Models for potentially biased evidence in meta-analysis using empirically based priors

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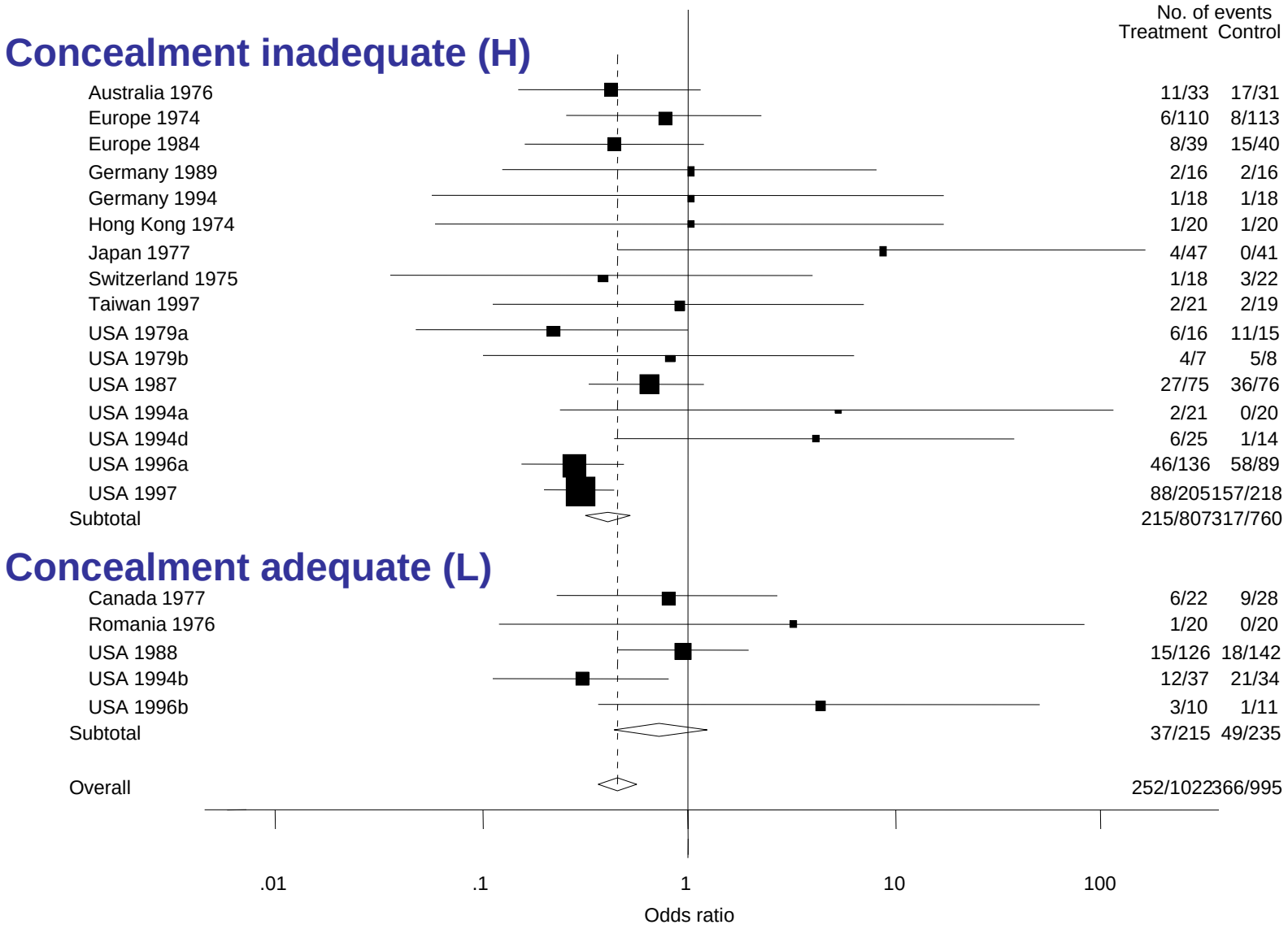
Introduction

- Meta-Analysis / Evidence Synthesis
  - Pooling of information from a set of RCT's comparing the same interventions
  - Pooled relative effect measure (e.g. Odds-Ratio)
  - To summarise a body of evidence (Cochrane)
  - Aid decision-making (Health Technology Assessment / NICE guidance)

Risk of Bias

- Pooled treatment effects and resulting decisions
  - rely on integrity of evidence on which they are based
- Randomised Controlled Trials (RCT's)
  - considered the gold-standard evidence to inform relative treatment efficacy
- Even RCTs vary in quality
  - Is randomisation allocation adequately concealed?
  - Is there appropriate blinding?
  - Quality information routinely collected (Cochrane risk of bias tool)

Clozapine versus neuroleptic medication for schizophrenia



Should we include evidence at high risk of bias?

- Best available evidence approach
  - ignore evidence at high risk of bias

  … but evidence at low risk of bias may be relatively sparse

- All available evidence approach
  - Somehow combine high & low risk of bias evidence
  - In spirit of NICE, where focus is on decision analysis that reflects body of evidence available

How to estimate and adjust for bias?

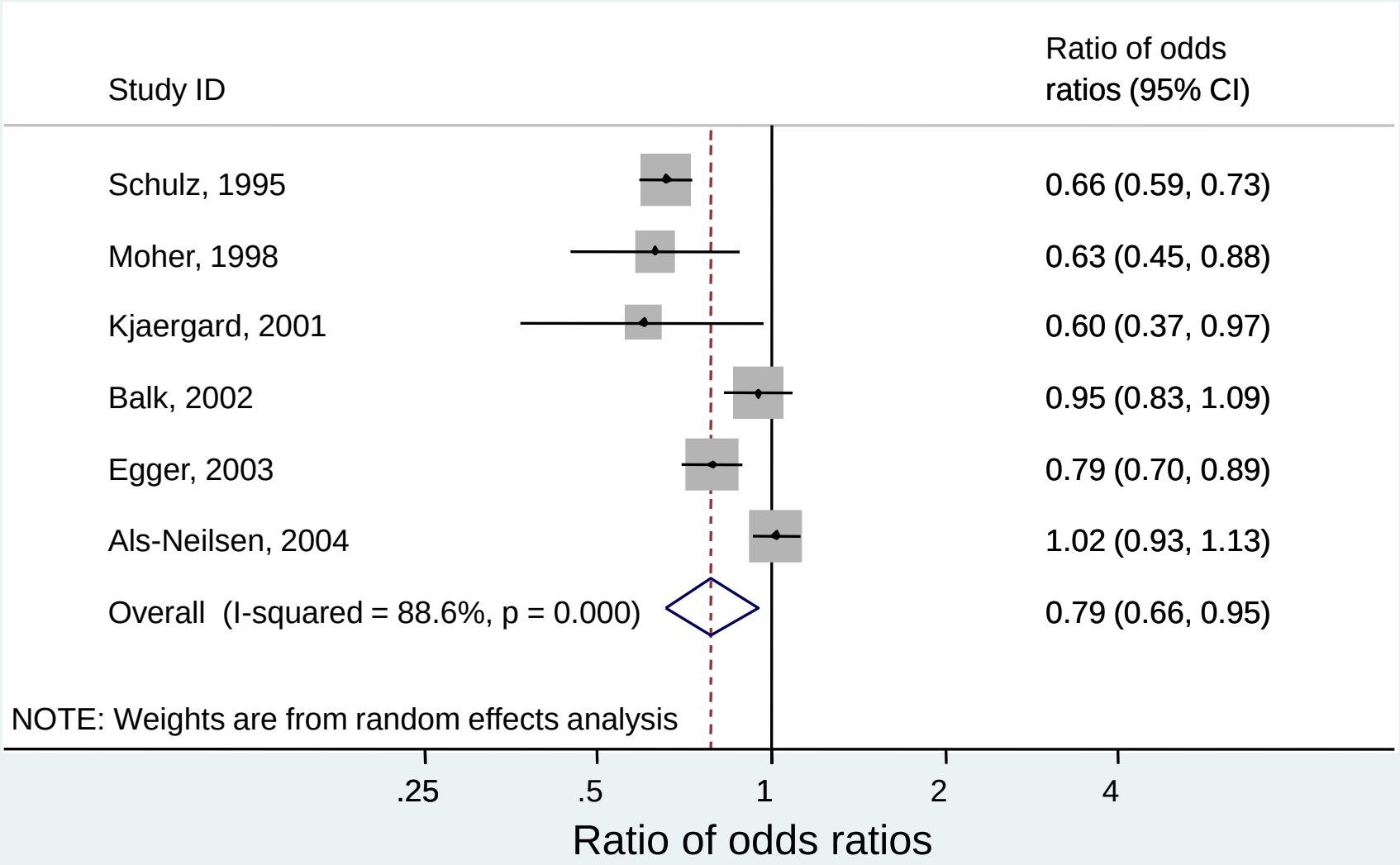
- Internally within meta-analysis?
  - High risk evidence contributes mainly to bias estimation, and very little to treatment effect estimates
- Use external evidence as priors
  - Elicitation from experts (Turner at al. JRSSA 2009)
  - Evidence-based from previous meta-analyses (Welton et al. JRSSA 2009)

Meta-epidemiology

(Naylor, *BMJ* 1997; 315: 617-619)

- Identify a large number of meta-analyses
  - "Meta-meta-analysis"
- Record characteristics of individual studies (eg adequate allocation concealment or blinding)
- Compare treatment effects *within* each meta-analysis (e.g. not double blind vs. double blind)
- **Ratio of odds ratios** comparing trials at high risk of bias (H) with those at low risk of bias (L)

Allocation concealment: combined evidence



Estimating bias

- Previous studies have focussed on estimating mean bias
- But …
  - there may be more between trial (within-meta-analysis) heterogeneity in H studies
  - expect mean bias varies between meta-analyses
- Suggests hierarchical model for bias
  - Estimated from meta-epidemiological data
  - Used to inform evidence based priors

Likelihood and treatment effect model

- Binary outcomes, r_{j,k,m^*}
  - Meta-analysis m*, study j, treatment k
  - Likelihood: $r_{j,k,m^*} \sim Bin(p_{j,k,m^*}, n_{j,k,m^*})$
- Logistic regression (bias indicator C):

$$logit(p_{j,k,m^*}) = \begin{cases} \mu_{j,m^*} & \text{Control Arm, k=0} \\ \mu_{j,m^*} + \delta_{j,m^*} + \beta_{j,m^*} C_{j,m^*} & \text{Treatment Arm, k=1} \end{cases}$$

Baseline **LogOR** **Bias**

- Random effects for treatment effects, log(OR)'s:

$$\delta_{j,m^*} \sim N(d_{m^*}, \tau^2_{m^*})$$

The Bias Model

- Study specific bias is exchangeable between studies, within meta-analysis:

$$\beta_{j,m^*} \sim N(b_{m^*}, \kappa^2)$$

- Meta-analysis specific mean bias is assumed exchangeable between meta-analyses:

$$b_{m^*} \sim N(b_0, \varphi^2)$$

- Uncertainty in overall mean bias:

$$b_0 \sim N(B_0, V_0)$$

- Use meta-epidemiological studies to provide inputs:

$$\kappa, \varphi, B_0, V_0$$

Forming Hierarchical Prior from Meta-Epidemiological Data

- Schulz et al (1995): 33 meta-analyses; 250 trials; 79 L and 171 H trials
- Same likelihood & treatment effect model:

$$r_{j,k,m} \sim Bin(p_{j,k,m}, n_{j,k,m})$$

$$logit(p_{j,k,m}) = \begin{cases} \mu_{j,m} & \text{Control Arm, k=0} \\ \mu_{j,m} + \delta_{j,m} + \beta_{j,m} C_{j,m} & \text{Treatment Arm, k=1} \end{cases}$$

Baseline **LogOR** **Bias**

$$\delta_{j,m} \sim N(d_m, \tau_m^2)$$

Forming Hierarchical Prior from Meta-Epidemiological Data

- Same bias model:

$$\beta_{j,m*} \sim N(b_{m*}, \kappa^2)$$

$$b_{m*} \sim N(b_0, \varphi^2)$$

- Priors are given to b_0, κ and φ
- The resulting joint posterior for b_0, κ and φ then provides the inputs for the new meta-analysis, m*
  - Could sample from the joint posterior to form prior
  - Or simply plug-in posterior summaries

Results from Schulz Analysis

Parameter	Mean	SD	Median	95% Credible Interval
Schulz Analysis (Fixed treatment effect; k2 fixed)				
b_0	**-0.46**	**0.108**	-0.47	(-.66, -.25)
κ	0.15	0.106	**0.13**	(0.01, 0.39)
φ	0.11	0.085	**0.10**	(0.00, 0.30)

$$\hat{\kappa} = 0.13 \qquad \hat{\varphi} = 0.10$$

$$\hat{B}_0 = -0.46 \qquad \hat{V}_0 = 0.108^2$$

- Ideally use joint posterior distribution for κ and φ
- We found results robust to simply plugging in posterior medians for κ and φ

Results: Clozapine

Data/Model	Mean (95% Credible Interval)
Adequate Concealment, Face Value	-0.065 (-1.68, 2.84)
Inadequate/Unclear Concealment, Face Value	-0.533 (-1.03, 0.13)
All studies, Face Value	-0.452 (-0.88, 0.08)
All studies, Bias Adjusted	-0.149 (-0.61, 0.43)

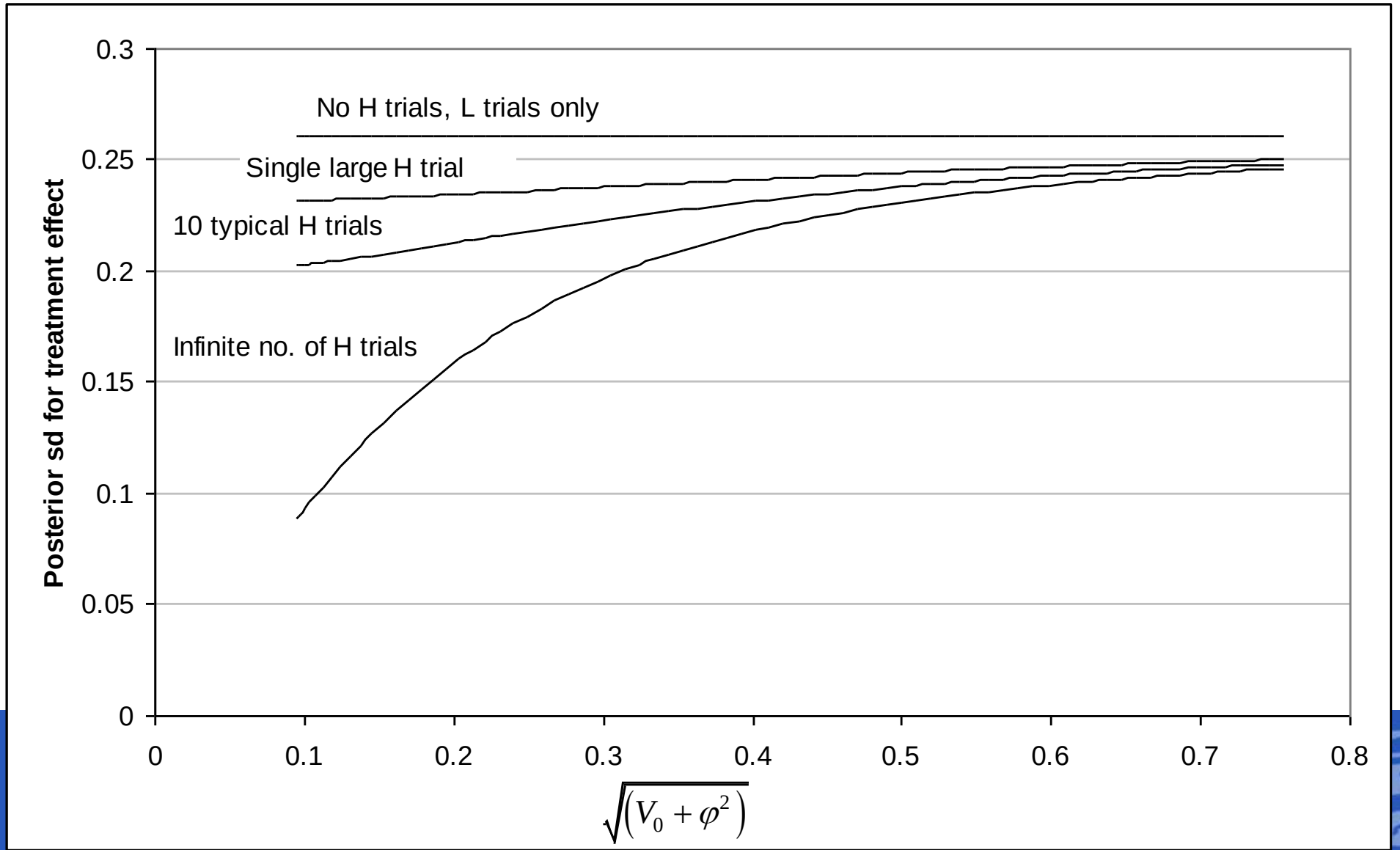
What have we assumed?

- Bias is exchangeable across trials within a meta-analysis (OK?)
- Mean bias is exchangeable across meta-analyses (BIG assumption)
  - More realistic if restrict to meta-analyses in similar clinical areas
  - … but then this reduces size of evidence base available to inform hierarchical prior

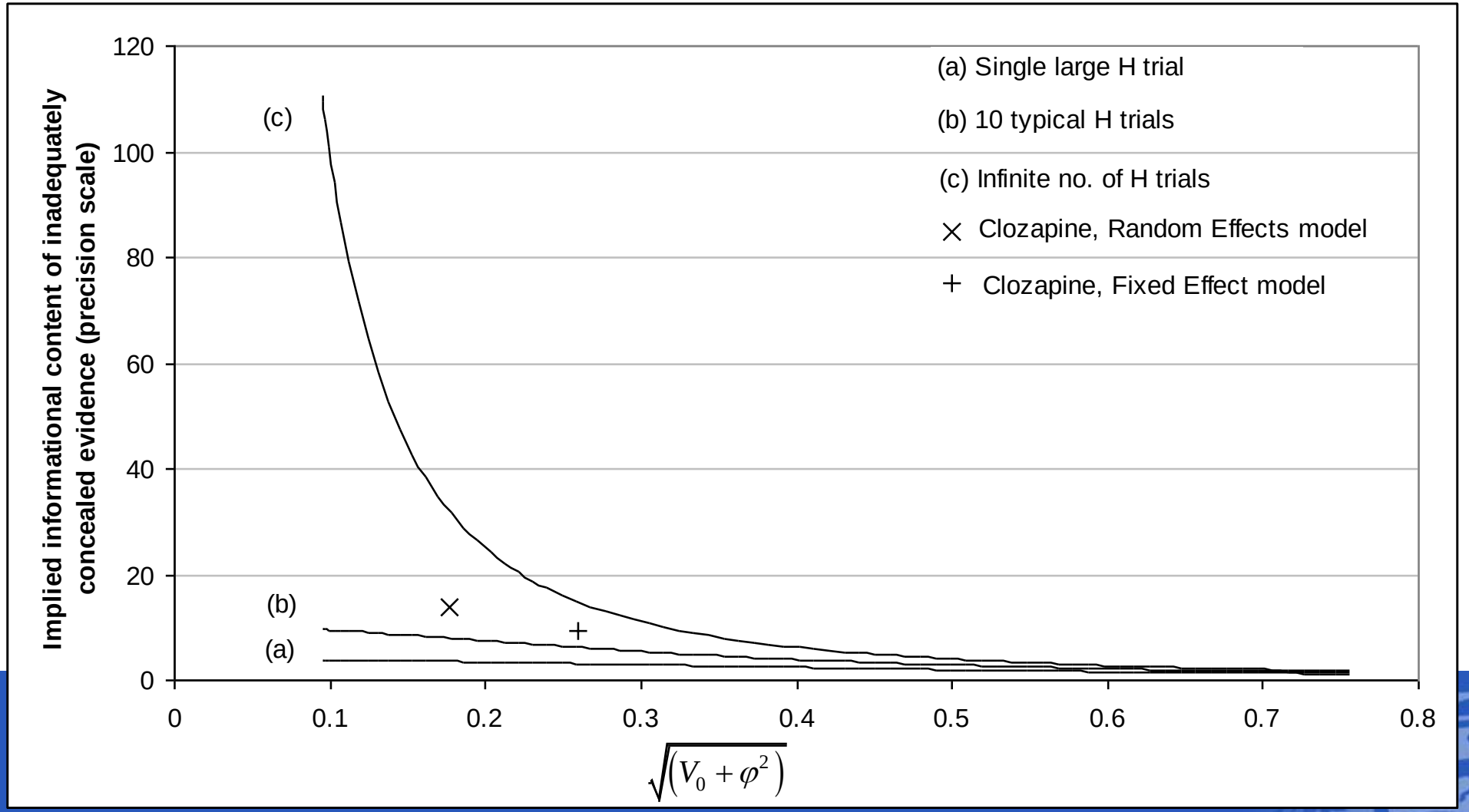
Comments

- The informational content of high risk trials is limited
  - Even large trials downweighted by $V_0 + \kappa + \varphi$
  - Even if infinitely many trials posterior variance depends on $V_0 + \varphi$
- Increasing no. of meta-analyses to form prior:
  - Potentially can reduce V_0, but not κ or φ
- Reducing variety of meta-analyses may reduce φ
  - But only at the expense of increasing V_0 …

Posterior sd of treatment effect



Informational content of high risk studies



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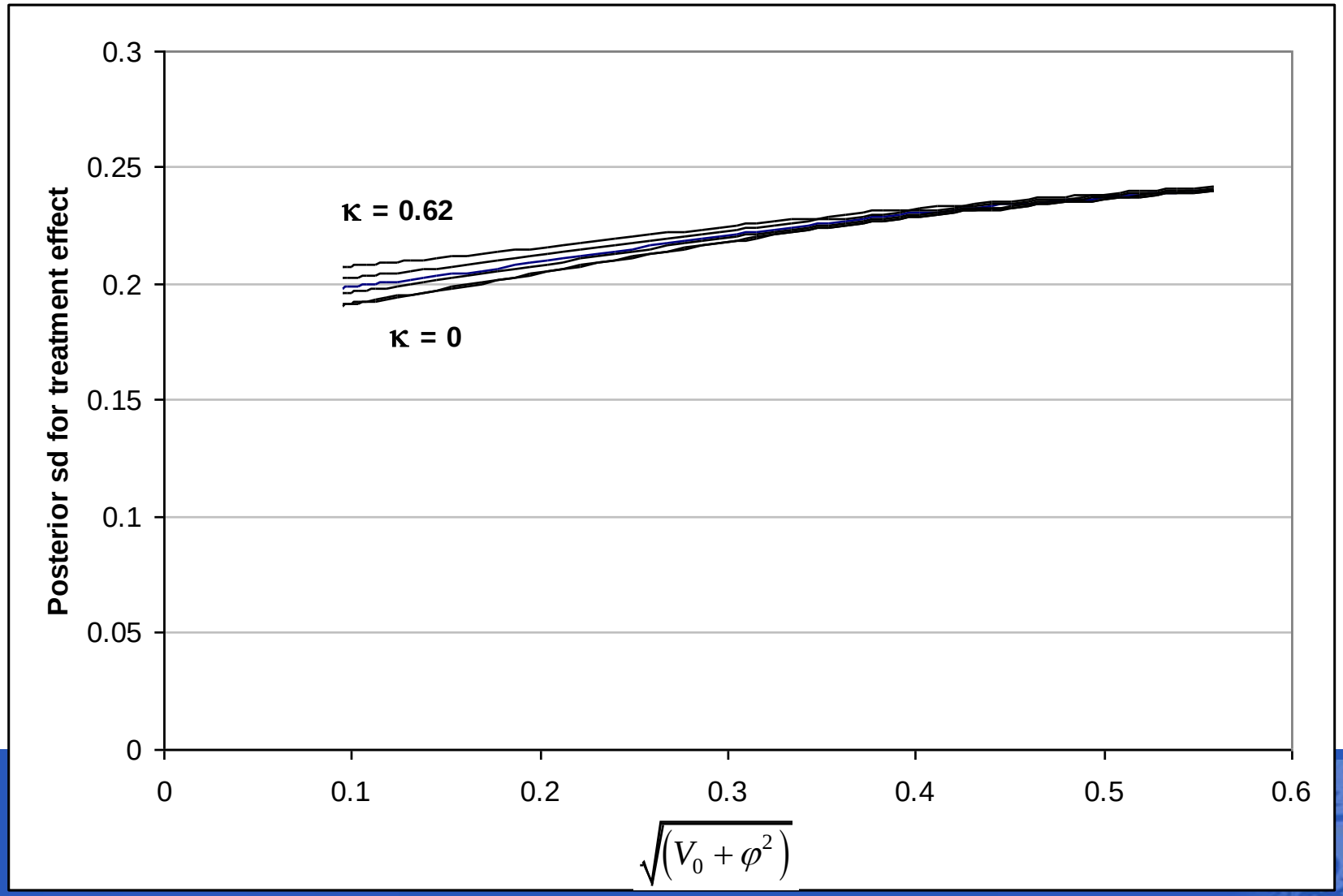

Consequences for Decision Modelling

- Decisions made by decision-makers such as NICE need to be accepted by patient groups, pharmaceutical industry …
- Down-weighting evidence may to lead to appeal
  - if dependent on choice of model
  - if dependent on inclusion criterion for evidence-based prior
- Assessment of model fit & sensitivity analysis to model inputs crucial if decisions based on these models are to have credence in practise

BRANDO (Bias in Randomised and Observational Studies)

- Previous meta-epidemiological studies produced conflicting results
- Combine data from all existing empirical studies into a single database
  - Seven studies contributed data on both trial characteristics and intervention effects
- Final database contains data on 2572 trials
- Restricted to meta-analyses where it was clear in which direction the bias acts

Sensitivity to priors

- Extreme sensitivity to priors for variance parameters
  - Although mean bias estimates robust
- Simulation exercise
  - Using typical study results from BRANDO
- Most priors performed badly
- Inverse-Gamma priors for variance parameters (e.g. IG(.001,.001)) performed best

Summary

- Evidence that poor methodological quality introduces bias
- In pairwise meta-analysis
  - can adjust for and down-weight studies using external evidence
- Sensitivity analyses important
- Assumes exchangeability within and between meta-analyses