Improving Outlier Detection in Subgroup Analysis using Bayesian Predictive Cross-validation Models

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Regulatory Guidance

EMA, 2019, Guideline on Subgroups:

"Evidence is considered to be more ***robust if treatment effects across the trials in the application,*** *as well as* ***in relevant subgroups within one trial … are consistent*** *and substantiate the claim to be made for the experimental treatment."*

EMA, 2001, Points to Consider on Meta-Analysis:

"Plan for evaluation of ***consistency and robustness****. This [meta-analysis] should aim to demonstrate* ***similar effects in alternative analyses of different endpoints, different sub-populations, different subsets of studies*** *…"*

Issues

- **Decision Errors (Precision, Reliability)**
  - Type 1 Error: multiple testing
  - Type 2 Error: insufficient sample size/power
- **Bias (Validity, Accuracy):** eg, selection of (positive) studies/subgroups
- **Separation of sources** of treatment heterogeneity:
  - (unsystematic) measurement error
  - random overall treatment effect
  - true differences between treatment effects caused by differences in study design (including patient population)

Examples

- **Example 1 (2009 – 2024):**
  - Indication: Acute Coronary Syndrom
  - Treatment: Ticagrelor (Brilinta, US; Brilique, EU)
  - Controversial data: PLATO RCT
  - Subgroup of interest: US

- **Example 2 (1984 – 2009):**
  - Indication: Acute Myocardial Infarction
  - Treatment: Intravenuous Magnesium Sulfate (MgSO4)
  - Controversial data: Meta-Analysis of 16 RCTs
  - Study of interest: ISIS-4 trial

Methods

- **Many methods** proposed (see reviews and tutorials on explorative subgroup analysis by Lipkovich, Dmitrienko, D'Agostino, 2017; Lipkovich, Svensson, Ratitch, Dmitrienko, 2024)

- **Bayesian Hierarchical Models** (BHM, "hierarchical models"), eg Ruberg et al. (2023)

- **Bayesian Predictive Cross-Validation Models** (BPCVM, "predictive models"), eg Diaz et al (2011/12c), Igl & Constant (2024)

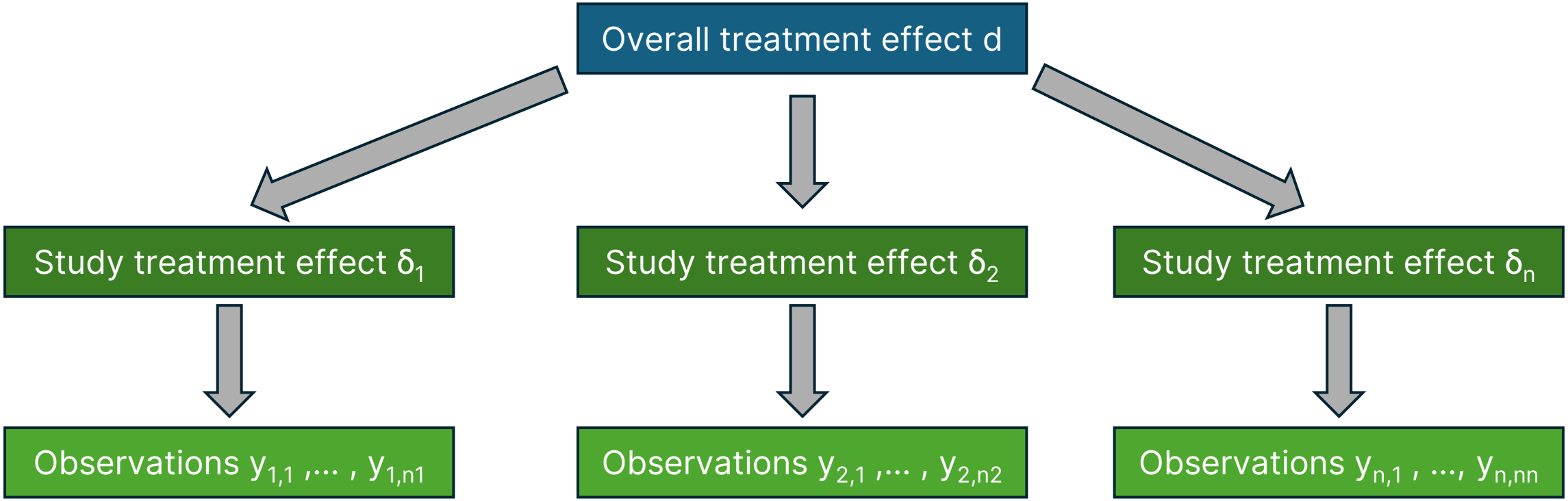
Some Recommendations

- **Bayesian Hierarchical Models promoted for subgroup analysis** (outlier detection) without addressing problematic assumptions (cf, Ruberg et al, 2023; Igl & Constant, 2024; Ruberg, 2024; Nature Reviews Drug Discovery)

- *"The appropriate tool for examination of single trials in a meta-analysis is **cross-validation based on a "leave one out"** approach."* (Dias, Sutton, Welton, & Ades, 2011/2012c, NICE Decision Support Unit)

- *"Plea for routinely presenting **prediction intervals** in meta-analysis."* (IntHout, Ioannidis, Rovers, & Goeman, 2016, BMJ Open).

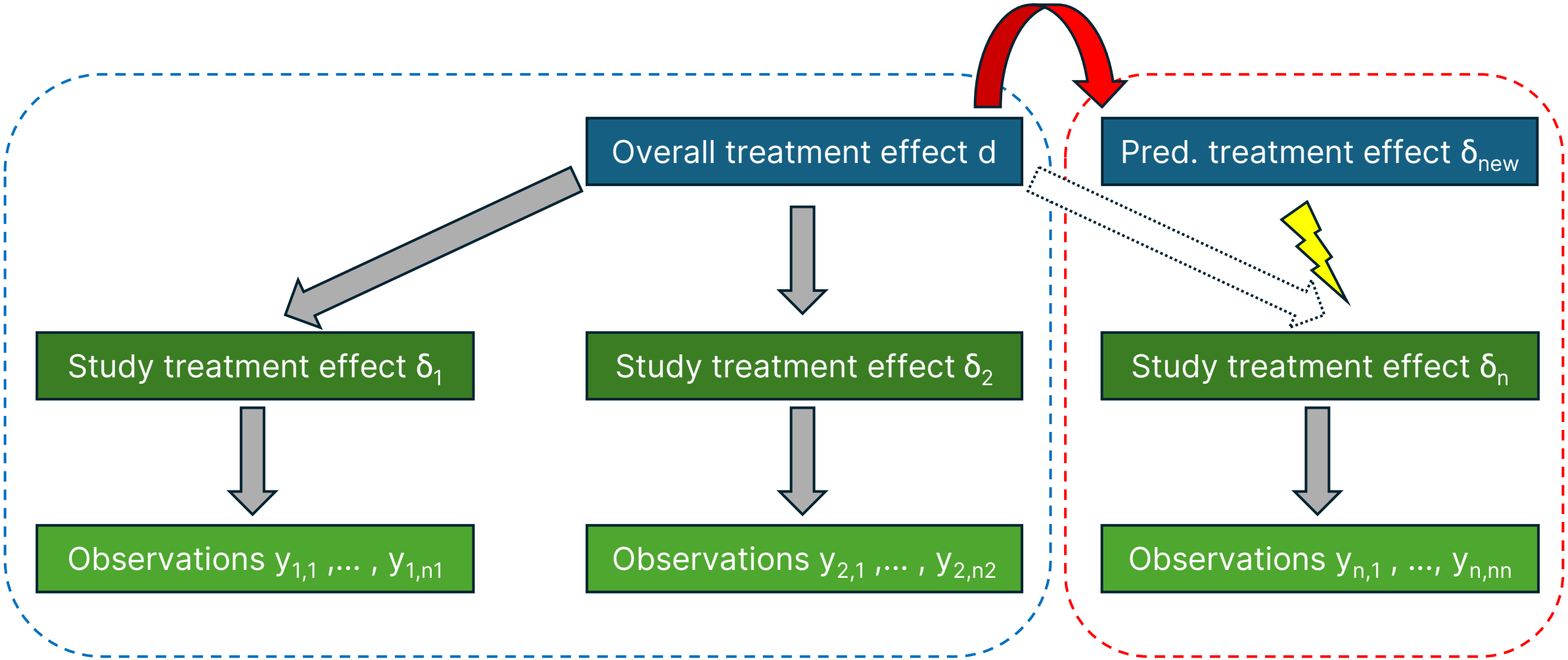
Bayesian Hierarchical Model



Bayesian Hierarchical Model

- **Basic Method:**
  - assumes overall treatment effect (including study of interest)
  - "borrows strength" between subgroups & "shrinks" estimates
  - estimates overall mean and its credible interval
- **Pros:**
  - widely used
  - available code
- **Cons:**
  - Assumption not appropriate for subgroup outlier detection
  - Overall mean and its credible interval less relevant
  - Crude interpretation: Overlap of CrI of treatment effect of trial & overall treatment effect

Bayesian Predictive Cross-Validation Model



Bayesian Predictive Cross-Validation Model

- **Basic Method:**
  - does not assume an overall treatment effect (incl. study of interest)
  - predicts the treatment effect in future subgroup like the study of interest based on all other subgroups.
- **Pros:**
  - (plausibly) assumes overall treatment effect only in other subgroups
  - Predictive mean & interval for future study like study of interest
- **Cons:**
  - less used
  - other assumptions still required, eg, exchangeability, representativeness

Example: Pairwise Meta-Analysis of treatment of Acute Myocardial Infarction

- **Disease**: Acute myocardial infarction
- **Treatments**: Magnesium (IV) vs Placebo
- **Studies**: 16 studies , incl. ISIS-4 "mega-trial"
- **Design**: Pairwise meta-analysis of randomized controlled trials

- **Controversially discussed treatment and indication** with randomized controlled trials and meta-analysis between 1984 and 2009, see reviews by Egger, Davey-Smith (1995), Higgins & Spiegelhalter (2002), Li et al. (2007/2009)

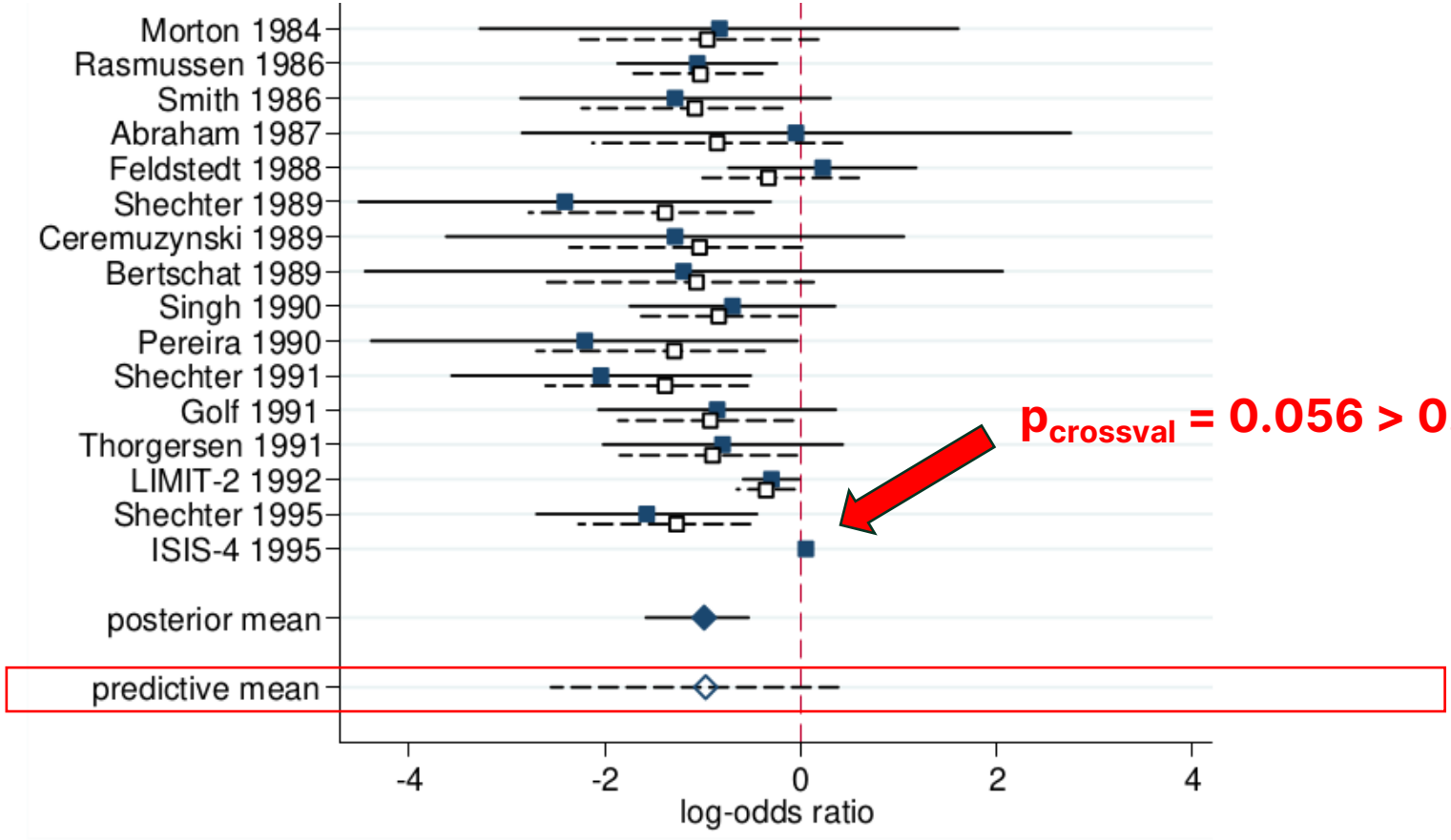
Meta-Analysis of 16 trials: Magnesium (IV) vs Placebo

Table 1 Number of deaths out of the total number of patients for 16 trials of intravenous magnesium against placebo, for patients with acute myocardial infarction.[27]

			Placebo		Magnesium	
Trial ID	Trial Name	Year	Deaths	Total	Deaths	Total
1	Morton	1984	2	36	1	40
2	Rasmussen	1986	23	135	9	135
3	Smith	1986	7	200	2	200
4	Abraham	1987	1	46	1	48
5	Feldstedt	1988	8	148	10	150
6	Shechter	1989	9	56	1	59
7	Ceremuzynski	1989	3	23	1	25
8	Bertschat	1989	1	21	0	22
9	Singh	1990	11	75	6	76
10	Pereira	1990	7	27	1	27
11	Shechter1	1991	12	80	2	89
12	Golf	1991	13	33	5	23
13	Thorgersen	1991	8	122	4	130
14	LIMIT-2	1992	118	1157	90	1159
15	Shechter2	1995	17	108	4	107
16	ISIS-4	1995	2103	29039	2216	29011

Diaz et al., 2011, p. 19

BPCVM with 15 Trials & ISIS-4



$p_{crossval} = 0.056 > 0.025$

Figure 3 Magnesium Example: Crude log-odds ratios with 95% CI (filled squares, solid lines); posterior mean with 95% CrI of the trial-specific log-odds ratios, "shrunken" estimates, (open squares, dashed lines); posterior mean with 95% CrI of the posterior (filled diamond, solid line) and predictive distribution (open diamond, dashed line) of the pooled treatment effect, obtained from a RE model excluding the ISIS-4 trial.

Conclusion

- **Methods:**
  - BPCVM conceptually superior to BHM
  - Technical barrier: WinBUGS system files (.odc) no longer available & WinBUGS no longer available

- **Example: Magnesium (IV) vs Placebo**
  Treatment effect as extreme as ISIS-4 is unlikely, but still possible, ie no outlier (cf, $p_{crossval} = 0.056$ > all two-sided decision thresholds)

- **Limitation:** Application of hierarchical models limited to scenarios were treatment effects are estimated in multiple subgroups, e.g. meta-analysis, less useful for analysis of few subgroups in a single clinical trial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  Note: see Appendix 3 for BUGS code for meta-regression approach adjusted for sample size
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Appendix

Bayesian Hierarchical (Logistic) Model

Likelihood Distribution

$$r_{ik} \sim \text{Binomial}(p_{ik}, n_{ik})$$

- r = #deaths, n = total #patients
- k = treatment arm, i = number of trial

Linear Predictor

$$\text{logit}(p_{ik}) = \mu_i + \delta_{i,1k} I_{\{k \neq 1\}}$$

- mu = treatment effect in placebo group
- delta = relative treatment in experimental group

Common Distribution

$$\delta_{i,12} \sim N(d, \sigma^2)$$

- d = overall treatment effect in experimental group

Prior Distributions

$$d \sim N(0, 100^2)$$
$$\mu_i \sim N(0, 100^2)$$
$$\sigma \sim U(0,5)$$

- Vague prior for overall treatment effect d
- Vague prior for treatment effect in control group mu
- Vague prior for between-study variance sigma^2

Dias et al. 2011/2012c

Sampling from Predictive Distribution

Predictive treatment effect in experimental group

$$\delta_{new} \sim N(d, \sigma^2)$$

- delta_new = treatment effect of **future trial of same size as study of interest**

Predictive treatment effect in placebo group

$$p_{base} \sim \text{Beta}(a, b)$$

- a = number of deaths
- b = number of non-deaths

Predictive absolute treatment effect in experimental group

$$\text{logit}(p_{new}) = \text{logit}(p_{base}) + \delta_{new}$$

- p_new = predictive probability of mortality in experimental treatment arm in a future study

Predictive number of deaths in experimental arm in future trial like study of interest

$$r_{new} \sim \text{Binomial}\,(p_{new}, n_{new})$$

- p_new = predicted number of deaths in experimental group in study of interest
- n_new = future (=observed) number of patients in experimental group in study of interest

Evaluation of Outlier

Probability of observing a result as extreme result as observed in study of interest, ie $\mathbf{p_{crossval}}$

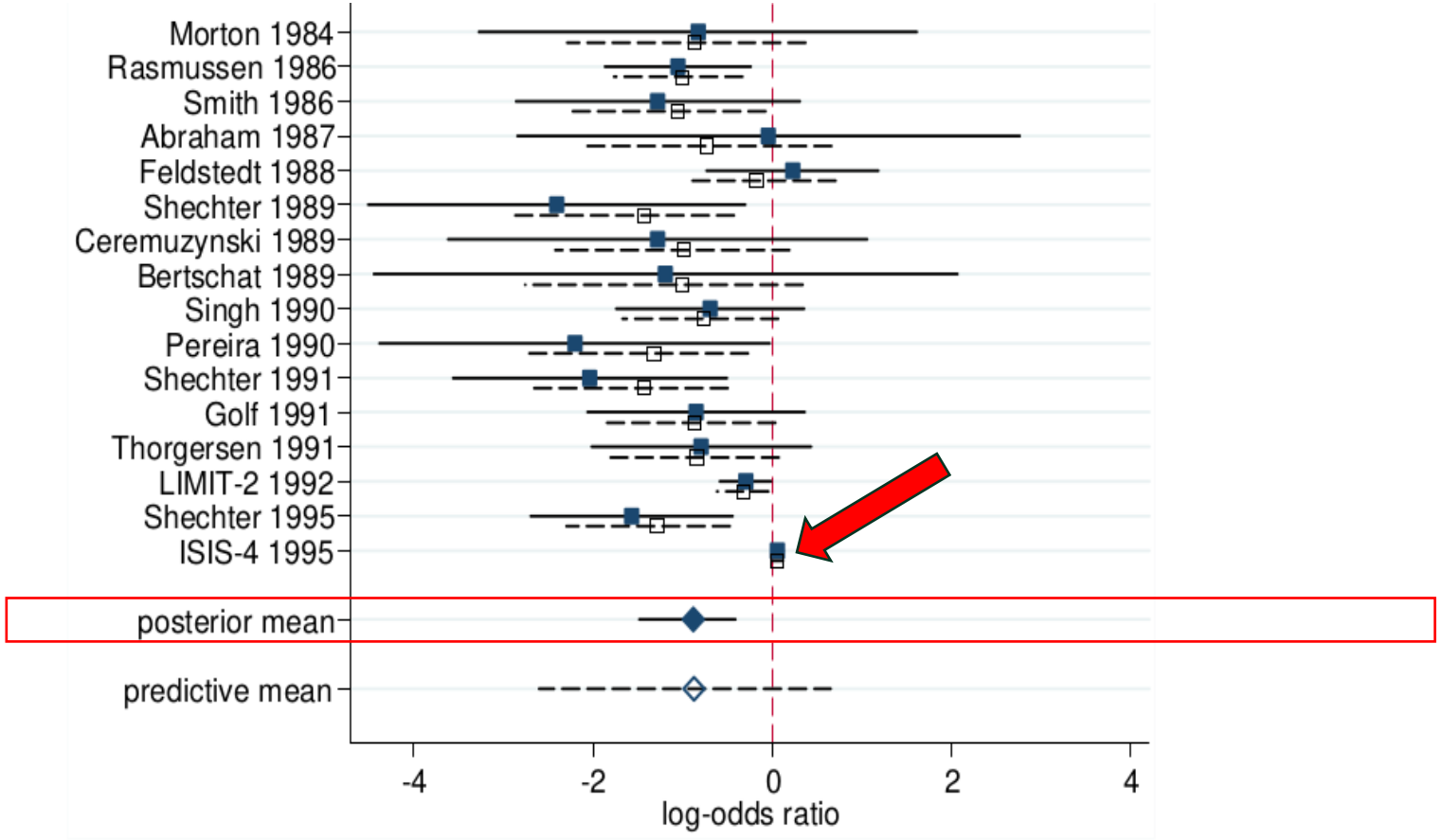
$$\Pr(r_{new} \geq r_{observed})$$

- r_{new}: Number of predicted deaths in experimental arm in observed study of interest
- $r_{observed}$: Number of observed deaths in experimental arm in observed study of interest

Evaluation Threshold:

- **Use conventional, nominal threshold**: $p_{crossval} \leq 0.05/2 = 0.025$
- **Use Bonferroni Method**: $p_{crossval} \leq 0.05/(2*n)$

BHM with all Trials (incl. ISIS-4)



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