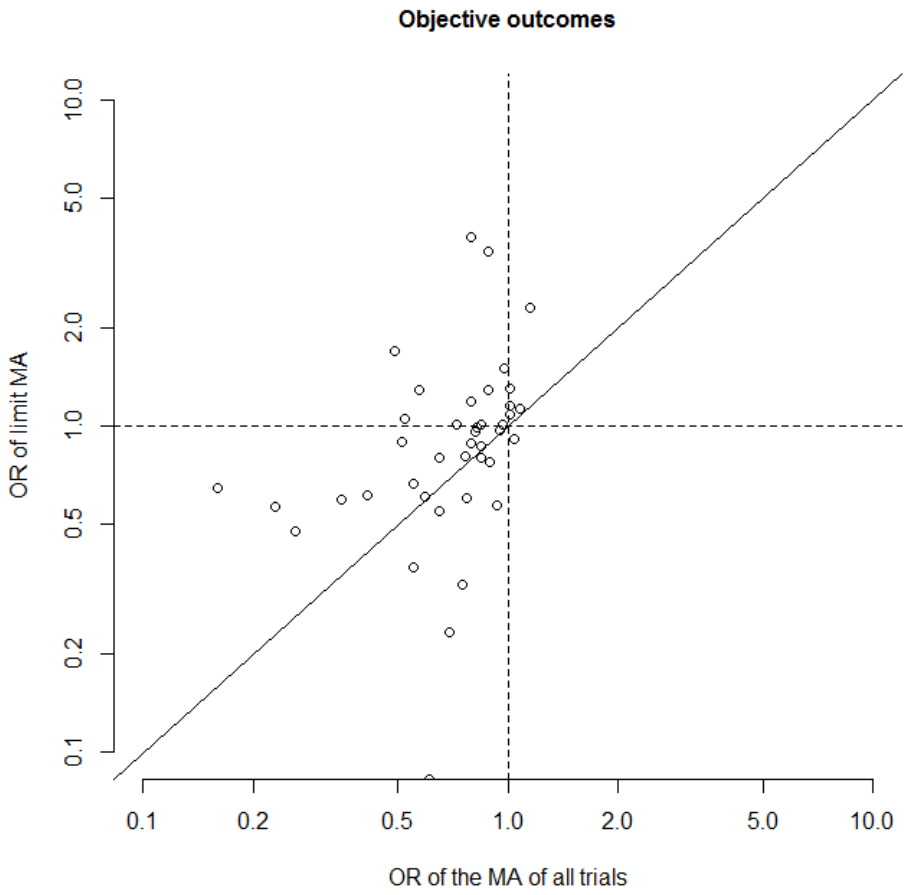


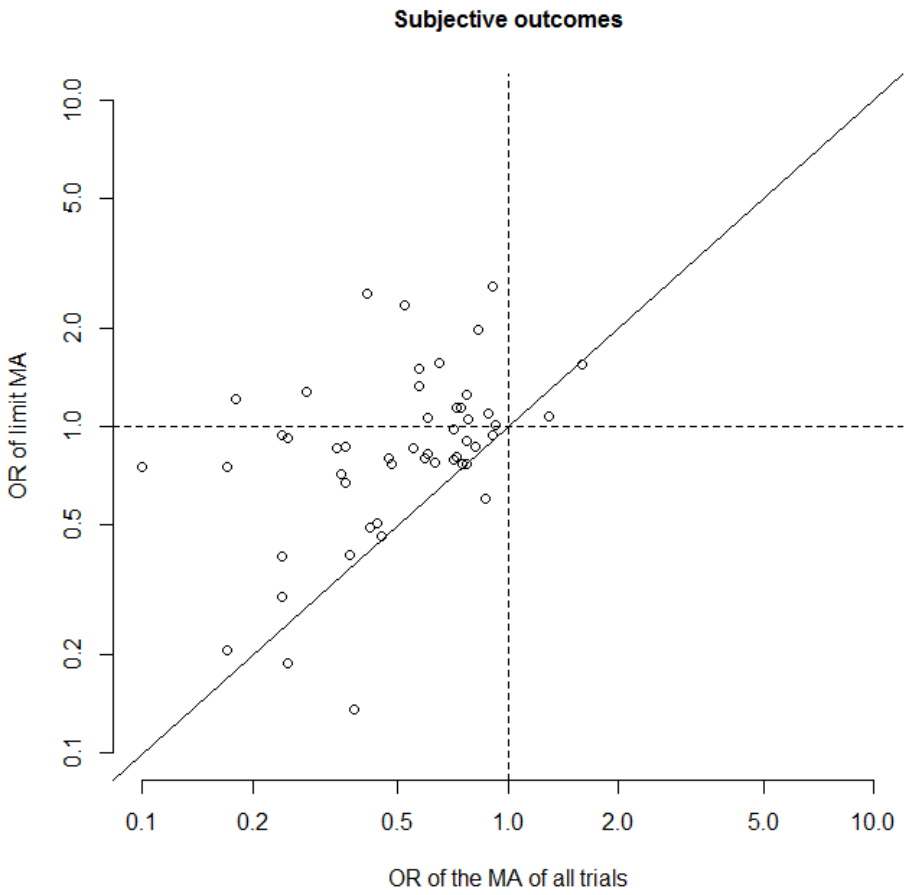
Comparison of treatment effect between the overall MA and MA restricted to trials with the largest sample size (4th quarter)





Comparison of treatment effect between the overall MA and the « limit » MA method



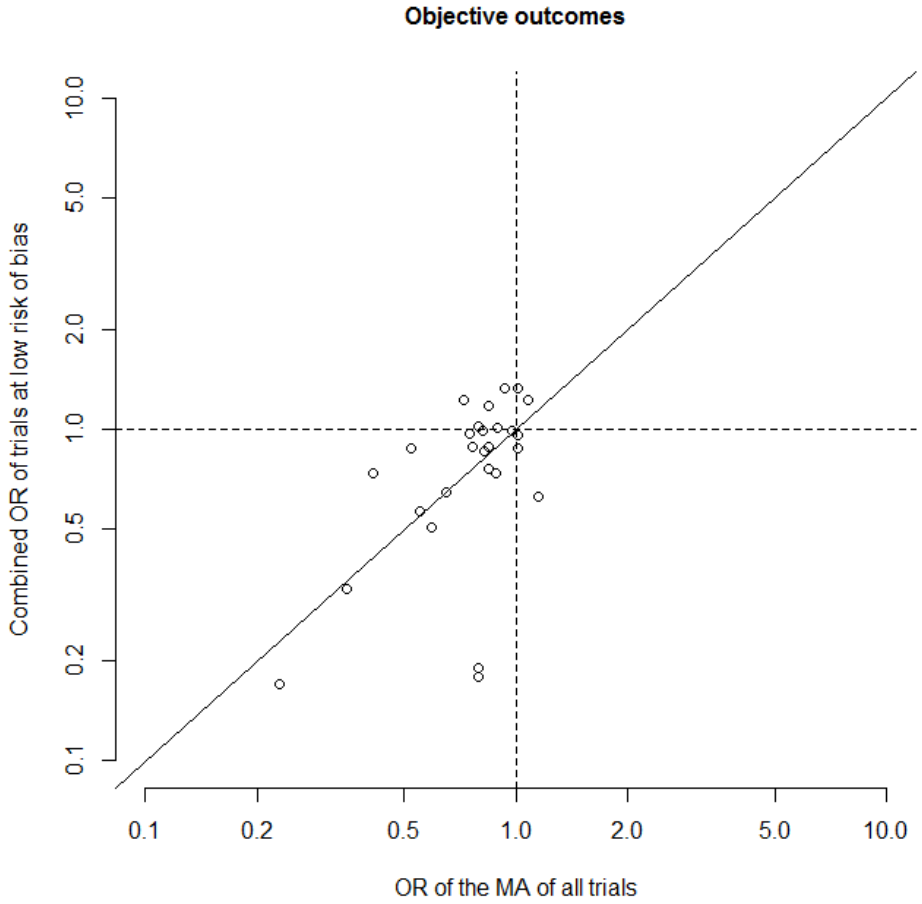


In summary

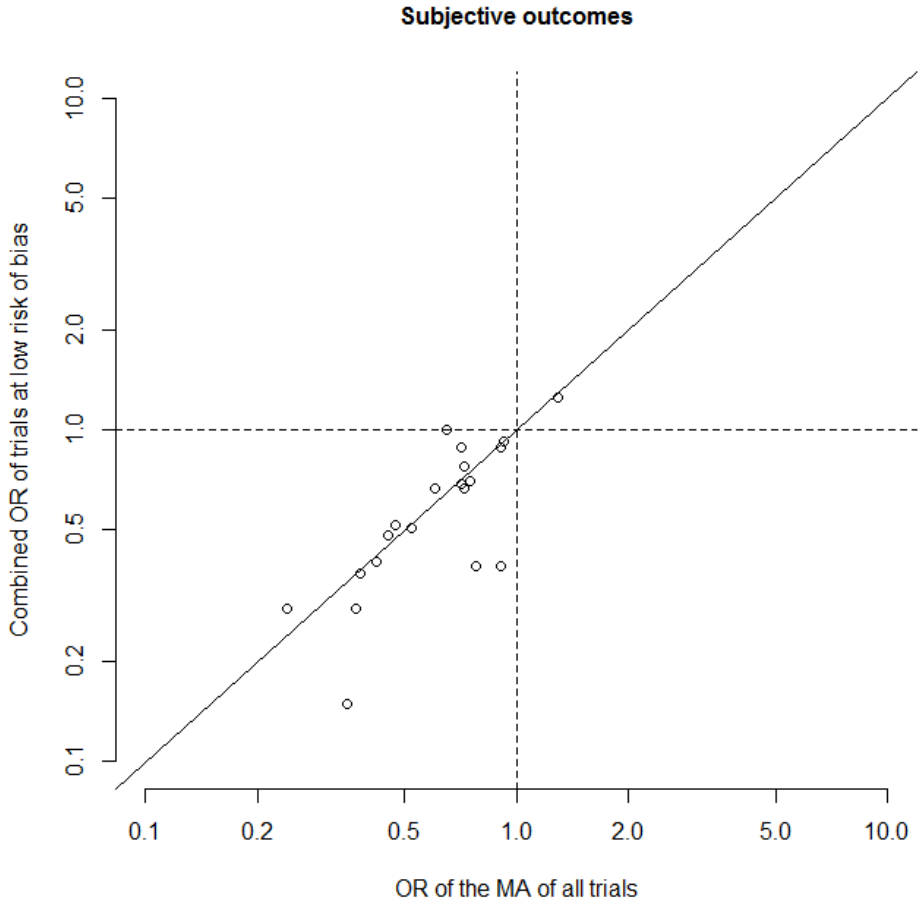
- Treatment effect is frequently larger in the meta-analysis of all trials than in the:
  - Most precise trial
  - Meta-analysis restricted to trials with the largest sample size (4th quarter)
  - « Limit » meta-analysis

- Our results suggest a difference between objective and subjective outcomes

Comparison of treatment effect between the overall MA and MA restricted to trials with low risk of bias

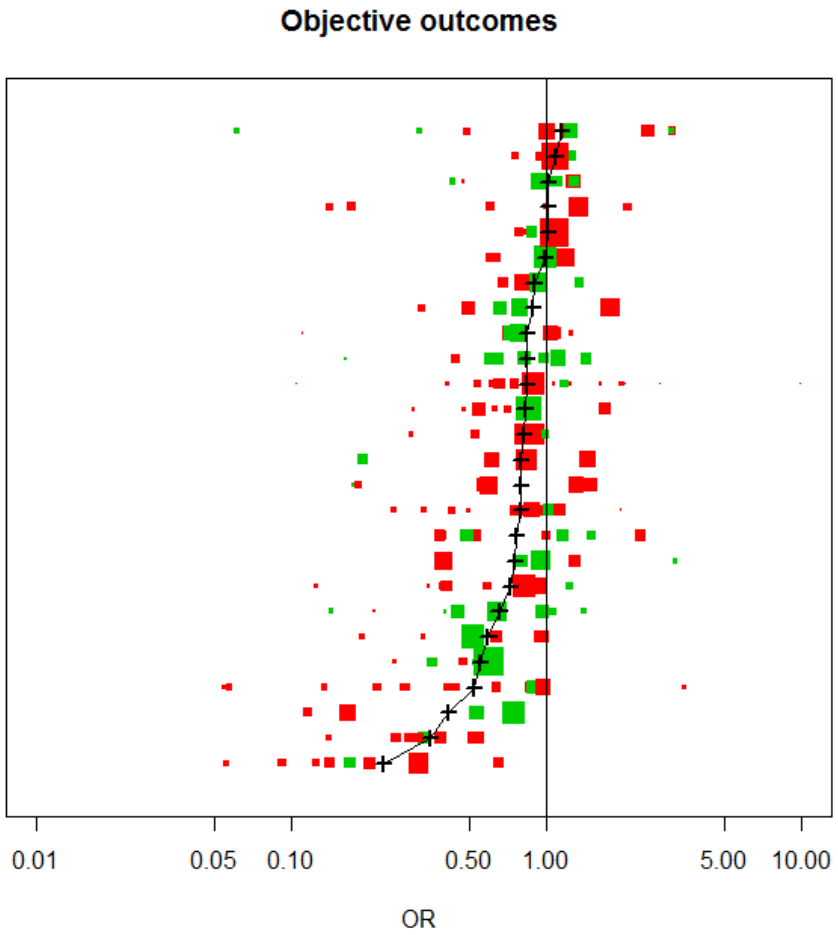


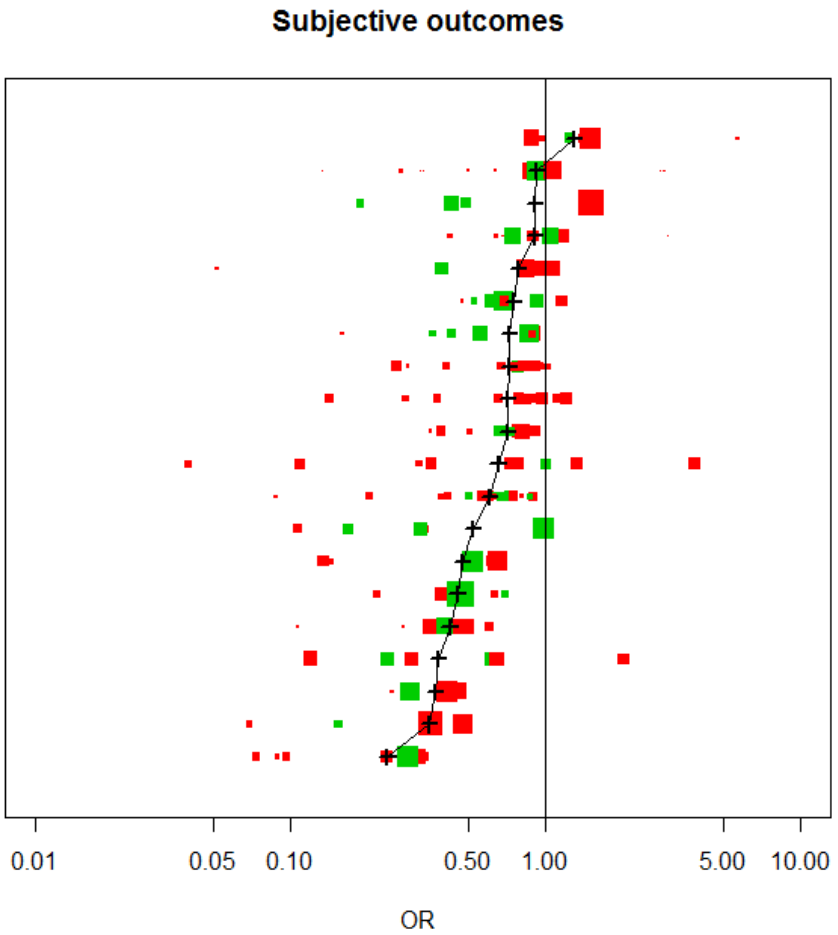
27/43 (63%) MAs with an objective outcome have at least 1 trial at low risk of bias



20/50 (40%) MAs with a subjective outcome have at least 1 trial at low risk of bias

Treatment effect according to risk of bias within each meta-analysis





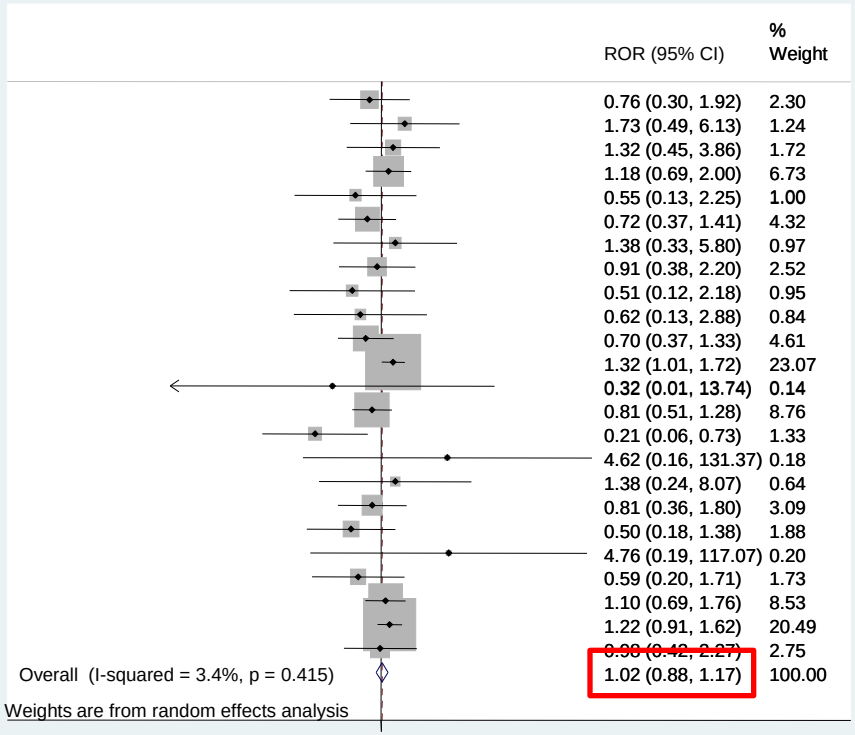
- Low overall risk of bias
- High/unclear overall risk of bias

In summary

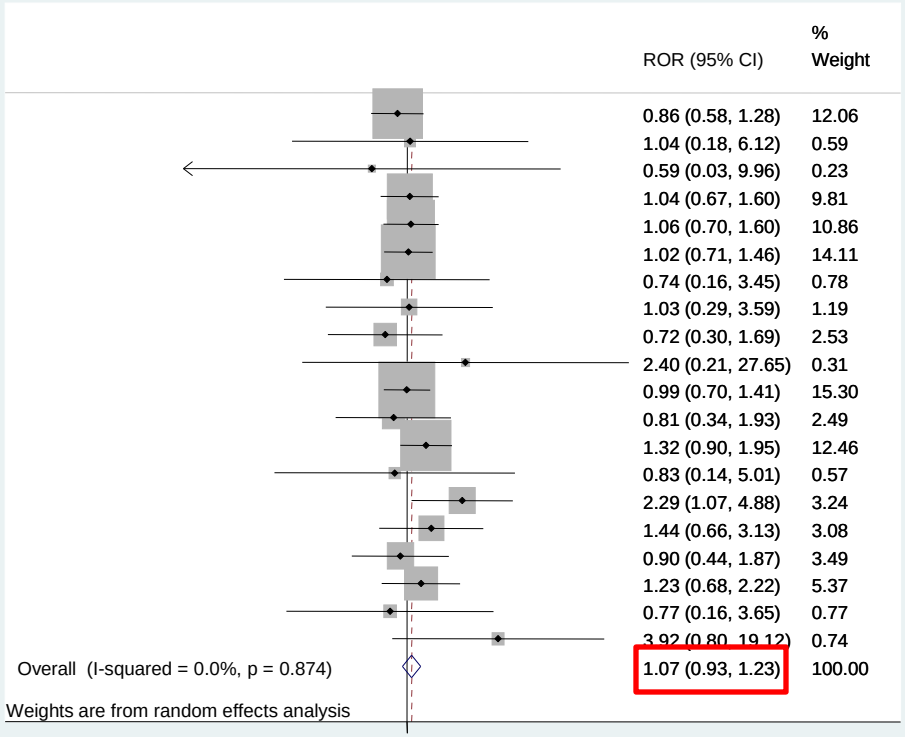
- Low number of meta-analyses with at least one trial at low overall risk of bias
- No evidence of larger treatment effect in the MA of all trials than in the MA restricted to trials at low risk of bias
- Results of meta-epidemiological studies suggested larger treatment effect estimates in trials at high or unclear risk of bias compared to those at low risk domain by domain
  - No meta-epidemiological study compared treatment effect according to overall risk of bias

Meta-epidemiological analysis: treatment effect by overall risk of bias

Objective outcomes



Subjective outcomes



Conclusions

- In a sample of meta-analyses, we compared meta-analyses of:
  - All available evidence
  - Best-evidence
    - Largest trials (Quarter 4), most precise trial, limit MA
    - Trials at low risk of bias

- Frequently larger treatment effect in the MA of all trials than in the « limit » meta-analysis, most precise trial or Quarter 4
  - More marked for subjective outcomes
  - Consistent results for the 3 comparisons

Conclusions: assessing trial overall risk of bias

- No difference of treatment effect according to overall risk of bias
- Difference of treatment effect domain by domain?
- Current definition of overall risk of bias
  - Same risk of bias for trials with 1 domain at high/unclear risk and all key domains at high/unclear risk of bias
  - Does not take into account potential interactions between domains
- Assessing risk of bias: « The why is easy, the how is a challenge »[1]
  - Difficult to understand bias and their impact on treatment effect

[1] Hrobjartsson et al. *Cochrane Database Syst Rev*. 2013

Thank you for your attention

- Acknowledgements:
  - Philippe Ravaud
  - Douglas Altman
  - Isabelle Boutron
  - Ludovic Trinquart
  - Sally Hopewell
  - Julian Higgins

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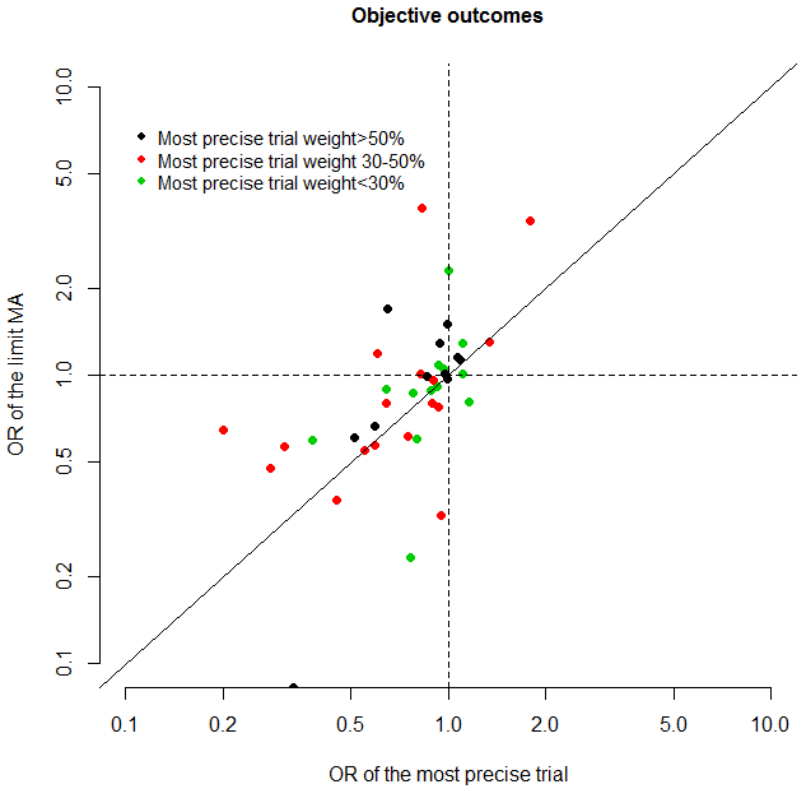
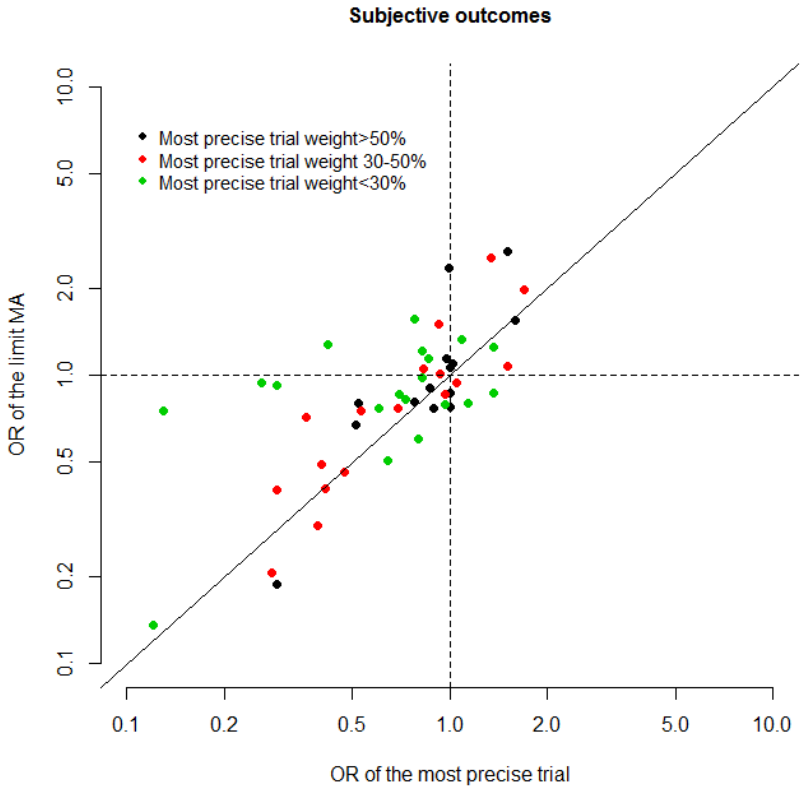
Limit MA versus most precise trial

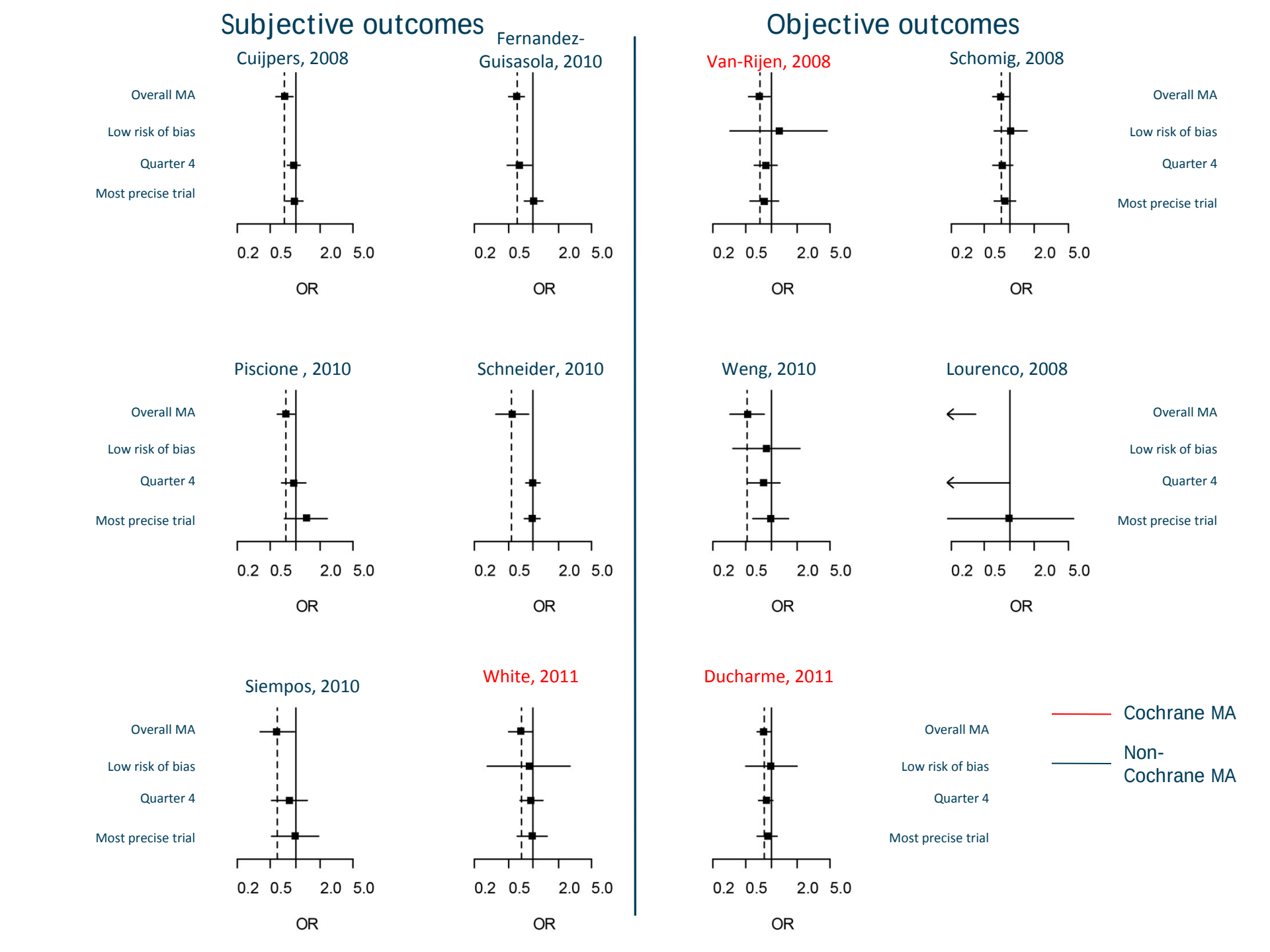




Modifications of conclusions

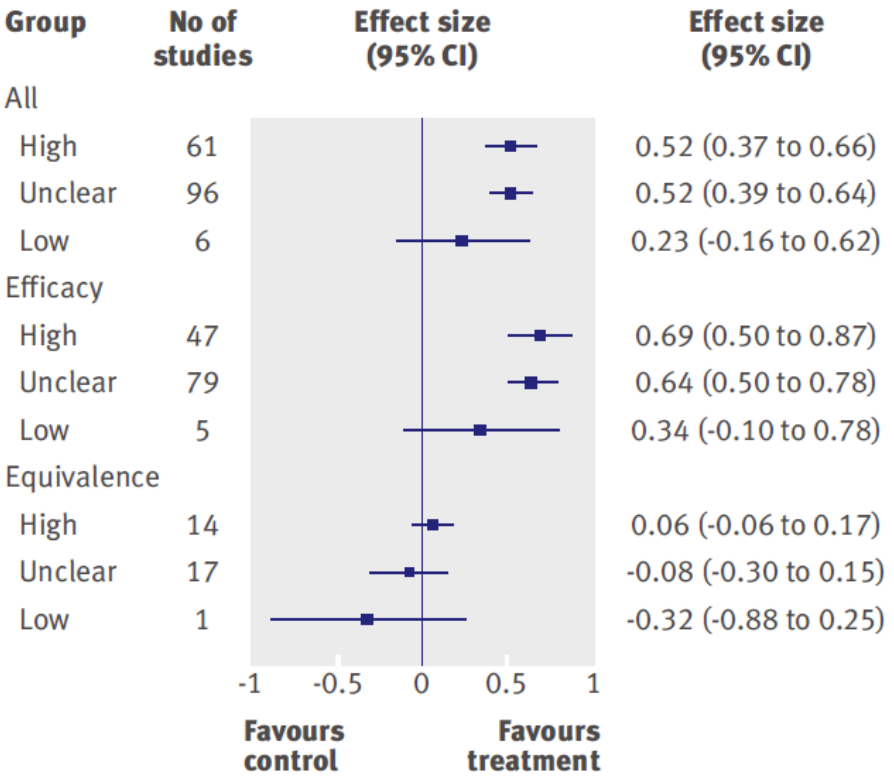
- Out of 48 meta-analyses showing statistically significant outcomes in favor of the experimental arm when including all trials
  - No difference in 11 (23%) meta-analyses using one of the alternative strategies for analysis

- None of the 47 meta-analyses without significant differences became statistically significant using one of the alternative strategies for analysis


Subjective outcomes
Objective outcomes
Cuijpers, 2008
Fernandez-Guisasola, 2010
Van-Rijen, 2008
Schomig, 2008
Piscione , 2010
Schneider, 2010
Weng, 2010
Lourenco, 2008
Siempos, 2010
White, 2011
Ducharme, 2011
Overall MA
Low risk of bias
Quarter 4
Most precise trial
0.2 0.5 2.0 5.0
OR
Cochrane MA
Non-Cochrane MA

Comparison of treatment effect according to risk of bias assessment

- Cross sectional study
- 163 trials in child health
- Effects sizes combined under DerSimonian and Laird random effects model
- Results:
  - Lower treatment effect in trials with low risk of bias trials than in those with high or unclear risk of bias



Effect size estimates according to risk of bias

Hartling et al. *BMJ*. 2009

Appearances can be misleading

- Same analysis using our data
- Comparison of treatment effect between low and high or unclear risk of bias without taking into account meta-analysis stratification
- DerSimonian and Laird random effects model