

Meta-Analysis to Meta-Cognition

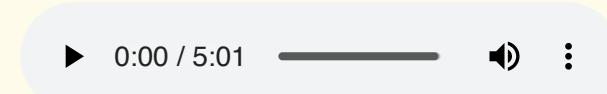
Following the Bayesian Highway

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Learning Objectives



Baba Brinkman - Good Bayesian

1. Understanding Bayesian Meta-analysis
 2. Understanding Meta-cognition
 3. Application to clinical examples
 - Colchicine post-ACS
 - Extended thrombolysis in acute ischemic stroke
 - Dexmedetomidine and post-operative delirium

Meta-Analysis (MA)

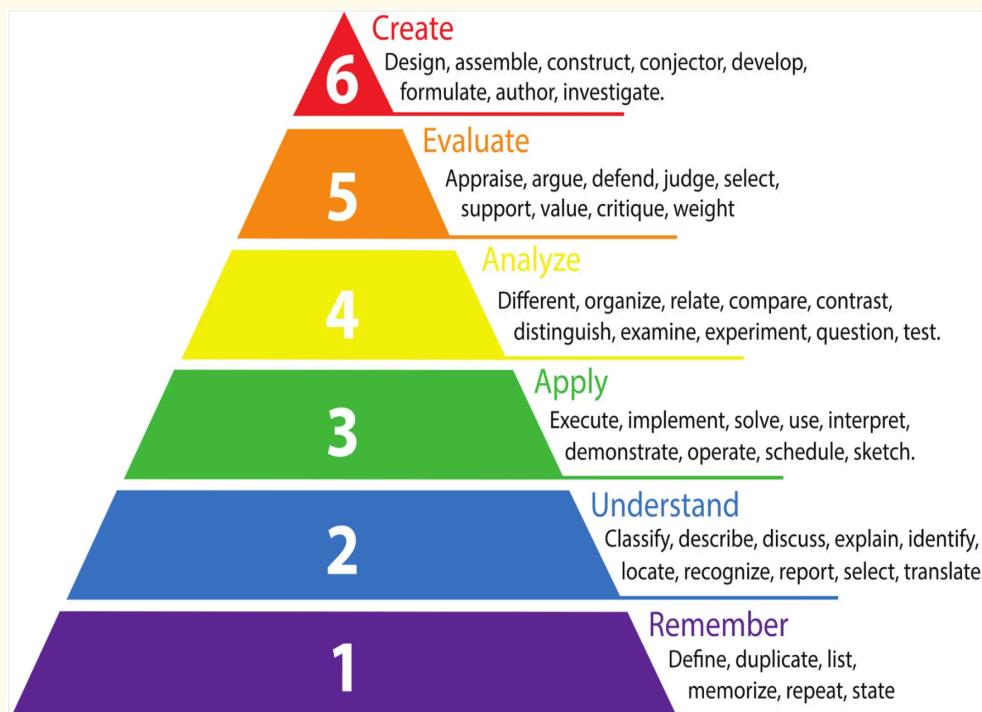
- Combines studies -> estimate common effect, θ & between-study variation, τ
- Very common (> 30,000 publications with MA in title so far in 2025)
- Frequentist statistical methods have limitations / assumptions
 - θ is a fixed (but unknown) constant, (only data are random)
 - Thus 95% CI is a property of the data procedure, not of θ
 - IOW, if study repeated many times, 95% of intervals would cover θ
 - Ignores prior ancillary θ knowledge
 - When combined with NHST -> dichotomous decisions ($p < 0.05$)
 - Probability statements like - "How likely is the effect clinically meaningful?" are impossible
- Bayesian MA overcomes these limitations at the price of a prior & more complex computations

Meta-Cognition

- **Meta-cognition = thinking about thinking**
- Traditional inference asks: “Is there an effect?”
- Example: RR = 0.82 with 95% CrI [0.66, 1.03], p = 0.11†
 - Typical thinking $p > 0.05$ - “negative” study
- Meta-cognition extends thinking with purposeful reflection and situational awareness:
 - Recognize $p > 0.05$ doesn’t imply clinical irrelevance
 - “Is the effect large enough to matter?”
 - IOW, P (benefit) $>$ (my) minimally clinically important difference (MCID) threshold?
 - Facilitate decision to act, wait, or gather more evidence

† POPular (AGE), *Lancet* 2020

Taxonomy of Learning



Overview Of Bloom's Taxonomy

- Meta-cognition - Top 2 tiers - **Appraisal with judgment and creation of new ideas**
- Enhances clinicians' ability to:
 - Question assumptions
 - Integrate uncertainty
 - Move beyond binary assessments (significant vs not)
 - Tailor decisions to context

Meta-Cognition and Bayesian Meta-Analysis

Meta-cognition: the destination — clinical wisdom beyond the numbers, deeper understanding -> better communication and wiser decisions

Bayesian meta-analysis: the statistical engine (the GPS) - navigating uncertainty with purpose - to get to this destination

Why Bayesian?

Better decisions since

- Principled, transparent accounting of assumptions & uncertainty
- Combines data & prior information
- Can model more complex data generating processes
- Informed decisions making based on probability statements

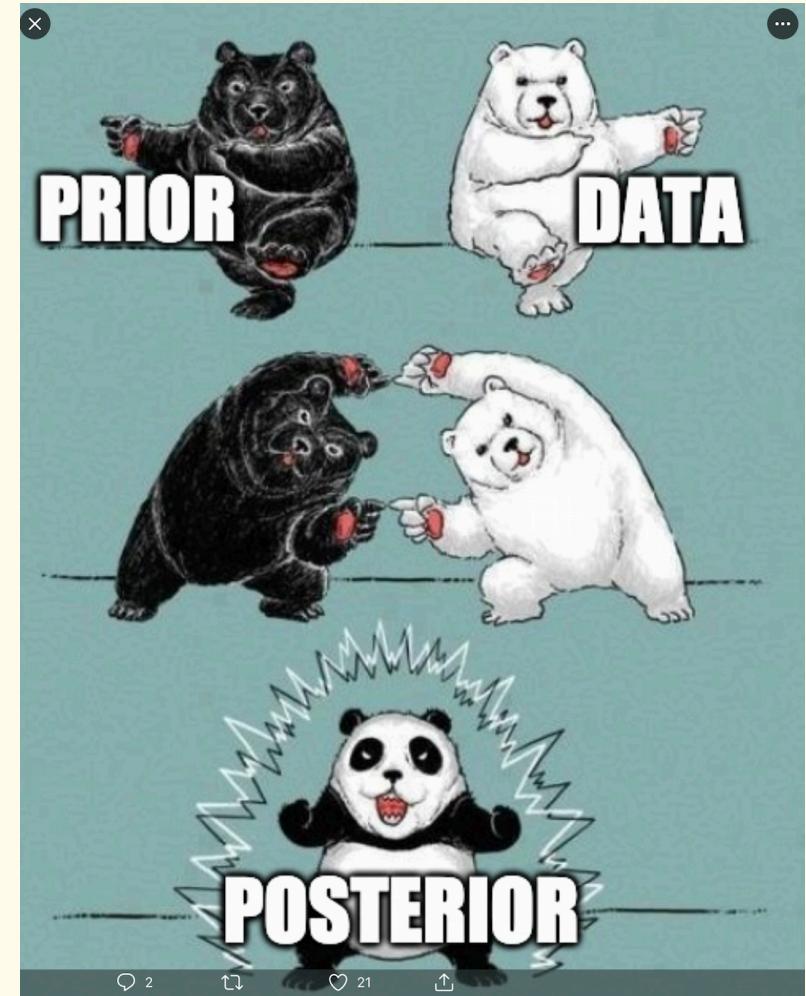
Caveats

- Results can be prior-sensitive when data are thin — need robustness checks
- Computation heavy (but modern techniques make this less problematic)

Bayesian Key Concept

Posterior \propto Likelihood \times Prior

- Prior: What you believe **before** the new evidence
- Likelihood: What the new data say
- Posterior: What you believe **after** combining both



Prior Knowledge: A Strength or Limitation (Bias)?

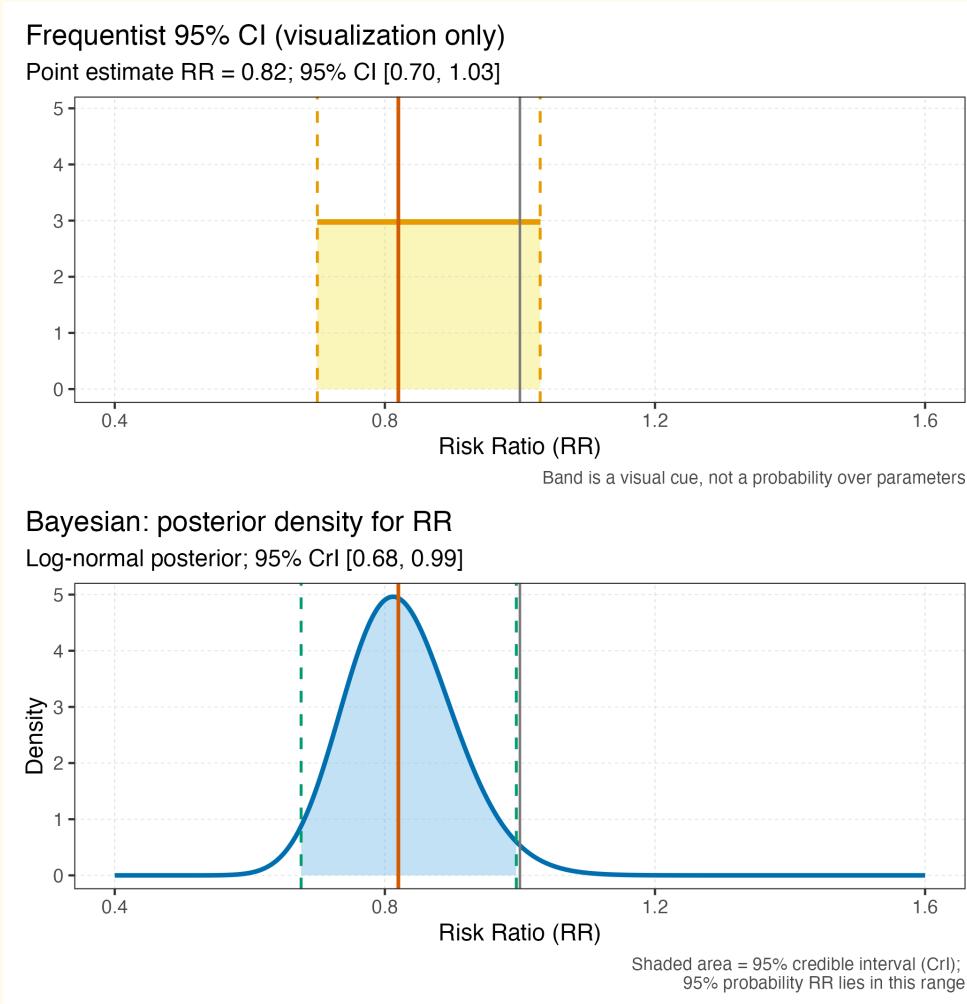
- Strength: allows probabilistic inference, enables cumulative learning
- Criticism: “Subjective”
- Response:
 - All models involve assumptions
 - Bayesianism just makes assumptions (priors) explicit
 - Assumptions can be tested via sensitivity analyses

Frequentist vs Bayesian Meta-analysis

Feature	Frequentist	Bayesian
Parameter interpretation	Fixed (unknown constant)	Random variable with probability
Interpretations	Long-run frequency: 95% of intervals cover true effect	95% chance the true effect lies within the interval
Probability Statements	No, impossible for fixed parameters	Yes, answers “how likely” questions
Prior inclusion	No	Yes
Tailored Inference	No	Yes (e.g., $P(RR < 0.9)$, threshold-specific)

These differences matter

Consider previous RR 0.82 95% CI 0.66, 1.03, $p = 0.11$, what does this mean?



Frequentist CI -

- 95% of CIs cover the fixed true RR if studies repeated (long run frequency)
- This single CI either covers or not
- No probabilities -> all values inside 95% CI equally compatible with set of values **not rejected** by $\alpha = 0.05$ test with these data.

Bayesian Crl -

- 95% ranked (centre > edges) RR probability RR (given prior + data)
- Compute ($P(RR \leq MCID)$) for decisions

MA Predictive Thinking: The Next Study

Pooled average = typical **average** effect across included studies

Predictive interval = likely interval for **next-study** range (includes between-study heterogeneity, τ^2)

Should be routinely reported (1,2)

Frequentist Interpretation:

(95%) probability that the next study's outcome falls within this interval, *if* the estimated fixed parameters are correct

Bayesian Interpretation:

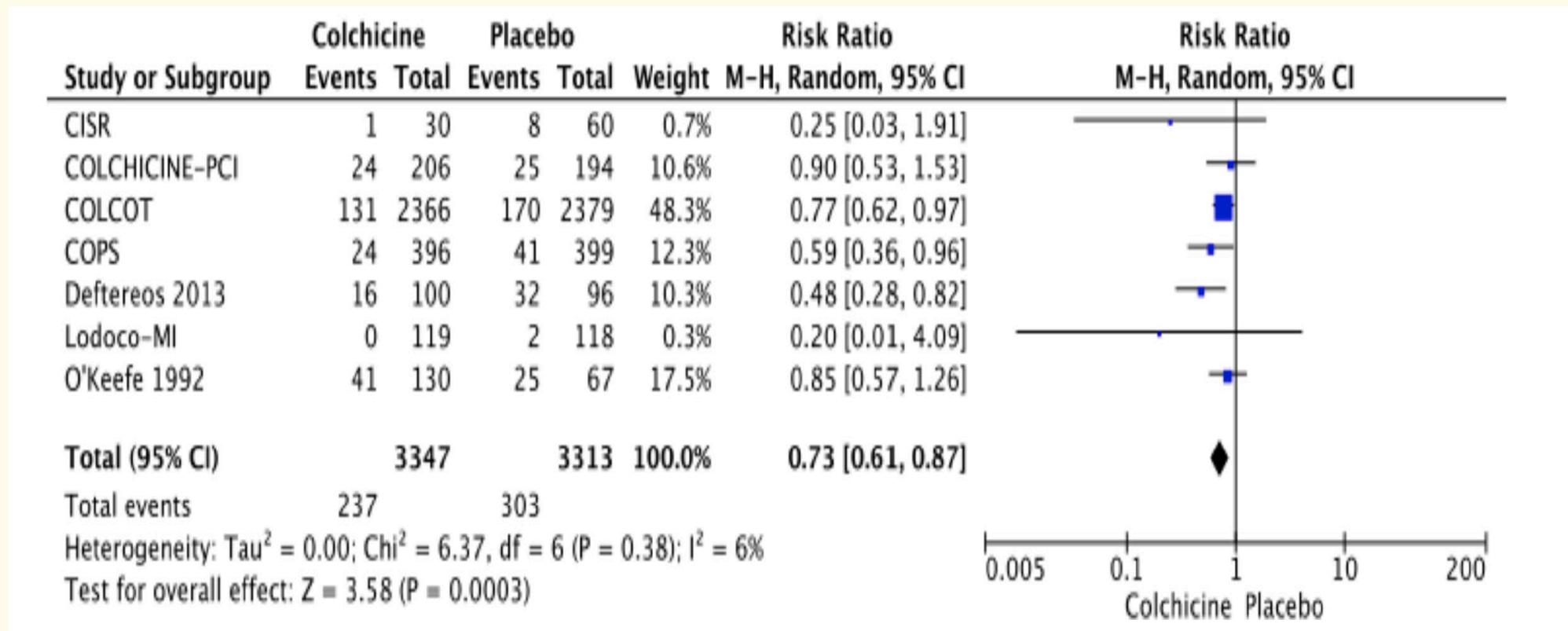
(95%) probability that the next study's outcome lies in this range, *given our data and prior*

Reference:

1. Riley RD, Higgins JPT, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.
2. IntHout, J., J. P. Ioannidis, M. M. Rovers, and J. J. Goeman. "Plea for Routinely Presenting Prediction Intervals in Meta-Analysis." *BMJ Open* 6, no. 7 (Jul 12 2016)

Colchicine in ACS

Colchicine's role in post-ACS care - a 2022 frequentist meta-analysis



Conclusion: Colchicine “significantly” reduced the risk of MACE in CAD patients

Q: Is the colchicine / ACS story over? Is further research ethically justified?

Not so fast...

- No prediction interval (PI) for next study provided
- Bayesian PI accounts for parameter & between study variability -> CI 0.35 - 1.29
- Provides more realistic heterogeneity estimate and justifies future studies

CLEAR Trial: Colchicine in ACS

NEJM 2025

- 7062 patients randomized at 104 centers in 14 countries
- Primary outcome: CV death, MI, stroke, or urgent revascularization
- Results: RR = 0.99 (95% CI 0.85–1.16, p=0.93)

Conclusion: “Treatment with colchicine, when started soon after MI and continued for a median of 3 years, did not reduce the incidence of the composite primary outcome.”

Remember: Absence of evidence is not evidence of absence!

Colchicine Meta-analyses in 2025

CLEAR investigators, definitely not Bayesians, but didn't believe that the story was over

10 meta-analyses have been published since CLEAR, 9 concluding colchicine is beneficial
 EHJ - IF 36.4 - "...colchicine reduced the composite outcome by 12%"

Colchicine for secondary prevention of vascular events: a meta-analysis of trials

Marc-André d'Entremont^{1,2,3,†}, Michiel H.F. Poorthuis⁴, Aernoud T.L. Fiolet^{5,6},
 Pierre Amarenco^{1,7}, Kevin Emery Boczar⁸, Ian Buysschaert⁹, Noel C. Chan¹⁰,
 Jan H. Cornel^{6,11,12}, Jalina Jannink¹³, Shirley Jansen¹⁴, Sasko Kedev¹⁵,
 Anthony C. Keech^{16,17}, Jamie Layland¹⁸, Nathan Mewton¹⁹, Gilles Montalescot²⁰,
 Domingo A. Pascual-Figal^{21,22}, Alfredo E. Rodriguez²³, Binita Shah^{24,25},
 Martin Teraa¹⁶, Aimee van Zelm²⁶, Yongjun Wang²⁷, Arend Mosterd^{1,6,13},
 Peter Kelly^{28,29}, John Eikelboom^{1,30}, and Sanjit S. Jolly^{1,2,*}; on behalf of the
 Colchicine Cardiovascular Trialists Collaboration

- CLEAR authors, published 3 months after CLEAR trial
- **Apparently frequentist statistics allows investigators to declare both that the treatment does not, and simultaneously does work, all with same available evidence!!!**

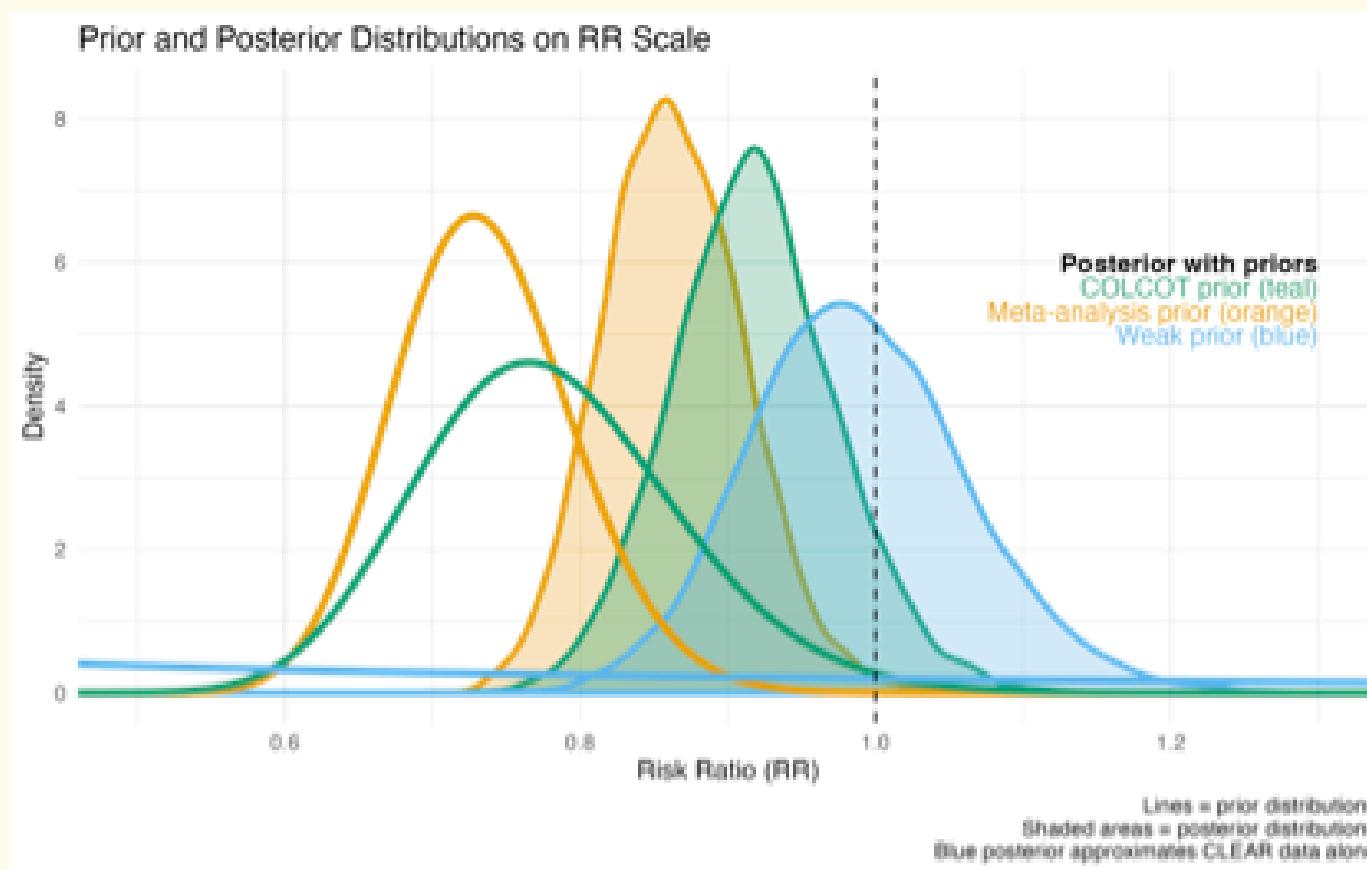
Anatomy of a Bayesian Meta-Analysis

1. Standard difficulties - searching relevant studies & critical quality assessment (GIGO)
2. Additional difficulty - define the priors
3. Specify likelihood model (random or fixed effects, bias corrections)
4. Combine likelihood & prior -> posterior (via numerical methods, MCMC)
5. Interpret full posterior distribution

```
1 # brms example for Bayesian meta-analysis
2 library(brms)
3 brm(r | trials(n) ~ 0 + treatment + (1 | Study),
4      family = binomial(),
5      data = nma_data,
6      prior = prior(normal(0, 2), class = b),
7      chains = 4, cores = 4)
```

Colchicine Prior Beliefs: Three Perspectives

- Use a community of prior beliefs to assess conclusions' robustness
- **Vague prior:** $N(0, 2)$ → allows CLEAR data to dominate
- **Focused prior:** Based on major pre-CLEAR trial – COLCOT as acknowledged by CLEAR
- **Comprehensive prior:** Based on 2022 meta-analysis (pre-CLEAR)



Following the Bayesian Highway

- Posterior mean RR:
- Vague: 0.99 (95% CrI 0.85–1.14)
 $P(RR < 1 = 58\%)$
- Focused (COLCOT): 0.92 (0.81–1.03)
 $P(RR < 1 = 92\%)$
- Comprehensive (2022 MA): 0.86 (0.78–0.96)
 $P(RR < 1 = 100\%)$

Probabilities for Clinical Thresholds

Prior	P(RR < 0.8)	P(RR < 0.85)	P(RR < 0.9)	P(RR < 1.0)	P(RR < 1.15)
Weak ($N(0,2)$)	0%	3%	11%	58%	98%
COLCOT-based	1%	11%	38%	92%	100%
Meta-analysis	9%	40%	78%	100%	100%

1. CLEAR alone (weak prior) -> 58% $P(RR < 1.0)$ vs. NEJM ($p = 0.93$) no effect
2. COLCOT & meta-analysis priors -> high $P(\text{some benefit}) = 92\text{-}100\%$ but very modest $P(\text{clinical significance i.e. } RR < 0.85) = 11\text{-}40\%$
3. Predictive interval CI 0.26 - 1.70 —> residual uncertainty
4. More informative than “12% reduction” with no uncertainty measure
5. Informs decision making
 - i. If your MCID is $\geq 15\%$ RRR, wait for more evidence
 - ii. If your MCID is $< 15\%$ RRR -> honest discussion of uncertainty + (maybe) target high-risk

Extended thrombolysis in acute ischemic stroke

- Guidelines recommend thrombolysis within a 4.5-hour time window from sx onset
- Six RCTs with guided advanced neuroimaging of extended thrombolysis (> 4.5h since sx onset)
- Seven published MAs!!!! all concluded benefit

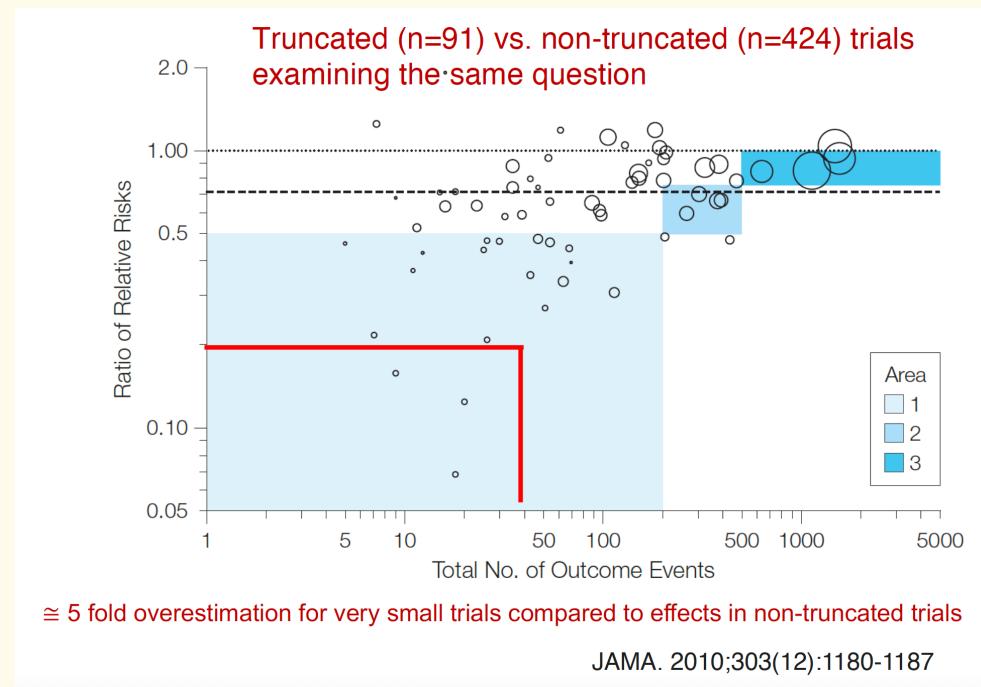
The RCTs

Remember: GIGO - garbage in, garbage out

Cochrane ROB 2.0 - some concerns in all trials

Trial	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Comments
WAKE-UP (2018) ⁶	●	●	●	●	●	●	<ul style="list-style-type: none"> Premature termination. Seven investigators with FCOI
ECASS-4 (2019) ⁹	●	●	●	●	●	●	<ul style="list-style-type: none"> Premature termination. Trial funded by drug manufacturer
EXTEND (2019) ⁷	●	●	●	●	●	●	<ul style="list-style-type: none"> Premature termination. Seven investigators with FCOI
THAWS (2020) ⁸	●	●	●	●	●	●	<ul style="list-style-type: none"> Open label treatment. Premature termination. Seven investigators with FCOI
TRACE-III	●	●	●	●	●	●	<ul style="list-style-type: none"> 9 baseline characteristics favored the teneceplase Observed allocation imbalance Open label treatment. Trial partially sponsored by the drug manufacturer.

Bias with early termination for benefit - overestimates effect size



The outcome measure

[Modified Rankin score - dichotomized at 0-1 vs 2-6

Score	
0	No symptoms at all.
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6	Dead

Typical meta-analysis

Supportive of benefit

EPUB stroke
Volume 56, Issue 3, March 2025; Pages 580-590
<https://doi.org/10.1161/STROKEAHA.124.048536>

CLINICAL AND POPULATION SCIENCES

Thrombolysis for Ischemic Stroke Beyond the 4.5-Hour Window: A Meta-Analysis of Randomized Clinical Trials

CONCLUSIONS: IVT for ischemic stroke beyond 4.5 hours, without MT, led to increased odds of excellent and good functional outcomes compared with standard medical care, despite higher odds of sICH, and a nonsignificant numerical increase in mortality.



Limitations

- Uses dichotomized mRS - loses information
- Inability to formulate meaningful probability statements
- e.g. "Nonsignificant increase in mortality" is not the same as "No increase in mortality"

utility-weighted mRS ordinal outcome

Ordinal regression with patient orientated utility weighting (UW) is preferred outcome
Avoids loss of information from dichotomization

Ensures quantitative outcome a valid reflection of patient-centered benefits / values

Utility weights <- c(1.00, 0.91, 0.76, 0.65, 0.33, 0.00, 0.00)

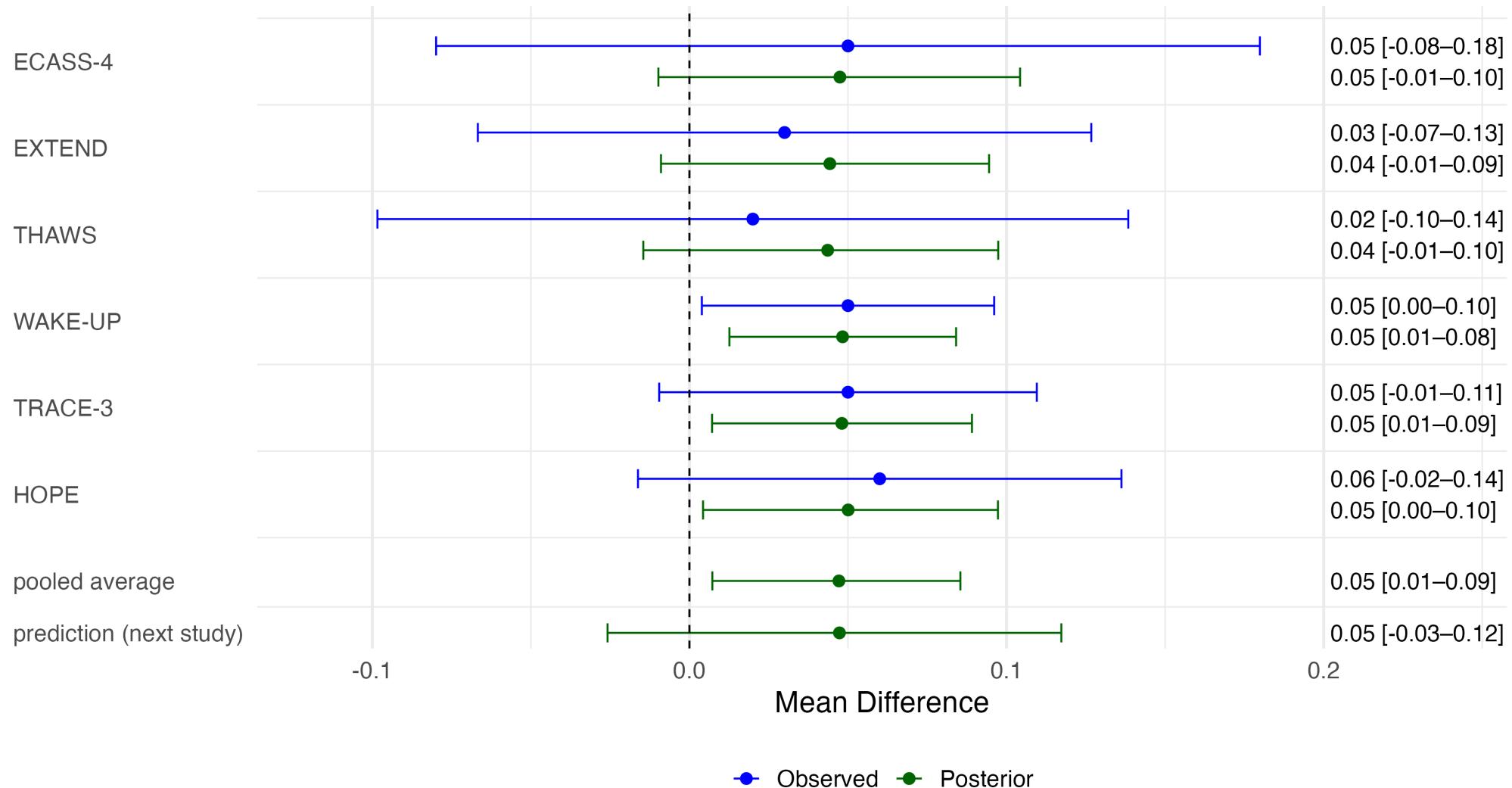
MCID threshold for the uw-mRS scale is $\geq .09$

Reference:

1. Chaisinanunkul N, Adeoye O, Lewis RJ, et al. Adopting a patient-centered approach to primary outcome analysis of acute stroke trials using a utility-weighted modified Rankin scale. *Stroke* 2015;46(8):2238-2243.
2. Zhou J, Wei Q, Hu H, et al. A systematic review and meta-analysis of health utility values among patients with ischemic stroke. *Frontiers in Neurology* 2023;14:1219679.
3. Chen P, Lin K-C, Liing R-J, Wu C-Y, Chen C-L, Chang K-C. Validity, responsiveness, and minimal clinically important difference of EQ-5D-5L in stroke patients undergoing rehabilitation. *Quality of life research* 2016;25:1585-1596.
4. Kim S-K, Kim S-H, Jo M-W, Lee S-i. Estimation of minimally important differences in the EQ-5D and SF-6D indices and their utility in stroke. *Health and Quality of Life Outcomes* 2015;13:1-6

Bayesian MA of UW-mRS

Forest Plot: Bayesian Meta-Analysis
Utility-weighted modified Rankin Scale score



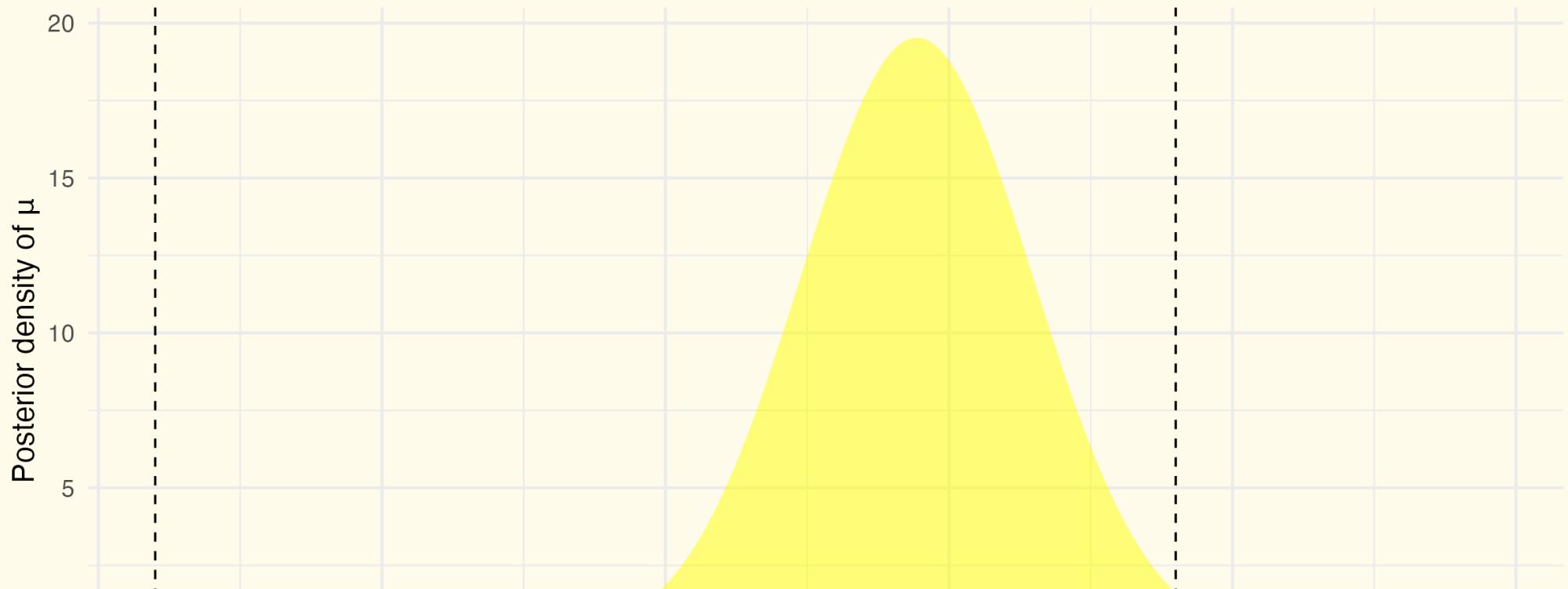
Bayesian MA of UW-mRS

uw-mRS Mean Difference (Thrombolysis – Control)

Yellow (ROPE): $-0.09 < \mu < 0.09$;

Green (thrombolysis clinically superior): $\mu \geq 0.09$;

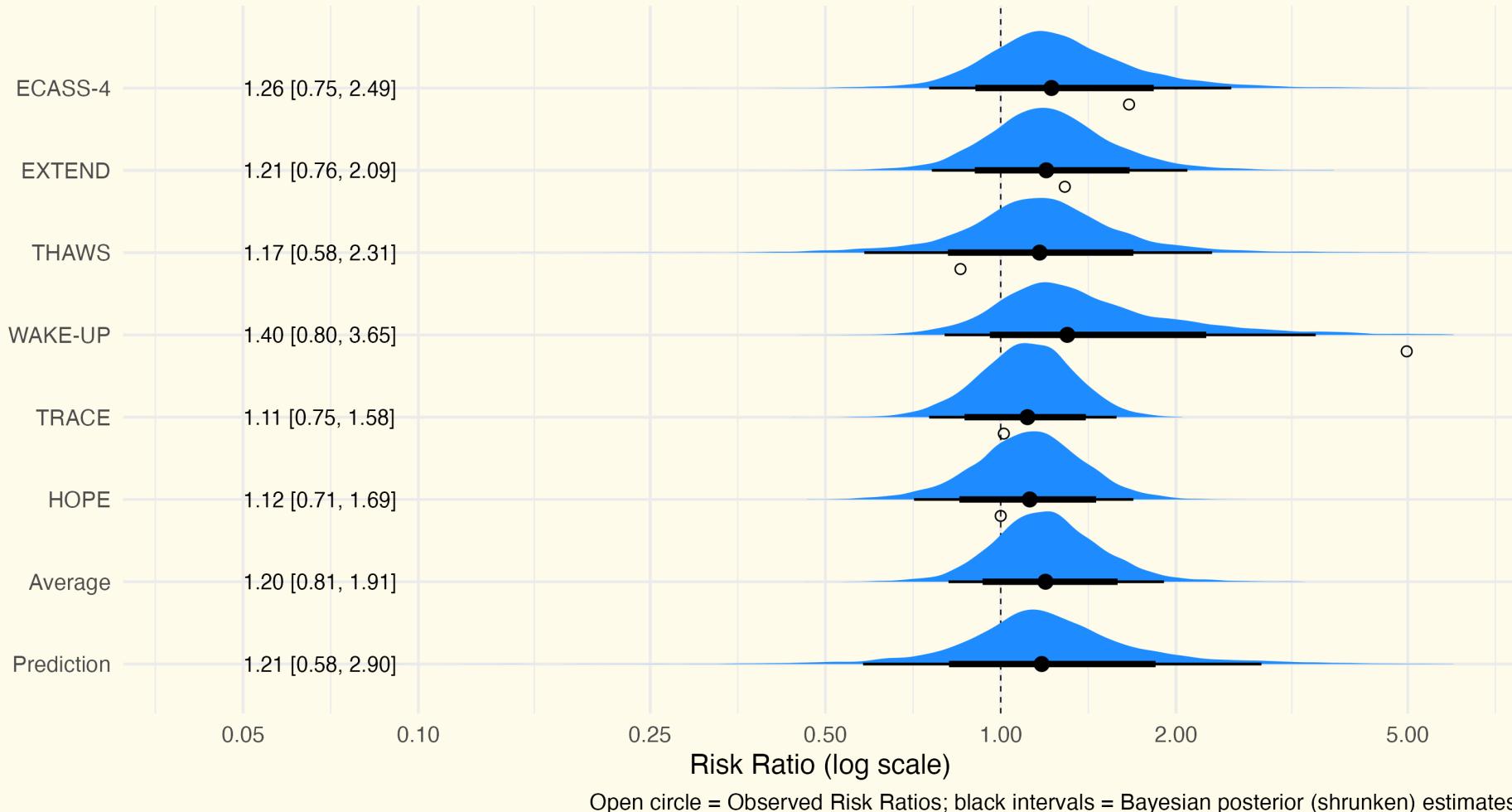
Red (thrombolysis clinically inferior): $\mu \leq -0.09$



Bayesian mortality (relative risk)

Bayesian Estimates of Total Mortality

Risk Ratios with 80% and 95% Credible Intervals (thin and thick lines)

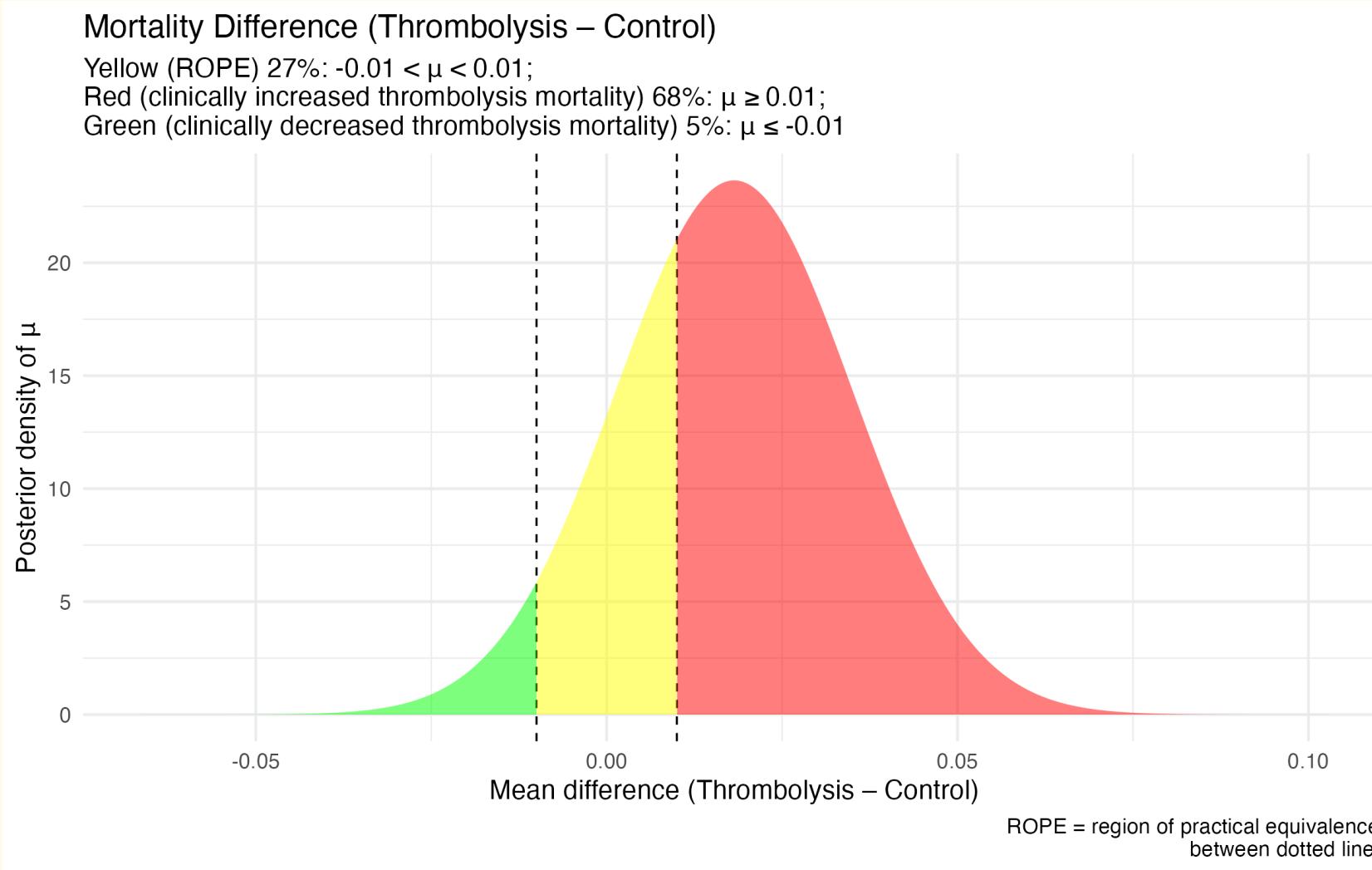


Probability mortality
RR > 1 = 76%

Bayesian mortality (risk difference)

What is MCID for stroke mortality?

Assume MCID threshold = .01 (1%) as for MI



Summary extended thrombolysis

- Six recent RCTs of extended thrombolysis with guided advanced neuroimaging & seven MAs have been performed - all using dichotomized mRS outcome
- Bayesian MA of UW-mRS outcome shows a high probability of a difference in favor of thrombolysis but only a trivial probability of clinically meaningful benefit
- Bayesian MA shows a moderate probability of increased mortality
- Bayesian methods provide a richer, more interpretable & nuanced analysis of trial data

Dexmedetomidine (Precedex) & post-operative delirium (POD)

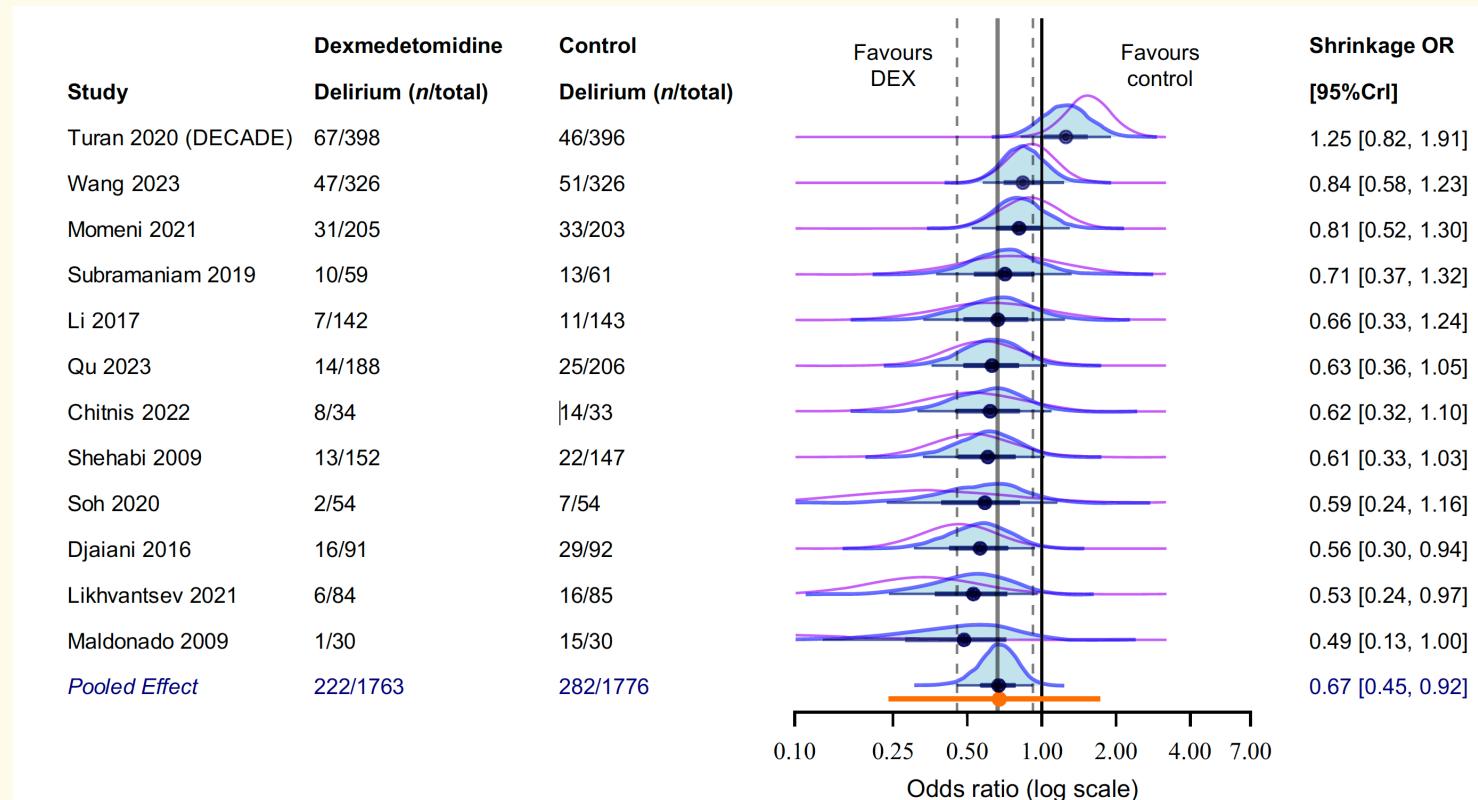
- Important to know if there are clinical advantages to offset the several fold higher costs compared to alternatives (placebo, opioid, or propofol)
- **14!!! prior meta-analyses** majority suggested benefit but DECADE (largest RCT) ↑ POD
- Bayesian framework to:
 1. better propagation of uncertainties
 2. re-analyze DECADE, largest trial, under multiple priors
 3. build more complex hierarchical models - quantify / adjust for possible (publication) bias
 4. provide decision-relevant probabilities

References:

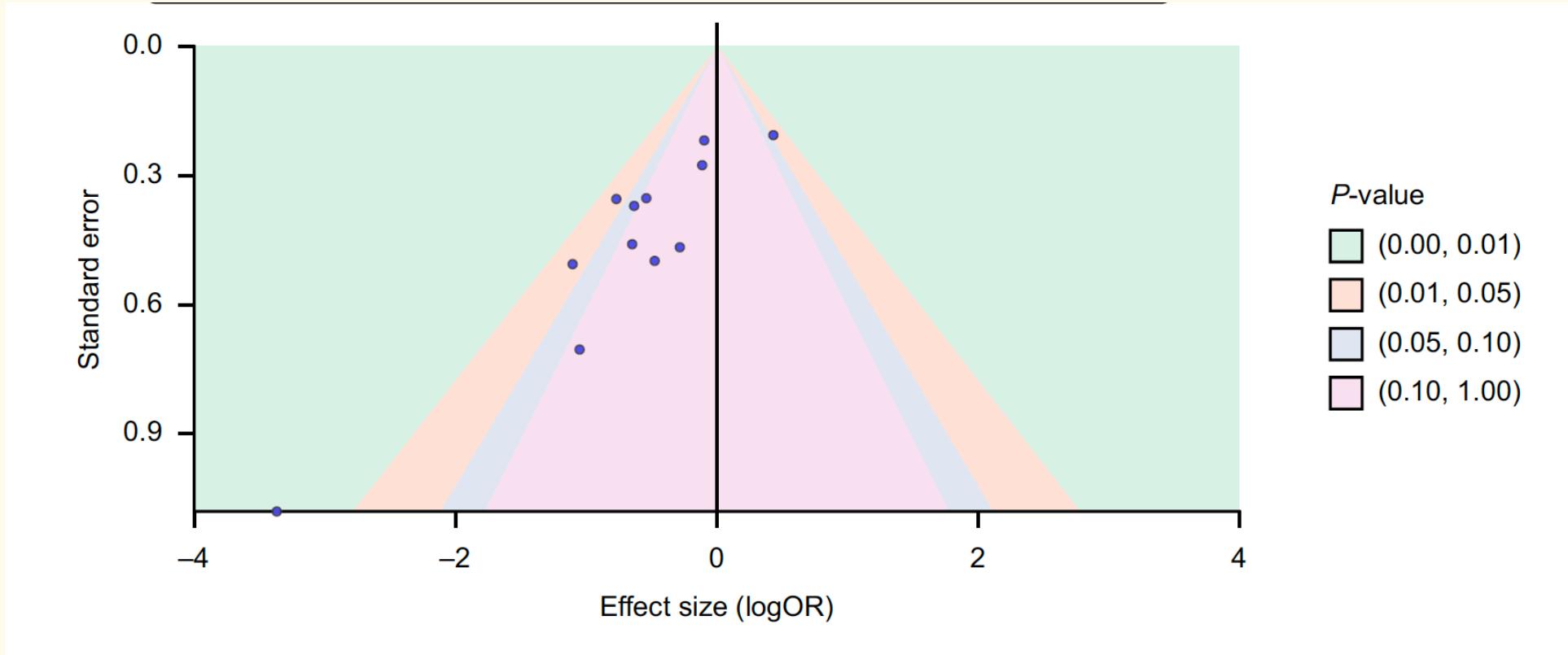
1. Dexmedetomidine for Sedation in the ICU or PICU: A Review of Cost-Effectiveness and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2014 Dec 17. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK268693/>
2. Turan A, Duncan A, Leung S, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. Lancet 2020; 396: 177e85

Evidence & modeling choices

- 12 RCTs, 3,539 participants; primary outcome: incidence of POD
- Pooled OR 0.67 ([0.45, 0.92])
- Ignores study heterogeneity (control - placebo, opioid, or propofol), potential biases, parameter uncertainty & P(MCID)
- PI 0.24–1.78 (orange line)



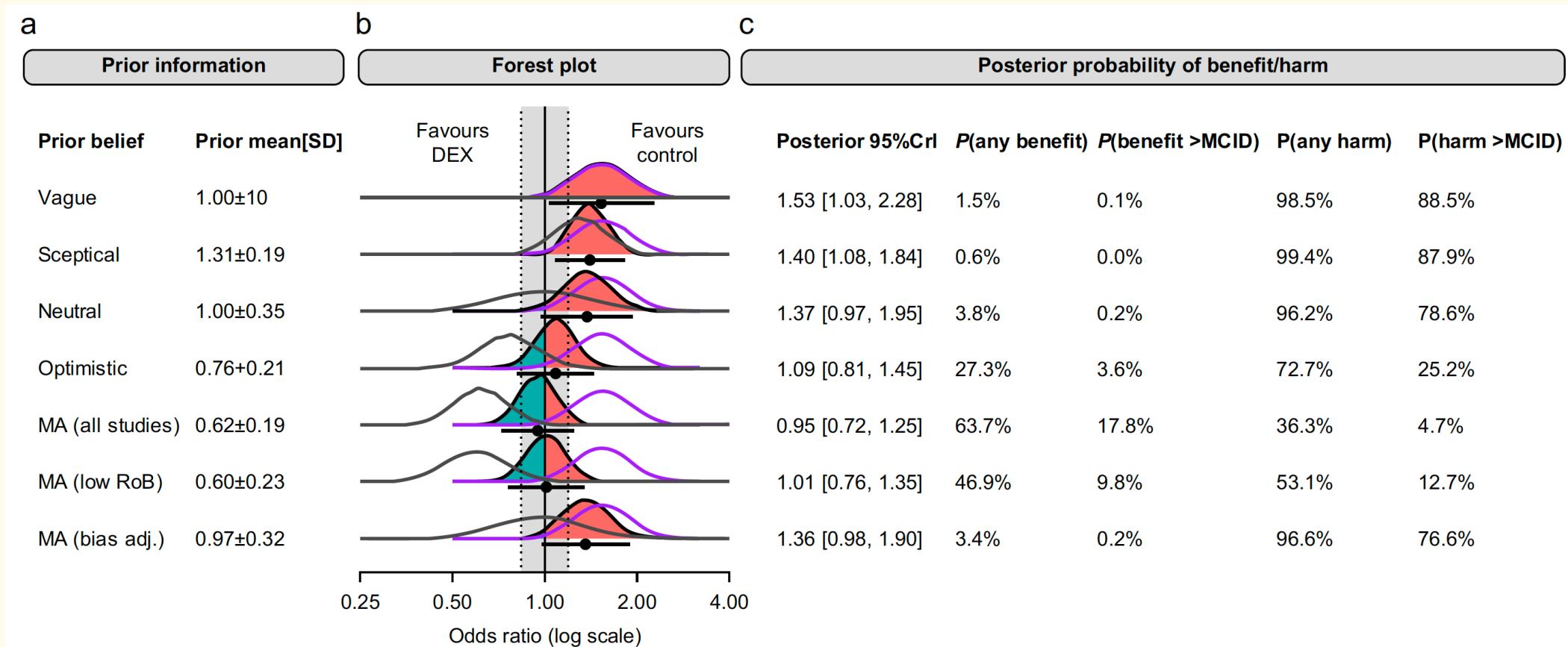
Publication bias: detect → adjust



- Bayesian funnel plot: strong asymmetry
 - regression slope $\beta \approx 3.86 [2.41, 5.50]$ → small-study effects likely.
- Robust Bayesian Model Averaging (RoBMA) over selection models:
 - Inclusion $BF_{10} \approx 214$ for bias; mean-effect evidence attenuates $BF_{10} \approx 0.58$
- Very strong evidence for publication bias -> ↓ effect size estimate

Bayesian Meta-analysis

DECADE reanalysis under multiple priors small probability of benefit



- Meta-analysis with adjustments for trials that had delayed registration and publication bias shows only small $P(\text{benefit} > \text{MCID})$ (0.2 - 17.8%)

Dexmedetomidine conclusions

- Beware of individual RCT biases (late registration, early stopping, selective reporting)
- Beware of meta-analytic biases (publication, selective inclusion)
- Bias awareness is insufficient, need to model (quantify) them
- Bias-aware analyzes align with no benefit / possible harm
- More research req'd to show definitive benefit

Take-Home Messages

- Meta-analysis is powerful, but not infallible
- Bayesian meta-analysis:
 - uses all available evidence
 - ↑ flexibility, complex models with transparent acknowledgement of model assumptions &uncertainty
 - minimizes cognitive biases (availability bias, dichotomization)
 - provides relevant probabilities
 - *What's the probability RR or RD > clinical meaningful effect?*
 - ↑ meta-cognition -> better decision making

Thank You

Let's keep thinking critically, questions?



Slides available at <https://www.brophyj.com/talks>

References

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- Heuts, S, Kawczynski MJ, Sayed A, Urbut SM, Albuquerque AM, Mandrola JM, Kaul S, Harrell FE, Gabrio A, and Brophy JM. 'Bayesian Analytical Methods in Cardiovascular Clinical Trials: Why, When, and How', *Can J Cardiol*, 41: 30-44 (2025)
- Brophy JM "Bayesian Methods in Cardiology: A Primer for the Non-Statistician." *Can J Cardiol* 39: 1481-92 (2023)]

In memory of Dr. Maurice McGregor (1920 -2025)



mentor, colleague, and critical thinker