MedtecHTA

Methods for Health Technology Assessment of Medical Devices: a European Perspective

Developing methods of HTA for medical devices: WP3 - Methods for comparative effectiveness research of medical devices
Final Conference November, 13th 2015

U. Siebert , P. Schnell-Inderst, C. Iglesias, O. Ciani, T. Hunger, M. Arvandi, R. Gothe, R. Taylor, M. Sculpher

Institute of Public Health, Medical Decision Making and Health Technology Assessment, UMIT - University for Health Sciences, Medical Informatics and Technology, Hall i.T., Austria

Centre for Health Economics, University of York, UK

Institute of Health Research, University of Exeter, UK

Project Funded under FP7 - HEALTH
Grant Agreement no.305694

WP 3 Objectives

Task 1+2

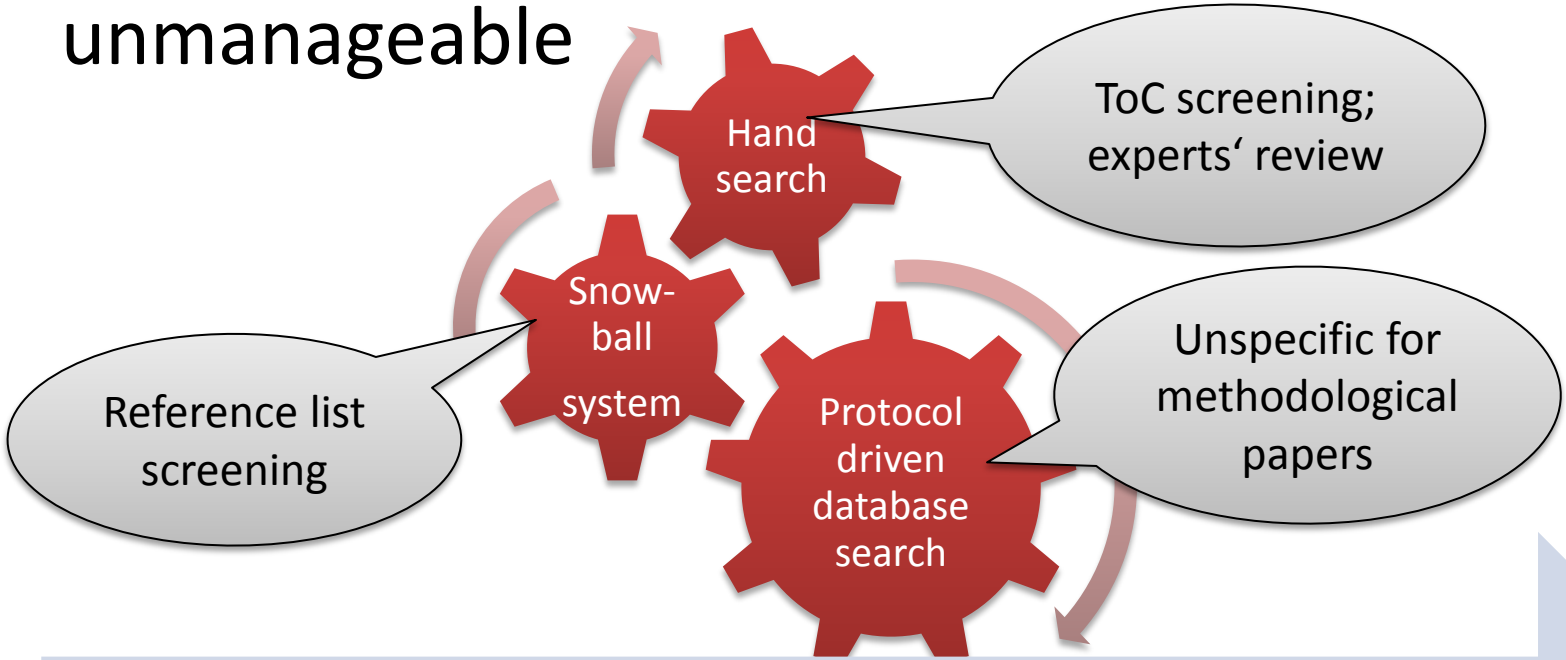
- Identification of challenges and gaps in current methods for comparative effectiveness of medical devices (MD)
- Development of a framework for comp. effectiveness of MD
  - *Interpret data from OS, administrative data, registries*
  - *Influence of learning curves on clinical effect*
  - *Methods of evidence synthesis*
- Recommendations

Task 3

- Test Framework: Case studies
  - *Learning curves, administrative data → fEVAR case study*
  - *Evidence synthesis methods (meta-analysis, of RCT+OS, effect modification) → Total hip replacement (THR) case study*

Methods: Targeted literature search and review

General systematic search turned out unmanageable



eunethta
EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

HTA Core Model ®

Framing the research question | Where to find information ? | What kind of information is required? | Appraisal tools | Analyzing/ synthesizing evidence | Reporting and Interpreting

Overview framework & recommendations

ELSEVIER

Journal of Clinical Epidemiology 66 (2013) 1209–1214

Journal of Clinical Epidemiology

Complex interventions and their implications for systematic reviews: a pragmatic approach

Mark Petticrew[a,*], Laurie Anderson[b], Randy Elder[c], Jeremy Grimshaw[d], David Hopkins[c], Robert Hahn[c], Lauren Krause[e], Elizabeth Kristjansson[d], Shawna Mercer[c], Teresa Sipe[c], Peter Tugwell[d], Erin Ueffing[f], Elizabeth Waters[g], Vivian Welch[d]

[a]*Department of Social & Environmental Health Research, London School of Hygiene & Tropical Medicine, London WC1H 9SH, United Kingdom*
[b]*Washington State Institute for Public Policy, 110 Fifth Avenue SE, Olympia, WA, USA*
[c]*Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA*
[d]*Institute of Population Health, University of Ottawa, Ottawa, Ontario, Canada*
[e]*Colorado School of Public Health, University of Colorado Denver, Denver, CO, USA*
[f]*Canadian Cochrane Centre, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada*
[g]*The McCaughey Centre, Melbourne School of Population Health, The University of Melbourne, Melbourne, Australia*

Accepted 10 June 2013; Published online 14 August 2013

Overview framework & recommendations

Area	Results
Framing the research question	Consider MD intervention **as complex interventions**: Multiple components, effect-modifying factors such as **user and context dependence**. Definition of intervention and comparators more demanding according to **incremental development. Use logic models.**
What kind of information is required? Primary research	Consider **specific RCT study designs** and analysis methods dealing with surgeons' and patients' **preferences, incremental development, user dependence** **Disease- or device-based high quality registries are needed** for safety and long-term effects, appropriate bias-adjustment methods
Where to find Information?	No specific methods, existing methods should be applied
Tools for critical appraisals	No specific tools, existing tools can be applied

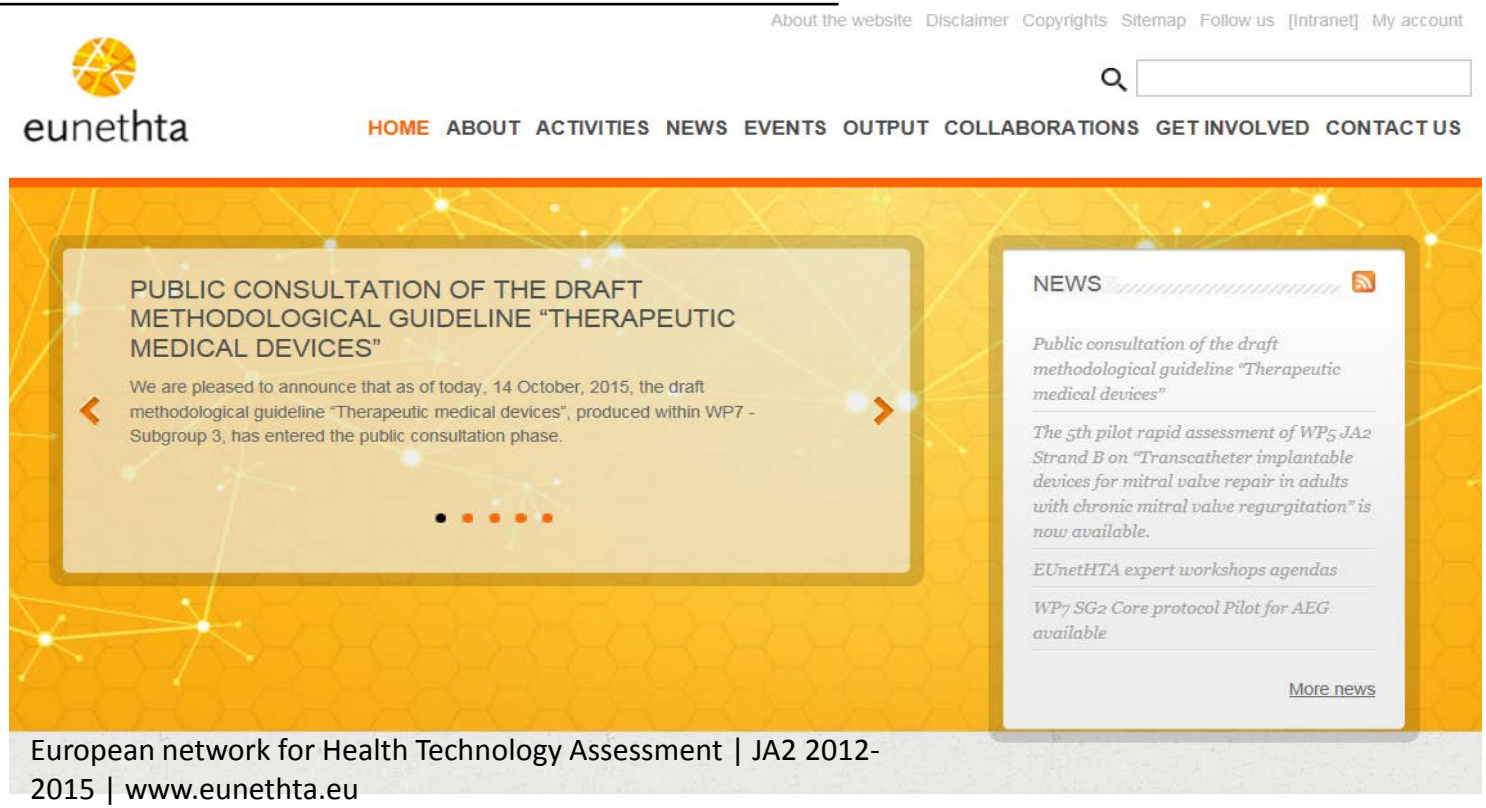
Overview framework & recommendations

Area	Results
Analyzing and synthesizing evidence	In principle, no specific methods but some challenges lie in the details: application of evidence synthesis methods of framework on complex interventions to MD e. g. considering learning curves, more OS data → e. g. **integration with cross-design meta-analysis**)
Reporting and interpreting	In principle, depending on the decision context, tools for grading the body of evidence such as GRADE for clinical guidelines can be applied **Heterogeneity** and **applicability** more important to consider

WP3 results fed into EUnetHTA JA2 WP7 SG3 methodological guideline

Guideline draft group: UMIT, IQWiG, G-BA, Osteba

Guideline “Therapeutic medical devices”



European network for Health Technology Assessment | JA2 2012-2015 | www.eunethta.eu

Total Hip Replacement Case Study

Rationale for choosing THR

- Life cycle of MD: Methodological aspects of technology which is already established and evidence is not scarce
- THR is an accepted clinically effective therapy to treat pain and disability resulting from late stage arthritis of the hip
- Incremental development: Evolving design
  - bone fixation methods (e.g., cemented, cementless, hybrid)
  - prosthesis femoral head size
  - bearing surface articulations (e.g., metal, ceramic, polyethylene)
- RCTs vs. registry studies vs. observational studies

Aim: To apply a method of bias modeling in evidence synthesis that allows meta-analysis of RCT and observational evidence adjusted for biases formally elicited from experts

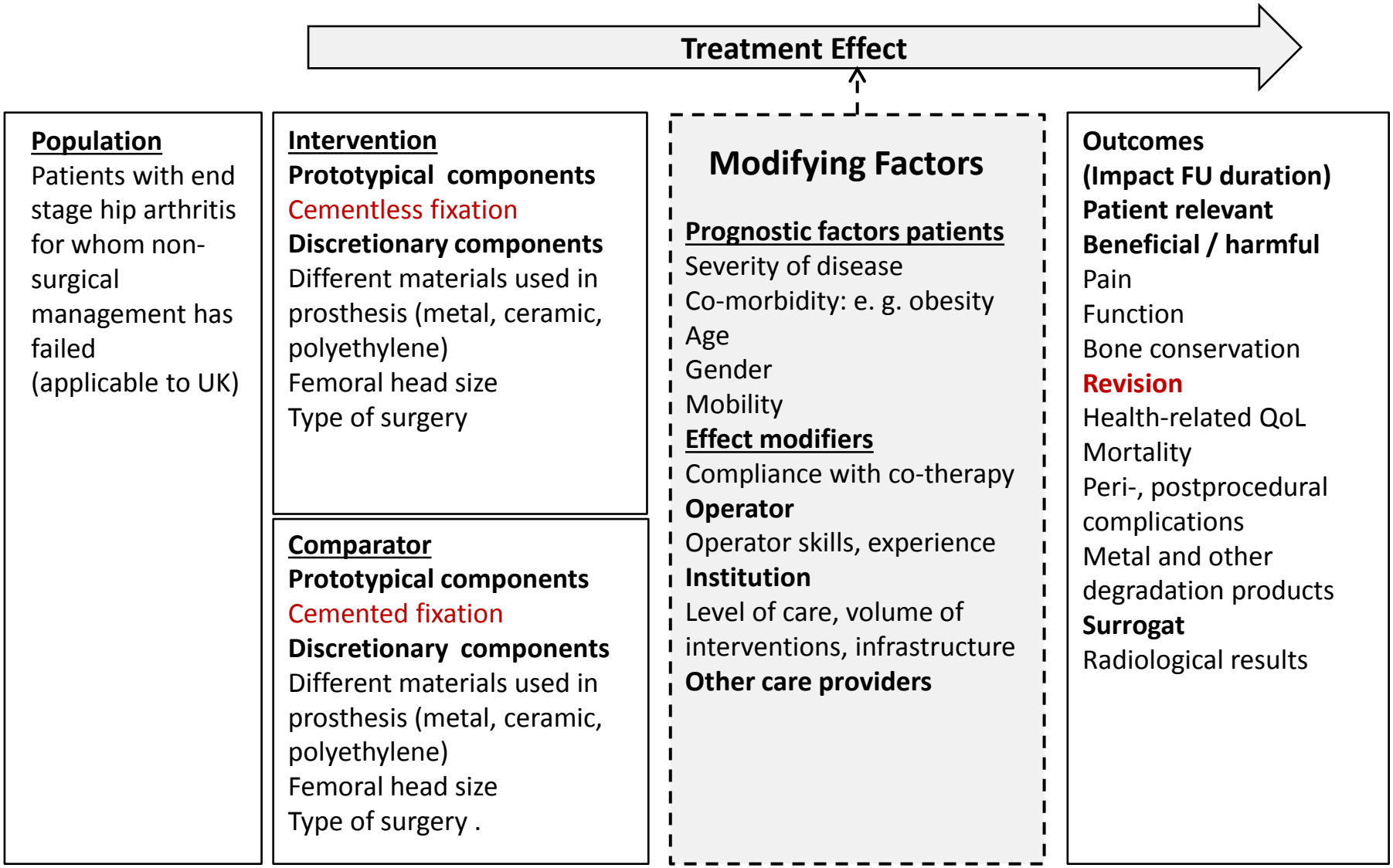
Turner & Spiegelhalter method key steps

Bayesian hierarchical bias modelling framework

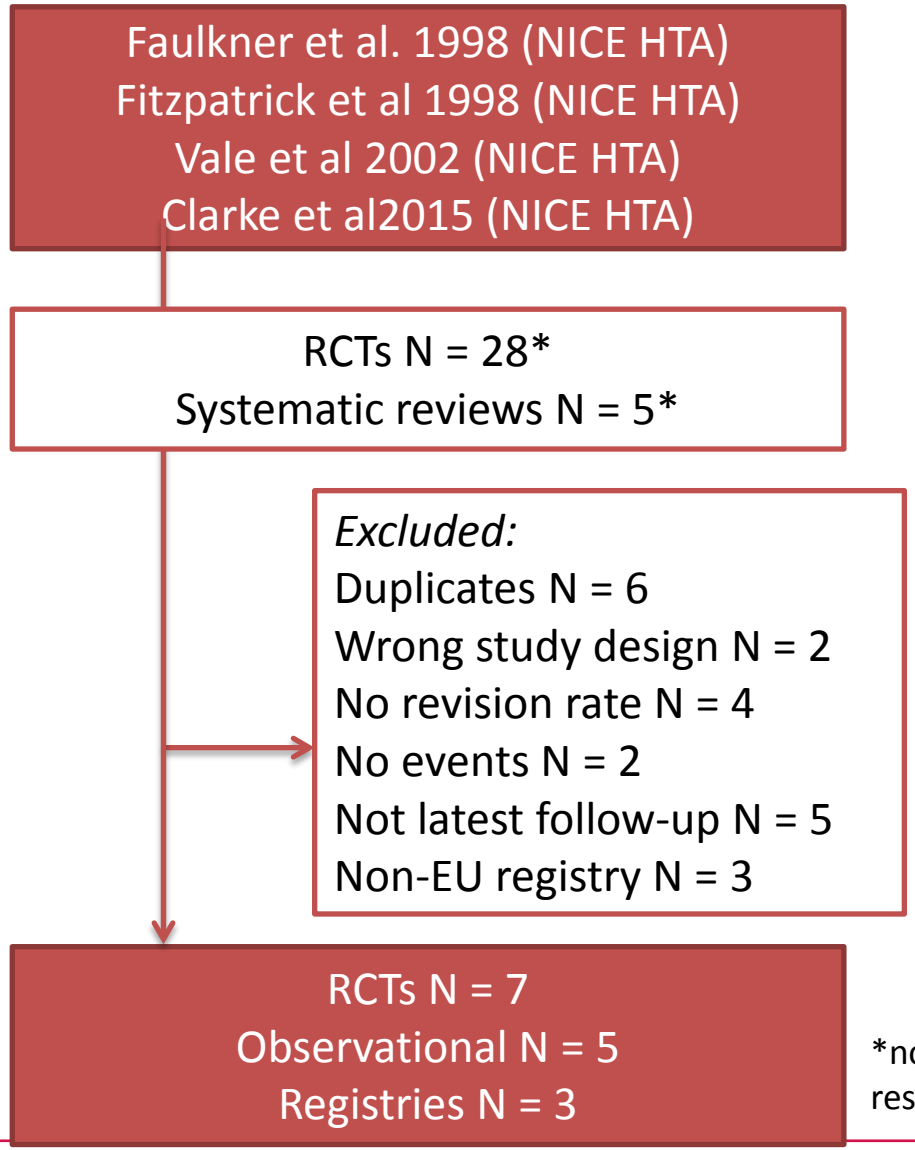
Aims: to ascertain and quantify potential sources of bias

1. Identify target question & setting
2. Identify eligible studies
3. Define idealised study (modified)
4. Identify biases: (modified)
   - Internal: Outcome, Attrition, Exposure, Confounding, Selection
   - External: Timing, Outcome, Exposure, Population
5. Bias elicitation and total bias estimates (modified)
6. Naïve meta-analysis
7. Bias-adjusted meta-analysis

Target question with a logic model



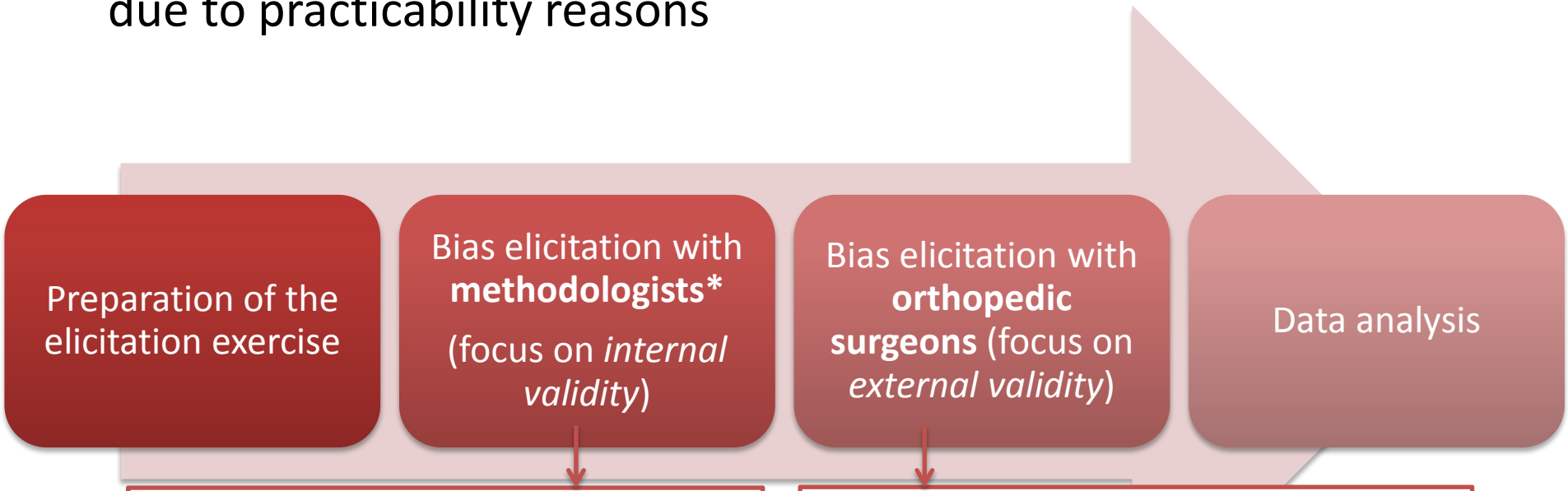
Evidence base



*not all focusing on the specific research question

Methods overview elicitation

We adapted the method of bias elicitation by Turner et al. 2009 due to practicability reasons



Tools:

- Abstract
- Prefilled PICOS
- Prefilled **Internal** Bias-checklist (selection bias, performance bias, detection bias, attrition bias…)
- Qualitative bias assessment tool
- Quantitative bias assessment tool

Tools:

- Abstract
- Prefilled PICOS
- Prefilled **External** Bias-checklist
- (eligibility criteria, treatment setting, treatment characteristics…)
- Qualitative bias assessment tool
- Quantitative bias assessment tool

*trialists, statisticians, epidemiologists

Methods evidence synthesis

- We compared 4 different meta-analysis models:

  (1) Frequentist FEM, (2) Frequentist REM,

  (3) Bayesian REM, (4) Bayesian 3-level hierarchical model including study type
- Stepwise analysis: RCTs only, RCTs+registries, RCTs+registries+cohort studies
- Bias-adjusted vs. unadjusted
- Subgroup analyses and uni-/bivariate meta-regression to explore heterogeneity/effect modification
- Sensitivity analysis of priors for Bayesian meta-analysis: non-informative priors and weak-informative priors

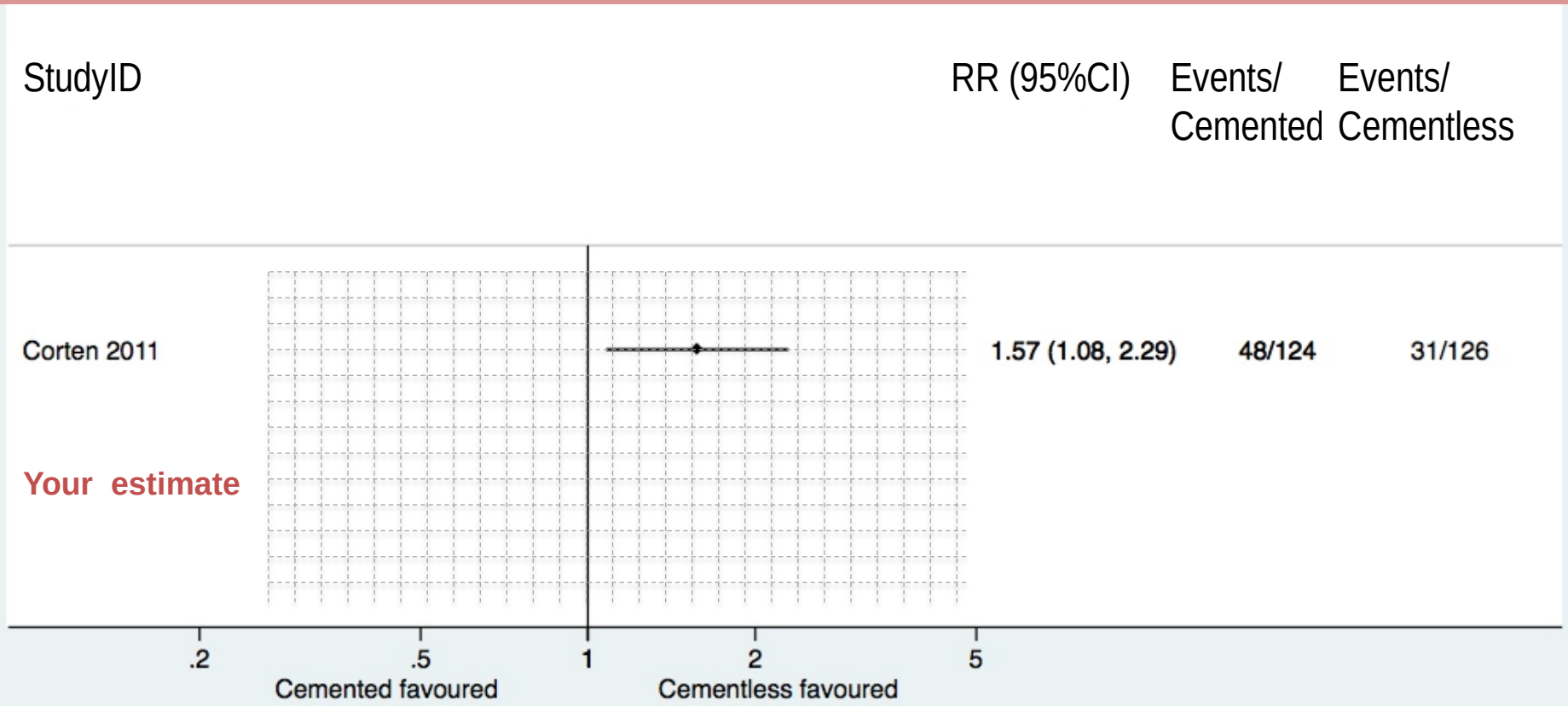
Expert elicitation

- Two workshops lasting about 3 hours
- 9 and 11 experts attended the methodologists and clinicians (orthopedic surgeons) workshops, respectively
- Each expert received (in random order) 6-8 studies to assess

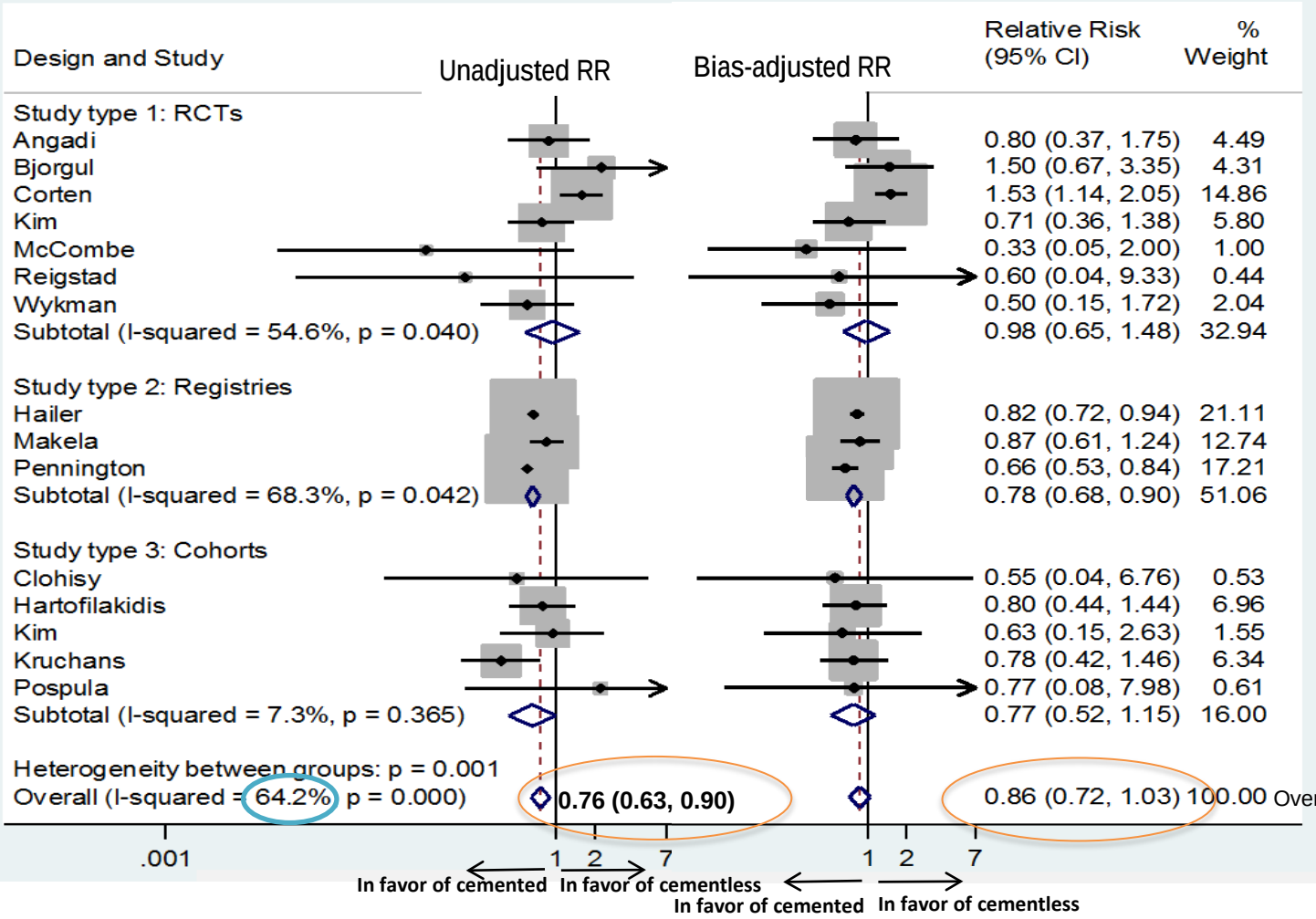
Tools for the elicitation meetings (methodologists)

Bias-adjusted treatment effect

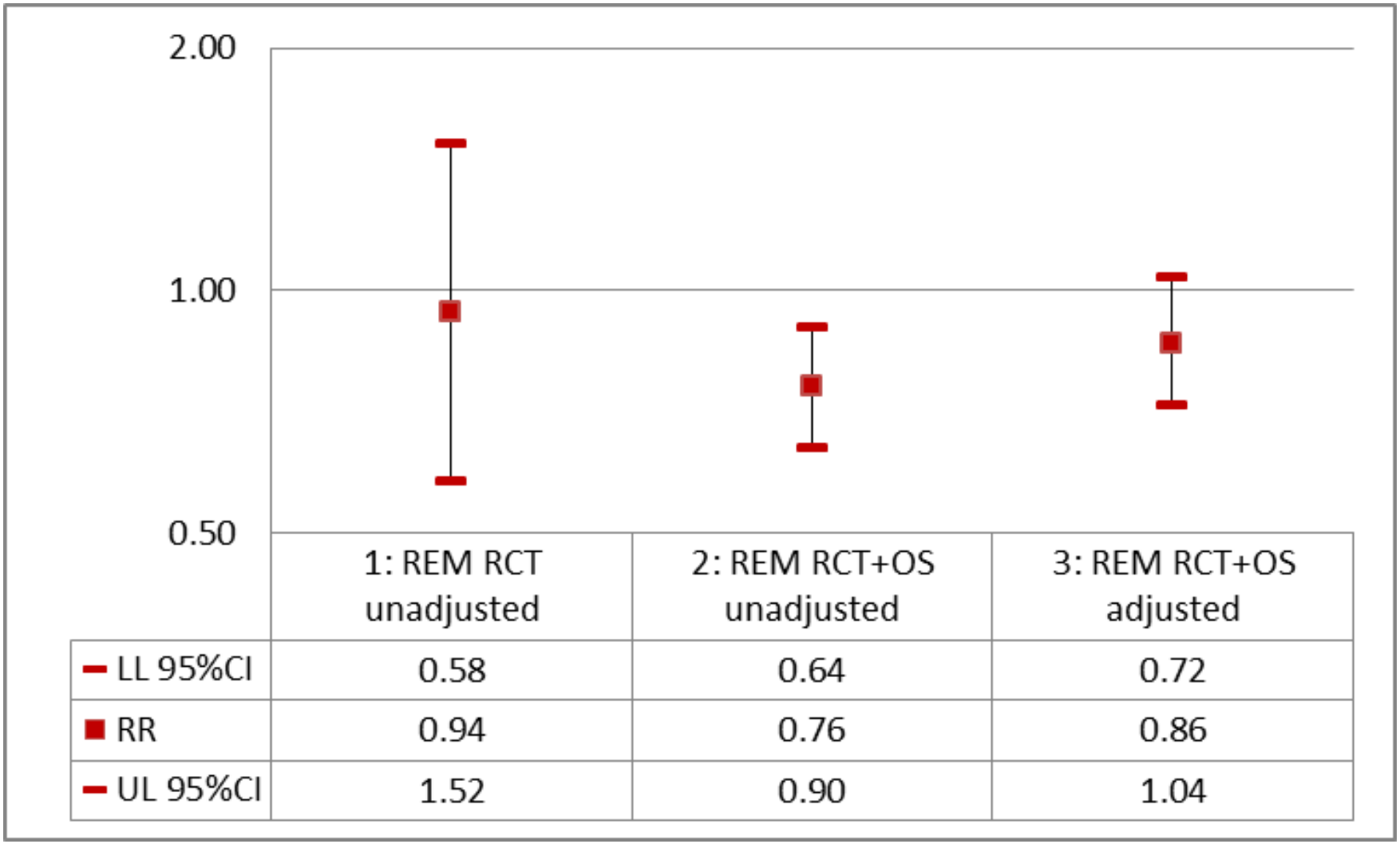
After considering the PICOS and bias checklist for the Corten et al. 2011 study, and your qualitative assessment of the bias' effect, what would your best estimate of relative risk (95%CI) for **revision rate** from this study be after removing the biases previously identified?



REM unadjusted and adjusted RR



Results: Stepwise meta-analysis REM



	1: REM RCT unadjusted	2: REM RCT+OS unadjusted	3: REM RCT+OS adjusted
LL 95%CI	0.58	0.64	0.72
RR	0.94	0.76	0.86
UL 95%CI	1.52	0.90	1.04

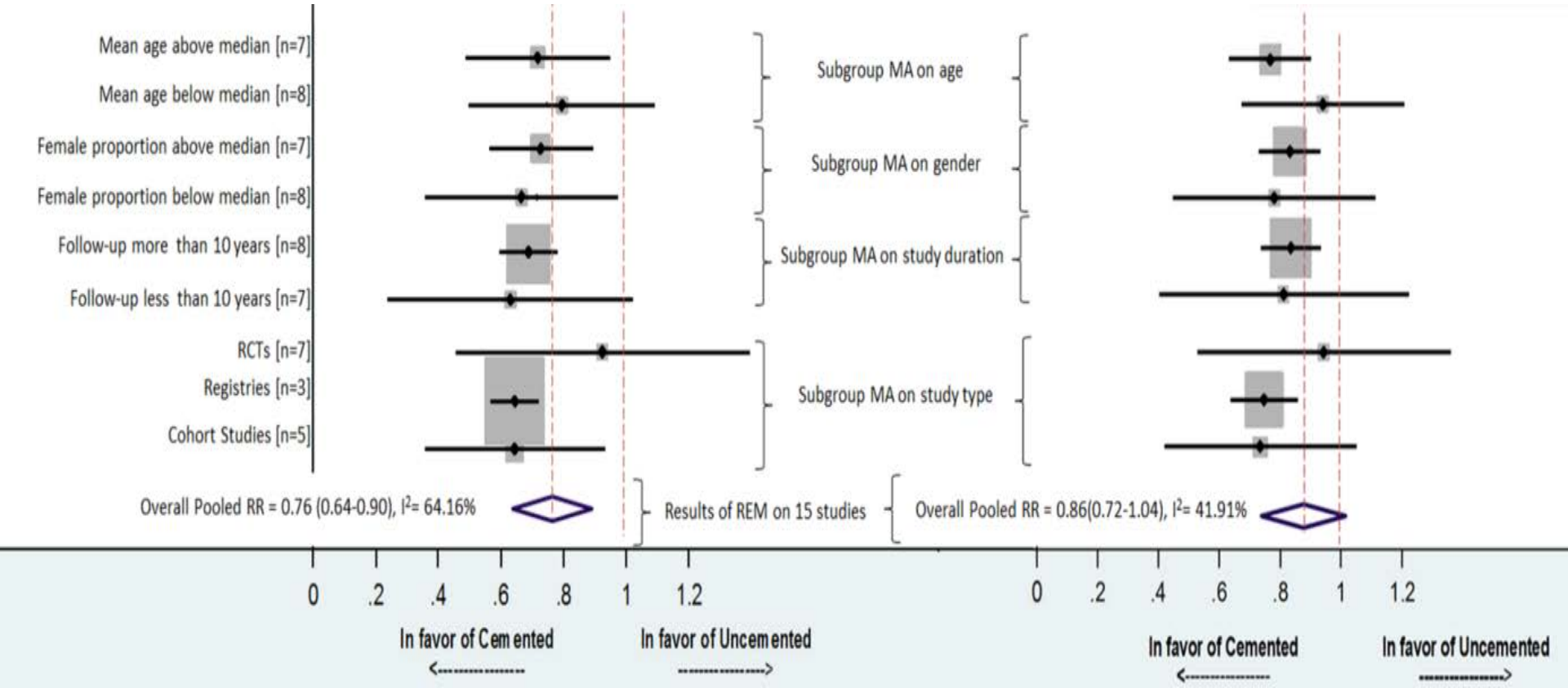
Results: Stepwise meta-analyses

Frequentist	Unadjusted RRs FEM*		Unadjusted RRs REM**		Bias-Adjusted RRs FEM		Bias-Adjusted RRs REM	
in Meta-analysis	RR (95%CI)	UB/LB	RR (95%CI)	UB/LB	RR (95%CI)	UB/LB	RR (95%CI)	UB/LB
RCTs	1.12(0.86-1.45)	1.69	0.94(0.58-1.52)	2.62	1.21(0.96-1.54)	1.60	0.98(0.65-1.48)	2.28
I^2	54.8%				42.2%			
RCTs and Registries	0.67(0.64-0.70)	1.09	0.78(0.65-0.95)	1.46	0.85(0.77-0.94)	1.22	0.88(0.70-1.11)	1.59
I^2	74.10%				62.00%			
All 15 studies	0.67(0.64-0.70)	1.09	0.76(0.64-0.90)	1.41	0.85(0.77-0.94)	1.22	0.86(0.72-1.04)	1.44
I^2	64.2%				41.9%			

Bayesian REM	Unadjusted Posterior RRs		Bias-Adjusted Posterior RRs	
Studies in Meta-analysis	RR (95%CrI)	UB/LB	RR (95%CrI)	UB/LB
RCTs	0.90(0.37-1.71)	4.62	0.94(0.46-1.62)	3.52
Tau^2	0.65		0.52	
RCTs and Registries	0.80(0.55-1.17)	2.73	0.87(0.62-1.18)	1.90
Tau^2	0.43		0.35	
All 15 studies	0.77(0.58-1.03)	1.78	0.85(0.66-1.07)	1.62
Tau^2	0.36		0.28	
3-Level Hierarchical ++	0.74(0.16-3.71)	23.19	0.82(0.21-3.31)	15.76
Tau2	0.80		0.69	

*FEM: Fixed-effect model. **REM: Random-effect model. +RR: relative risk, ++Levels of study type: RCTs, registries and cohort studies.LB: Lower bound of 95%-CI or CrI respectively; UB: Upper bound of 95%-CI or CrI respectively

Subgroup analyses



Sensitivity analysis on priors

Baseline 3-level Hierarchical Bayesian	RR (95%CI)
With uniform distributions	0.74 (0.16-3.71)
Sensitivity analysis on mean	**RR (95%CI)**
T-Distribution	0.74 (0.14 - 3.91)
Sensitivity analysis on variance	**RR (95%CI)**
Gamma Distribution	0.73 (0.46 - 1.24)
Inverse-Gamma Distribution	0.75 (0.31 - 1.82)
Half-Cauchy Distribution	0.73 (0.49 - 1.14)

Discussion

- We successfully adapted and applied a method of bias-adjusted evidence synthesis based on expert elicitation
- Quantifying bias is a conceptually & practically difficult task (especially internal validity for methodologists)
- Original analysis of observational studies should adjust for confounding to minimize need for post-hoc subjective bias adjustment
- In our case, adding observ. studies strengthened body of evidence
  - potentially overoptimistic effect estimates were reduced by bias-adjustment from expert elicitation
- With the adapted elicitation and analysis approach
  - ("simple") frequentist approach of meta-analysis can be used
  - Bayesian meta-analysis yielded similar effects (with greater uncertainty)
- Feasibility-validity trade-off

Limitations

- Small and not representative sample of experts reduces generalizability of our results
- Not all biases might have been captured (heterogeneity did not fully disappear)
- Insufficient reporting quality in original papers limits potential to identify biases
- Time-to-event data would have been more adequate outcome measures, but were not available in published studies
- Integration of individual patient data from registries may allow for fitting empirical survival functions, → requires individual data, is resource and time consuming, but possible

Conclusions

- We derived a methodological compromise for bias-adjusted meta-analysis between more sophisticated methods (validity) and crude (unadjusted) evidence synthesis (oversimplification)
- This approach should be considered
  - in the context of assessing the existence/direction/magnitude of bias
  - if there are a priori reasons to assume bias
  - if there is hesitancy in performing meta-analysis because of high heterogeneity or differences in study design / methodological quality
  - if single best estimate is needed, e.g., as input in cost-effectiveness analysis
- If data from large registries are available to be included in the evidence synthesis in HTA, bias-adjustment based on expert elicitation should be considered as one scenario within the sensitivity analyses

THANK YOU FOR YOUR ATTENTION