Variation in bias associated with different trial characteristics: combined evidence from meta-epidemiological studies

Lesley Wood,[1] Matthias Egger,[1,2] Lise Lotte Gluud,[3] Kenneth Schulz,[4] Douglas Altman,[5] Peter Jüni,[2] Jonathan Sterne[1]

[1] Bristol, UK; [2] Berne, Switzerland; [3] Copenhagen, Denmark; [4] N Carolina, USA; [5] Oxford, UK

MRC Medical Research Council

HSRC Health Services Research Collaboration

Acknowledgements

- MRC/HSRC for PhD funding

- Our collaborators for the generous sharing of data, without which there would have been no project

Outline of talk

- Objectives
- Background
- Derivation of the dataset
- Results
- Discussion and conclusions

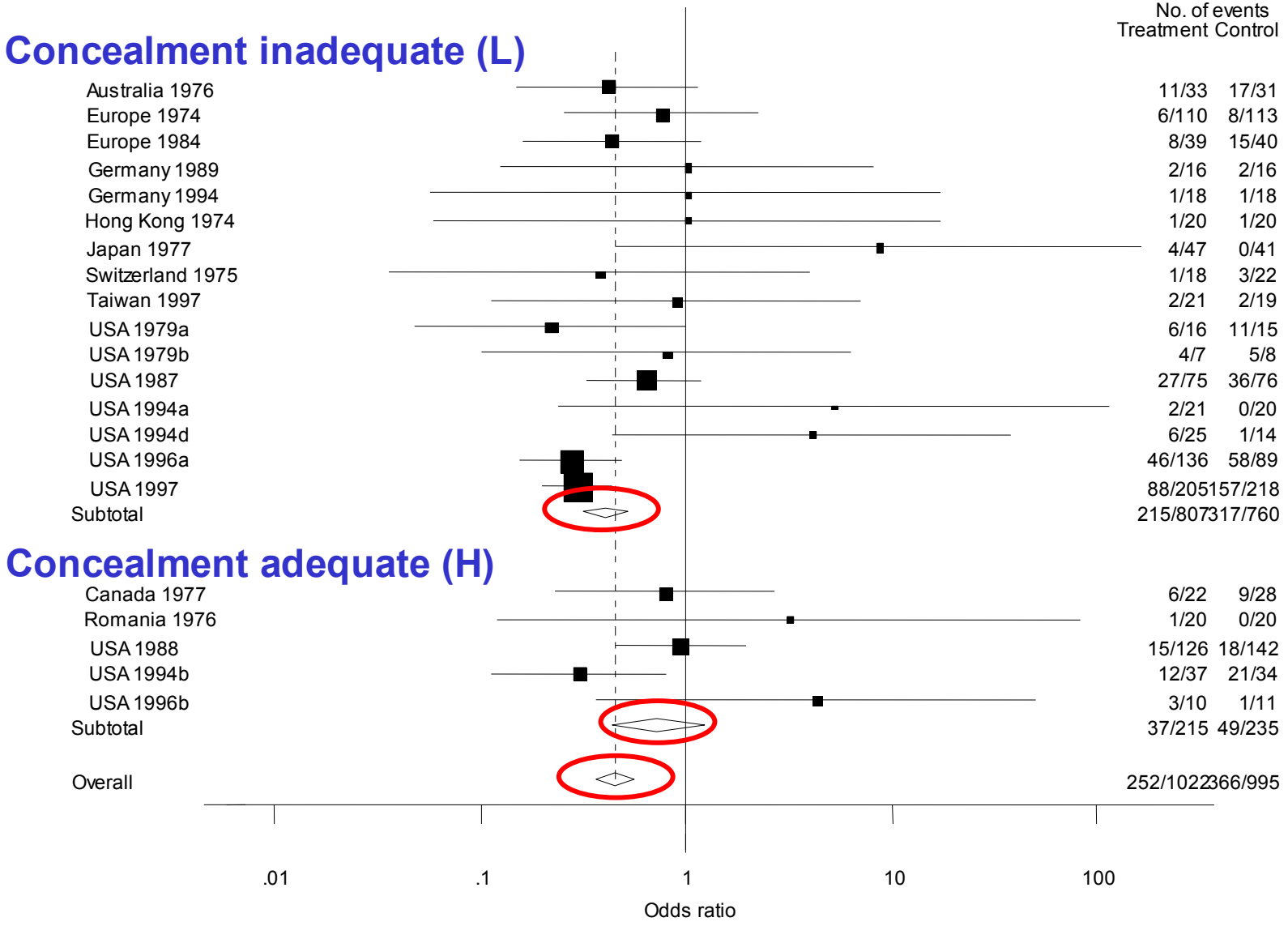
Objectives

1) To use data combined from previous meta-epidemiological studies to investigate bias in results of RCTs associated with:
    - Inadequate/unclear allocation concealment
    - Lack of blinding
2) To examine whether such bias varies with type of intervention or type of outcome

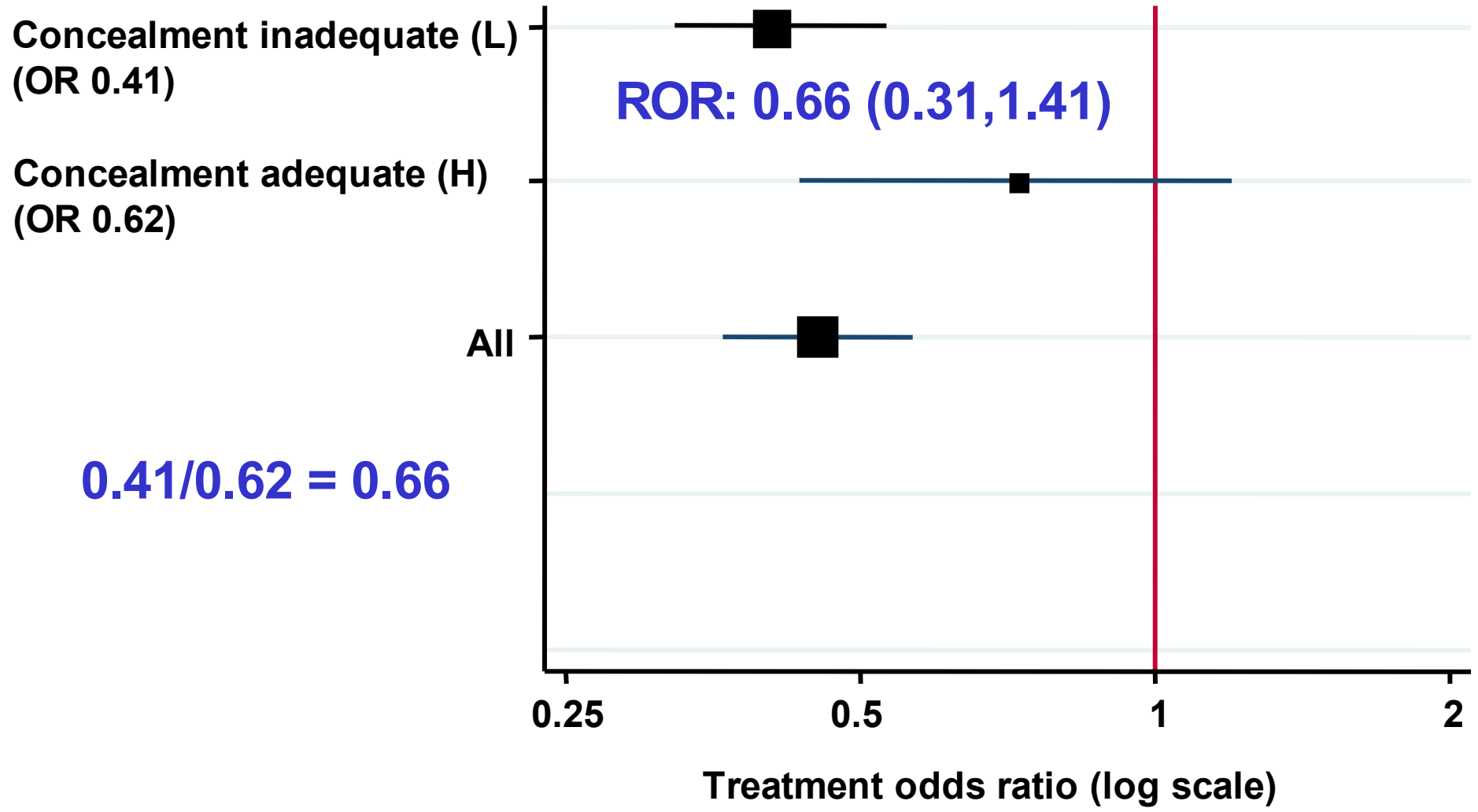
Background: empirical evidence of bias in the results of RCTs

- Meta-epidemiological studies consist of collections of meta-analyses in which the characteristics of each RCT contributing to each meta-analysis are assessed, e.g.
  - adequacy of allocation concealment
  - use of blinding
- Such studies have been used to examine whether flaws in the design of RCTs lead to bias in treatment effect estimates
- The following slides illustrate the basic principle for one meta-analysis

Clozapine versus neuroleptic medication for schizophrenia



Clozapine versus neuroleptic medication for schizophrenia



0.41/0.62 = 0.66

Methods (1)

- We used data from three meta-epidemiological studies to develop a combined dataset
- Overlapping meta-analyses were removed (see Poster no. 328)
- Interventions were classified as pharmacological *vs*. non-pharmacological
- Outcomes were classified as:
  - 1) all-cause mortality *vs*. other
  - 2) objective *vs*. subjective

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias - Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995; 273(5):408-412

Kjaergard LL, Villumsen J, Gluud C. Reported methodological quality and discrepancies between large and small randomized trials in meta-analyses. Ann Intern Med 2001; 135:982-989.

Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. Health Technology Assessment 2003; 7

Results

Numbers of trials and meta-analyses contributed by each study:

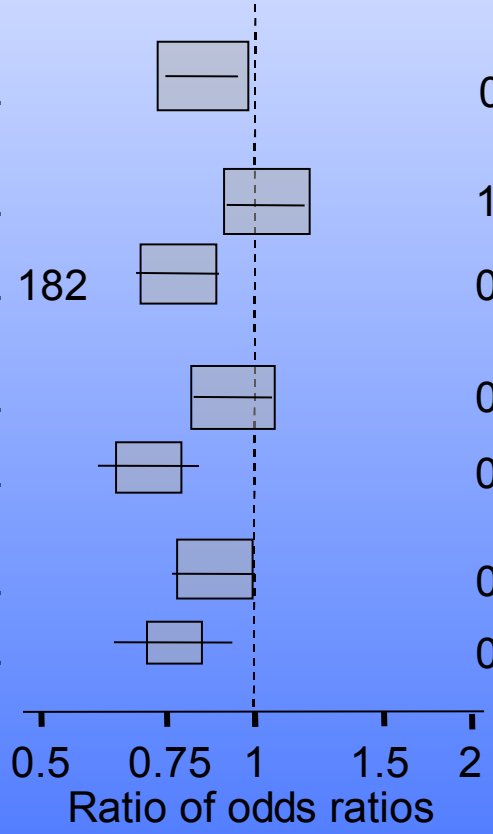
Study	MA	RCT
Schulz *et al*.	27	213
Kjaergard *et al*.	7	95
Egger *et al*.	112	1038
Total	146	1346

Numbers of trials and meta-analyses stratified by type of intervention or type of outcome:

		MA	RCT
Intervention	Pharmacological	89	919
	Non-pharmacological	57	427
Outcome	All-cause mortality	27	295
	Other	119	1051
Outcome	Objective	78	718
	Subjective	68	628

Effect of inadequate/unclear versus adequate allocation concealment

Comparison (number of meta-analyses)	Number of trials	ROR (95% CI)	Heterogeneity variance (p value)
Overall (102)	532 *vs.* 272	0.83 (0.74, 0.93)	0.11 (p<0.001)
All-cause mortality (23)	117 *vs.* 90	1.01 (0.90, 1.15)	0.02 (p=0.235)
Other outcomes (79)	415 *vs.* 182	0.76 (0.66, 0.87)	0.14 (p<0.001)
Objective outcomes (62)	310 *vs.* 174	0.91 (0.80, 1.03)	0.11 (p<0.001)
Subjective outcomes (40)	222 *vs.* 98	0.69 (0.59, 0.82)	0.07 (p=0.011)
Drug intervention (65)	411 *vs.* 205	0.87 (0.76, 1.00)	0.09 (p<0.001)
Other intervention (37)	121 *vs.* 67	0.77 (0.64, 0.93)	0.16 (p<0.001)

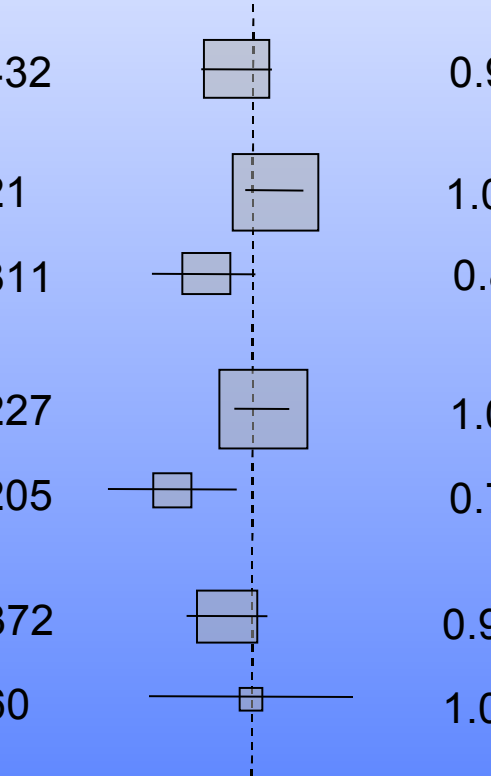


Inadequately concealed more beneficial Inadequately concealed less beneficial

MRC Medical Research Council HSRC Health Services Research Collaboration

Effect of inadequate versus adequate blinding

Comparison (number of meta-analyses)	Number of trials	ROR (95% CI)	Heterogeneity variance (p value)
Overall (76)	314 *vs*. 432	0.93 (0.83, 1.04)	0.11 (p<0.001)
All-cause mortality (18)	79 *vs*. 121	1.04 (0.95, 1.14)	0.01 (p=0.265)
Other outcomes (58)	235 *vs*. 311	0.83 (0.70, 0.98)	0.18 (p<0.001)
Objective outcomes (44)	210 *vs*. 227	1.01 (0.92, 1.10)	0.08 (p<0.001)
Subjective outcomes (32)	104 *vs*. 205	0.75 (0.61, 0.93)	0.14 (p<0.001)
Drug intervention (57)	250 *vs*. 372	0.92 (0.81, 1.05)	0.10 (p<0.001)
Other intervention (19)	641 *vs*. 60	1.00 (0.71, 1.39)	0.22 (p=0.003)



MRC Medical Research Council
HSRC Health Services Research Collaboration

Discussion and conclusions

- Meta-analyses of RCTs are not immune from bias
- In general the effect of inadequate allocation concealment is greater than inadequate blinding
- Magnitude of bias due to trial quality characteristics varies according to the type of outcome variable
- Variation in the effect of inadequate allocation concealment with type of outcome was unexpected
  - selection bias should operate regardless of the type of outcome
  - the effects of bias due to inadequate allocation concealment and lack of blinding may be more closely linked than has previously been thought
- Our findings may explain apparent discrepancies in the results of previous meta-epidemiological studies

Questions?

Association between **blinding** and treatment effect estimates stratified by type of outcome, restricted to adequately concealed trials

	ROR (95% CI)	Between MA bias variance
All RCTs (12 MAs; 60 RCTs)	1.02 (0.92 to 1.14)	$\tau^2 = 0.0$
Objective outcomes (7 MAs; 42 RCTs)	1.03 (0.92 to 1.16)	$\tau^2 = 0.0$
Subjective (5 MAs; 18 RCTs)	0.80 (0.48 to 1.32)	$\tau^2 = 0.0$

Associations controlling for the other variable of interest

- We used adjusted analyses to control for the other characteristic of interest
- All RCTs:
  - little change in ROR for allocation concealment after adjustment for blinding
  - ROR for blinding was slightly attenuated after adjusting for allocation concealment

Associations controlling for the other variable of interest, stratified by type of outcome

- All-cause mortality:
  - No effect for either variable after controlling for the other variable
- Outcomes other than all-cause mortality:
  - The effect shown by each variable is slightly attenuated after controlling for the other variable
  - The effect for blinding adjusted by allocation concealment is attenuated to a slightly greater extent than that for allocation concealment adjusted by blinding
- Stratifying by objective / subjective outcomes gave similar results to above

Summary (1)

- **Allocation concealment:**
  - **Overall**: 17% more beneficial treatment effect estimates in inadequately concealed trials compared with adequately concealed trials
  - **Intervention**: Similar effects in trials stratified by type of intervention
  - **Outcome**: Effect is much stronger in trials of subjective outcomes (31% difference) compared with objective outcomes (9% difference)

Summary (2)

- **Blinding:**
  - **Overall**: 7% more beneficial treatment effect estimates in inadequately blinded trials compared with adequately blinded trials
  - **Intervention**: Similar effects in trials stratified by type of intervention
  - **Outcome**: Effect is stronger in trials of MAs of subjective outcomes (25%) compared with objective outcomes (1% in the opposite direction)
  - **Restricted to trials with adequate allocation concealment:** Bias associated with blinding is restricted to trials assessing subjective outcomes