

Bayesian de-escalation trials

Operating characteristics for time-to-event outcomes

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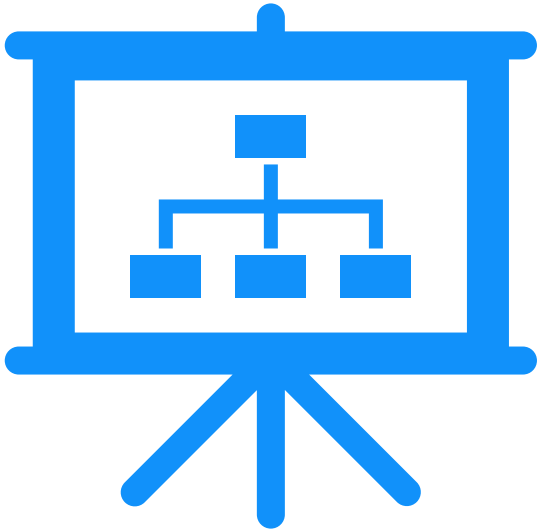
Outline

① Clinical motivation: CROSSROADS

② Non-inferiority trial: design and analysis

③ Simulation study

④ Conclusion and future directions



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Motivation – CROSSROADS study

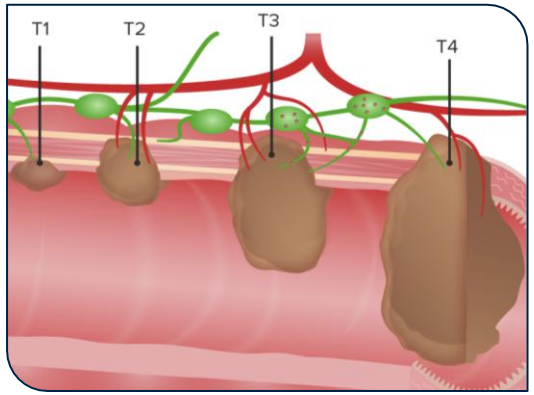
- Incidence of T1-2 colorectal cancer (CRC) increases
- All patients treated with local excision

Until recently

Patients with >5% risk of LNM further treated with completion surgery

However

LNM only found in minority of surgical specimens



CRC - size and lymph node involvement

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CROSSROADS

Non-inferiority trial

Frequentist hypothesis:

H0: HR $> \delta^*_{HR}$ vs H1: HR $< \delta^*_{HR}$ for $\delta^*_{HR} > 1$

Frequentist definition:

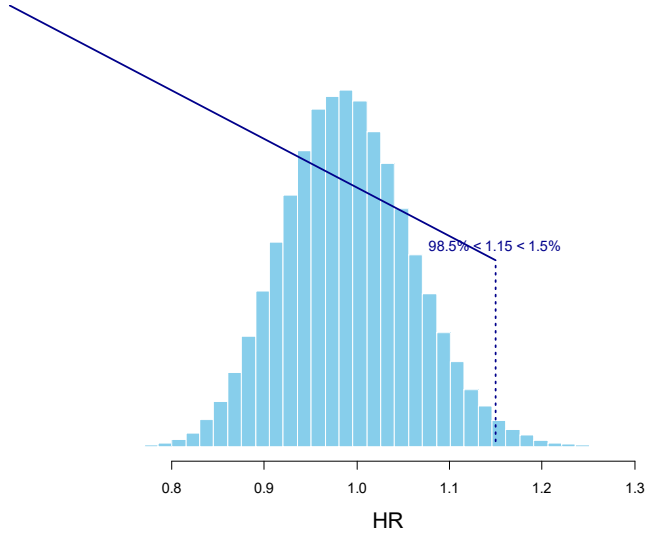
upper bound $100\times(1-2\alpha)\%$ CI $< \delta^*_{HR}$

Bayesian definitions:

a) upper bound $100\times(1-2\alpha)\%$ HDI/ETI CrI $< \delta^*_{HR}$, or

b) Posterior probability of non-inferiority

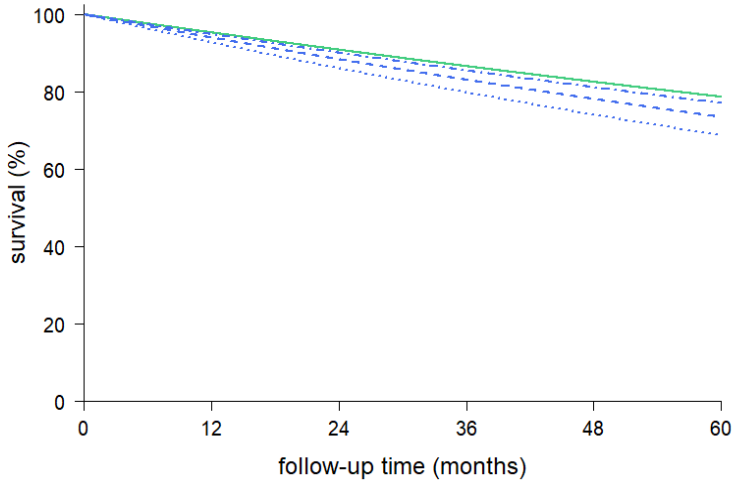
$\pi(\mathrm{HR} < \delta^*_{HR} \mid \mathcal{D}_n) > 1-\alpha$



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Data generating mechanism

- Time to event: Cox PH model $h(t|X) = h_0(t) \cdot \exp(\beta_0 \cdot X)$
  - $h_0(t) = \lambda_0$ [exponential]
  - $\beta_0 = 0, \beta_0 = 0.25 \cdot \ln(\delta^*_{HR}), \beta_0 = 0.75 \cdot \ln(\delta^*_{HR})$, and $\beta_0 = 1.33 \cdot \ln(\delta^*_{HR})$, for $\delta^*_{HR} = 1.4$
  - X: treatment arm [1:1;
    A = treatment as usual
    B = de-escalated treatment]
- Time to censoring: uniform(36, 60)



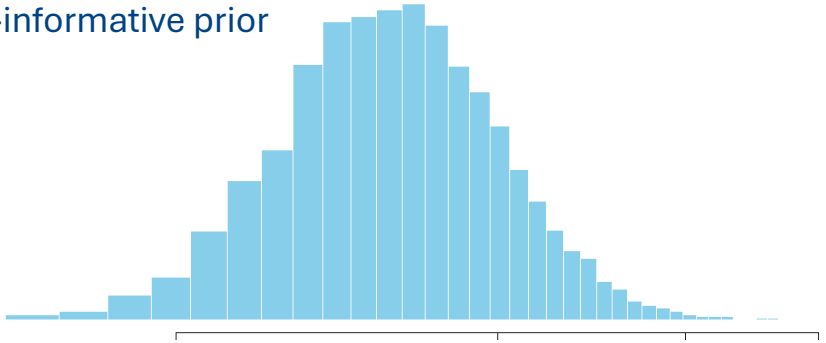
Priors

1. non-informative: $\beta \sim \mathcal{N}(0,10^2)$
2. no difference prior: $\beta \sim \mathcal{N}(0,0.5^2)$
3. optimistic prior: $\beta \sim \mathcal{N}(-0.5 \cdot \ln(\delta^*_{HR}), 0.5^2)$
4. skeptical prior: $\beta \sim \mathcal{N}(0.5 \cdot \ln(\delta^*_{HR}), 0.5^2)$
5. half-normal prior: $\beta = |\theta|, \text{ for } \theta \sim \mathcal{N}(0, 0.5^2),$
6. asymmetric mixture prior: $\beta \sim 0.9 \cdot \mathcal{N}(\ln(1.1), 0.1^2) + 0.1 \cdot \mathcal{N}(0,1^2)$

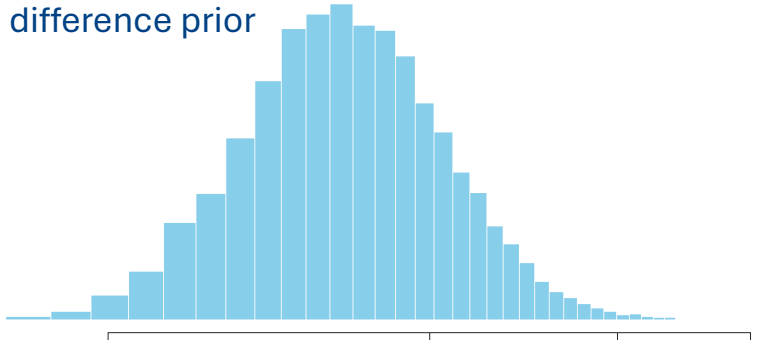
Posterior distributions

$\beta_0 = 0, n = 200$

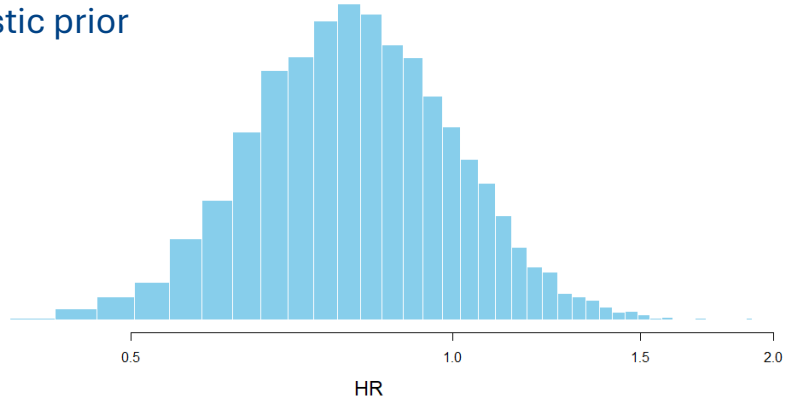
non-informative prior



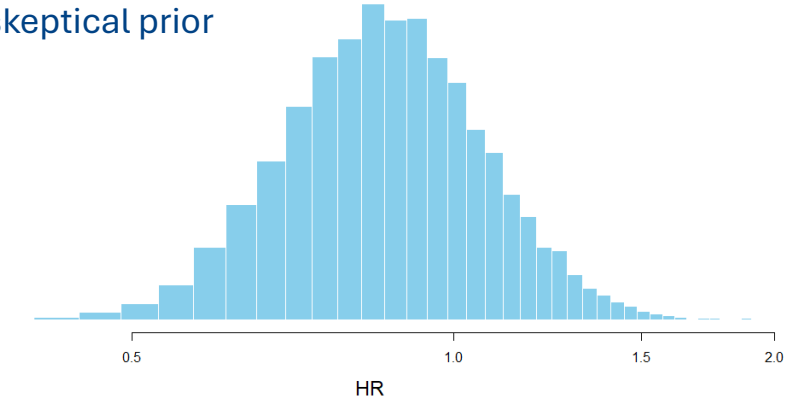
no difference prior



optimistic prior



skeptical prior



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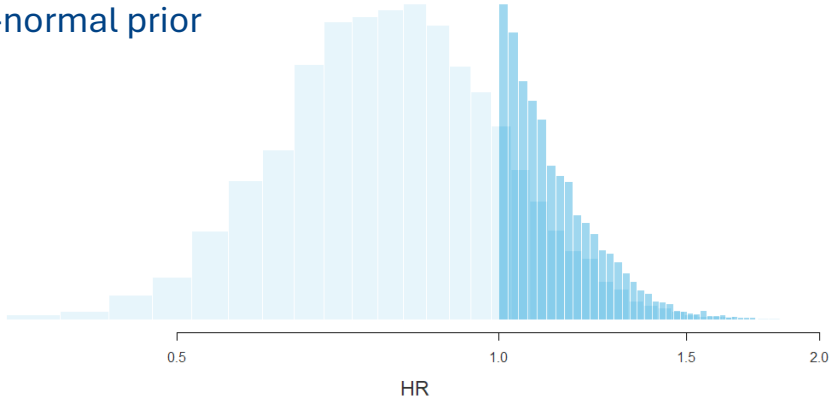
Posterior distributions

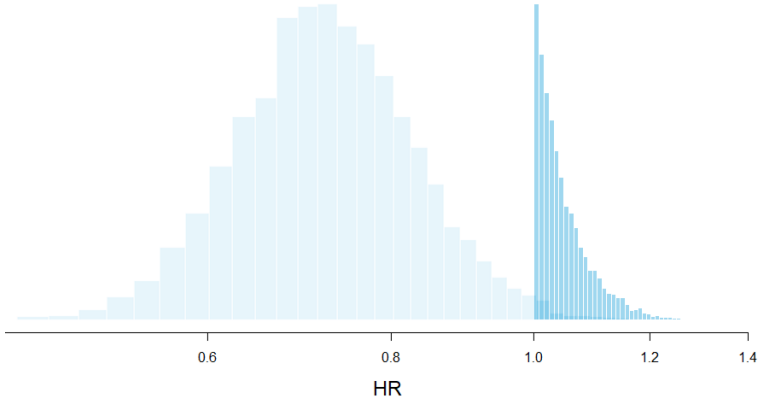
$\beta_0 = 0, n = 200$

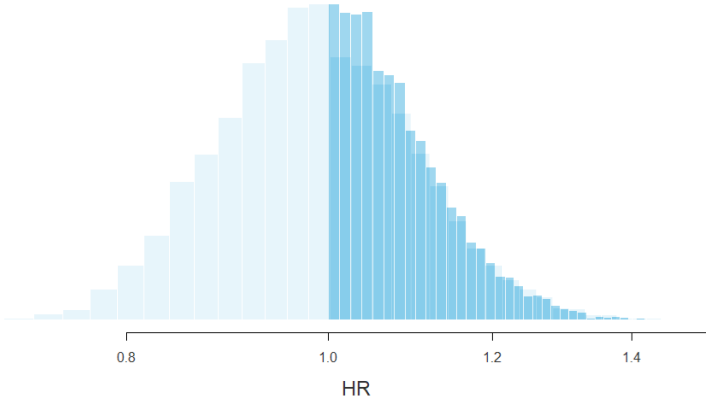
$n = 600$

$n = 1000$

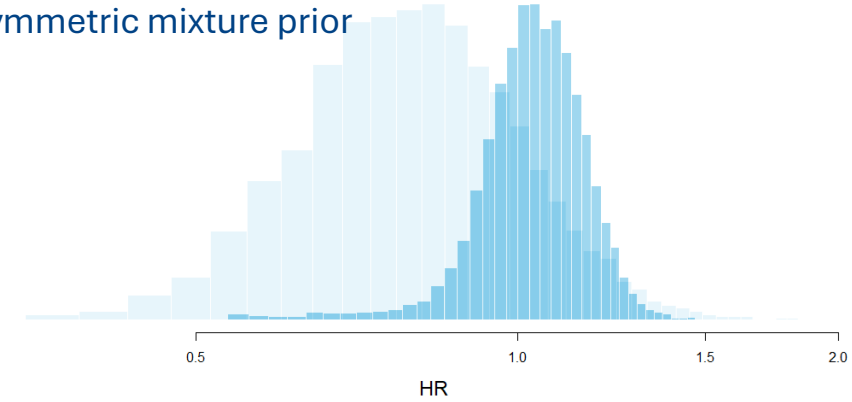
half-normal prior

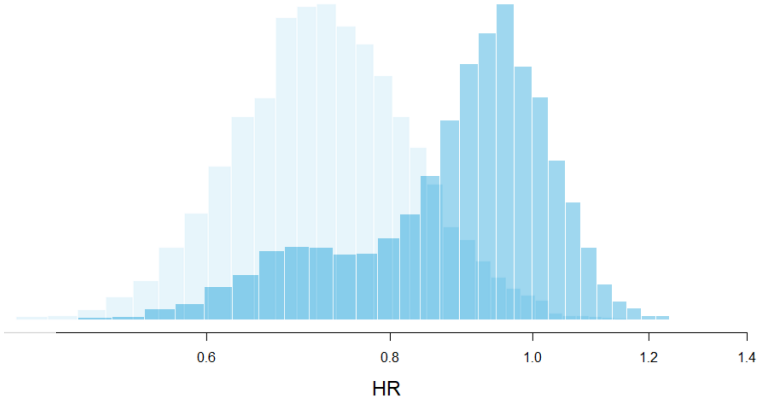


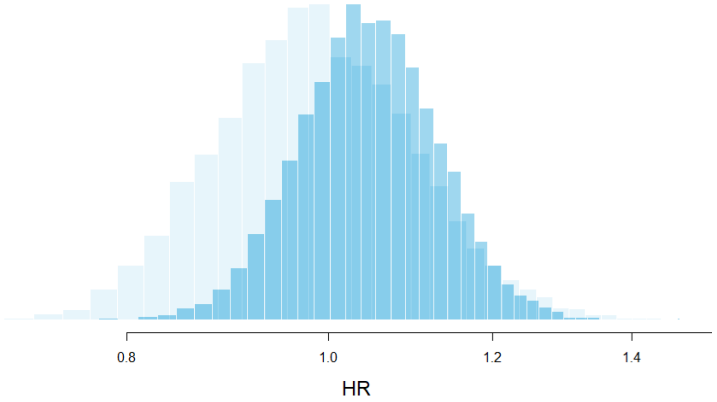




asymmetric mixture prior







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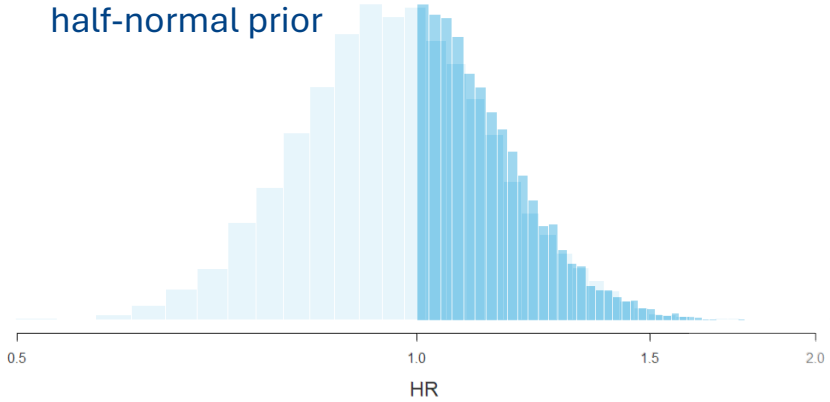
Posterior distributions

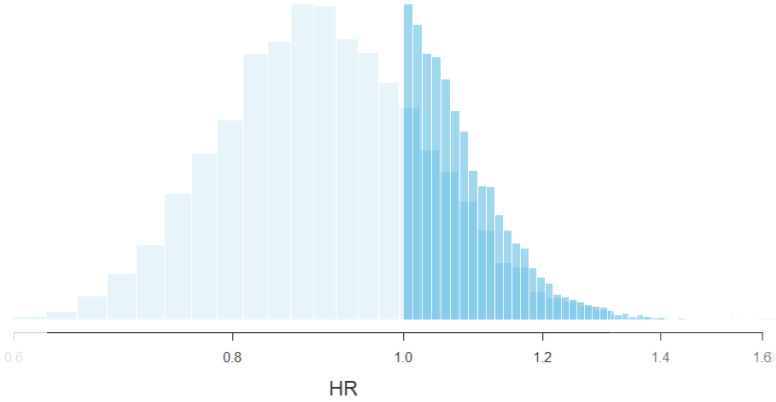
$\beta_0 = 0.25 \cdot \ln(\delta^*_{HR}), n = 400$

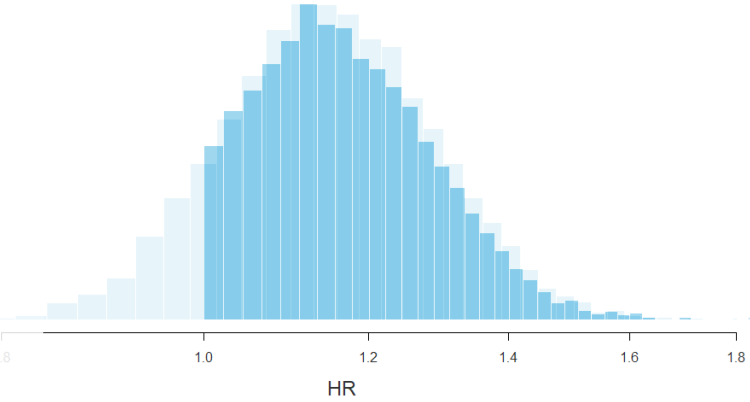
$n = 600$

$n = 800$

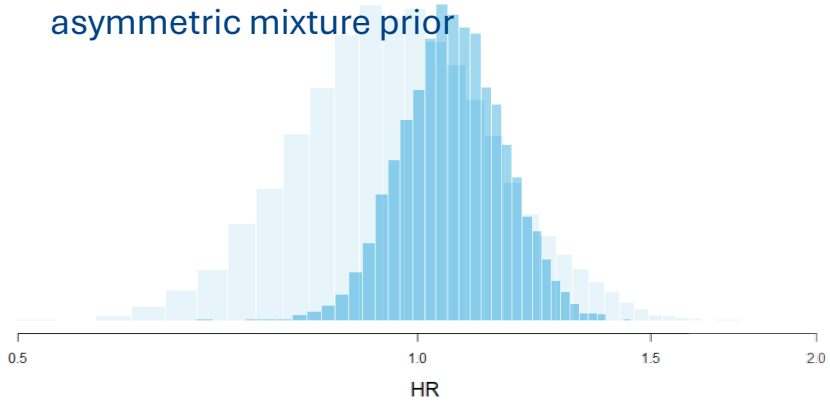
half-normal prior

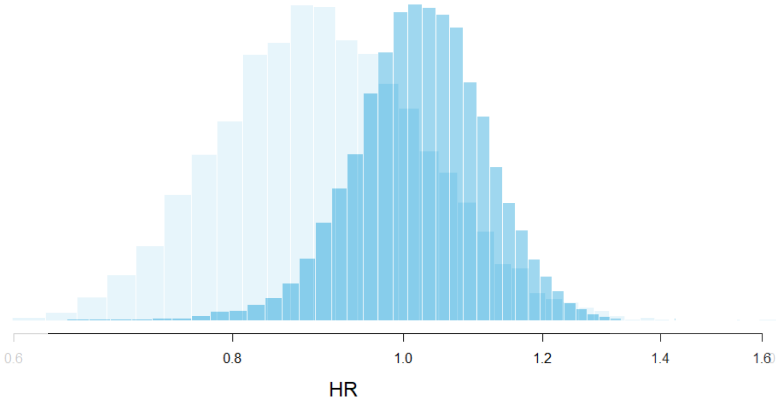


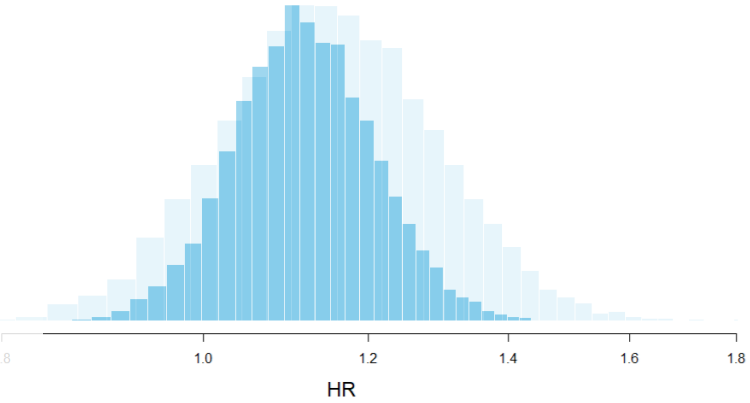




asymmetric mixture prior







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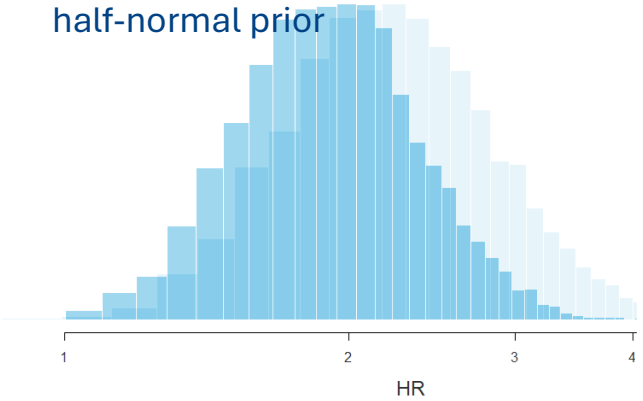
Posterior distributions

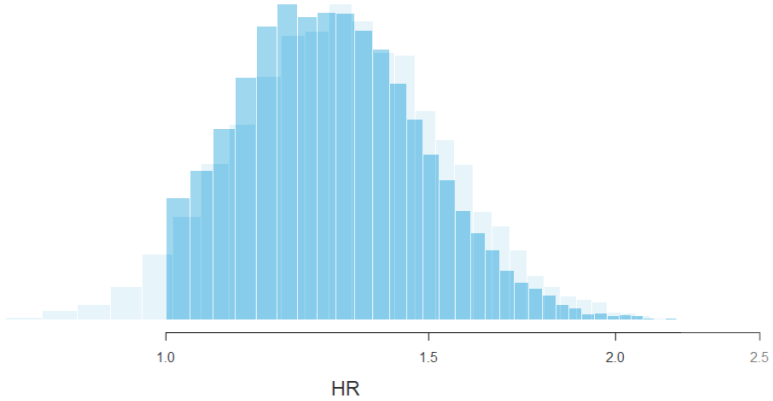
$\beta_0 = 1.33 \cdot \ln(\delta^*_{HR}), n = 200$

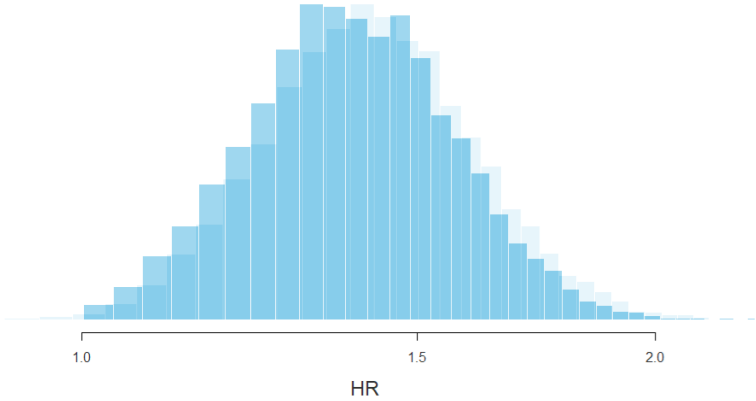
$n = 400$

$n = 600$

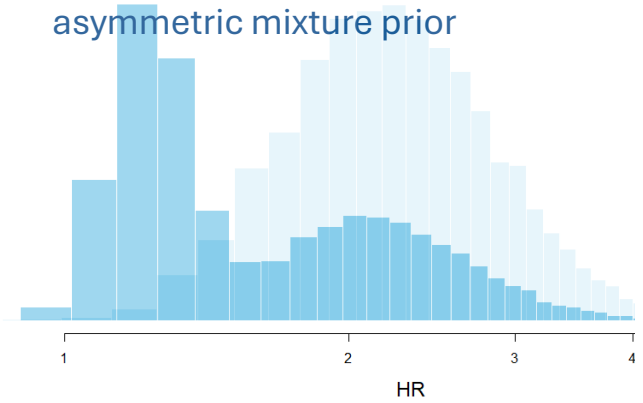
half-normal prior

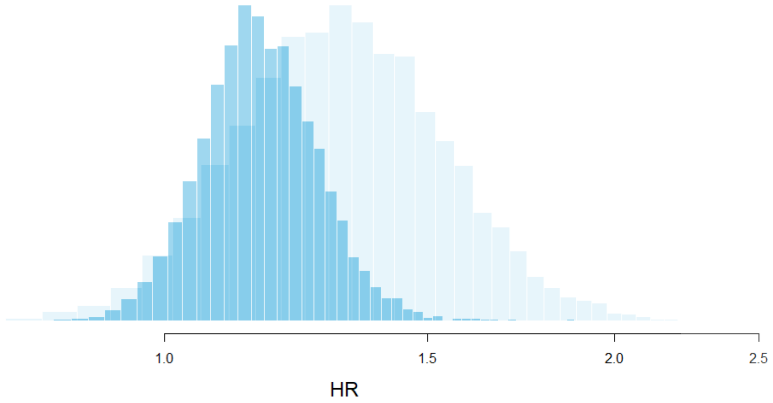


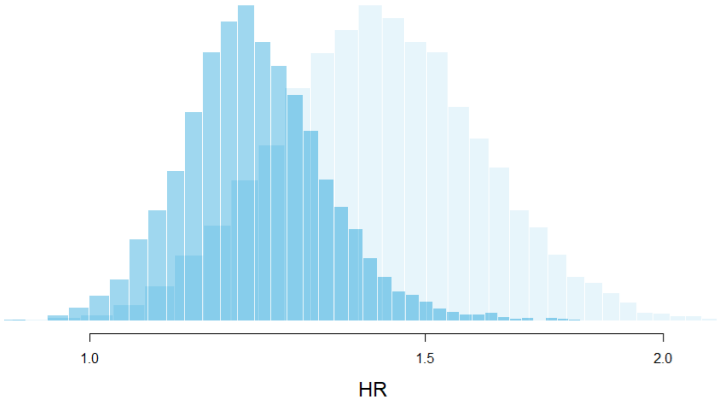




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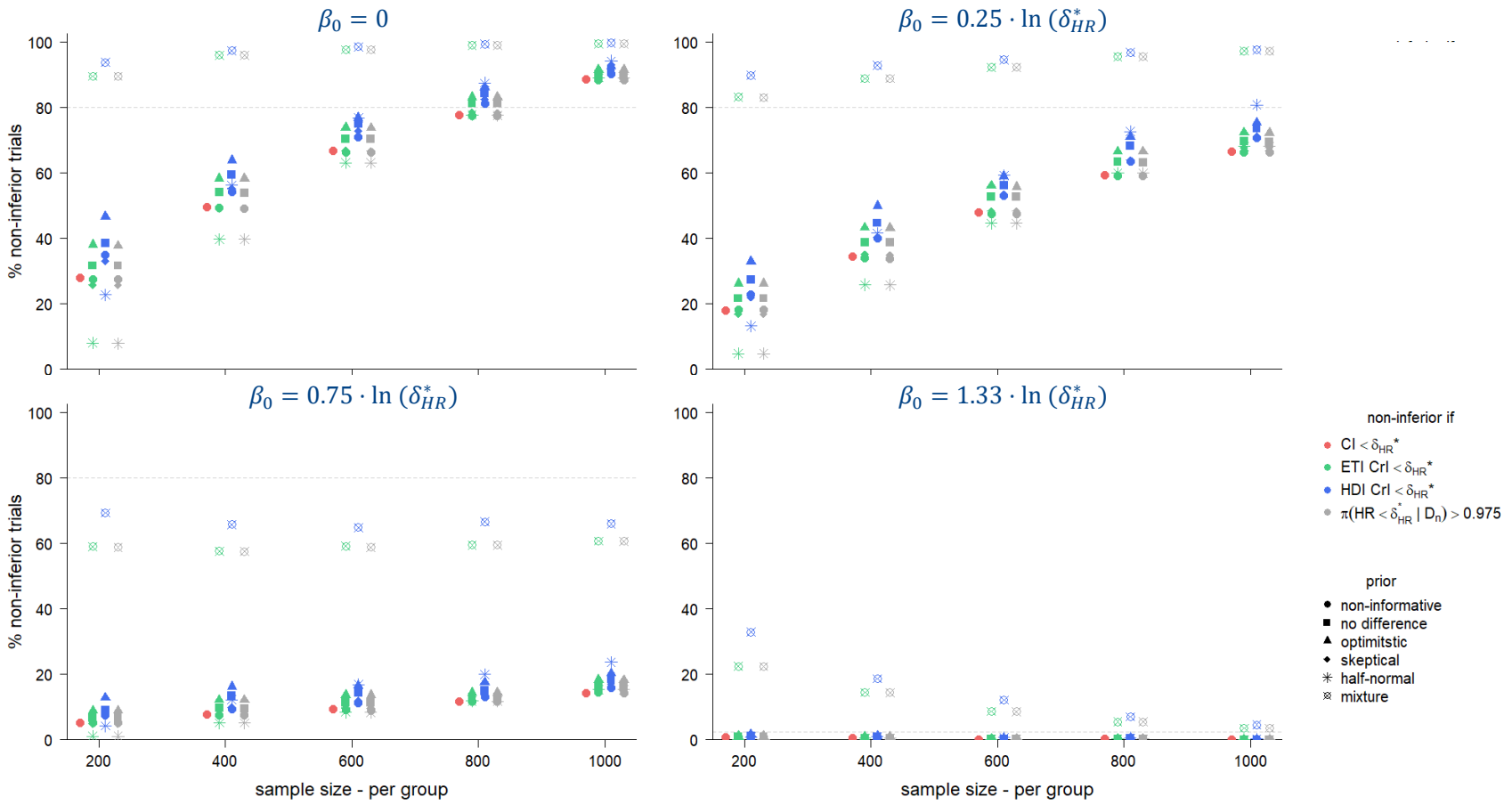
Operating characteristics

Operating characteristics

- (Bayesian) predictive power for different definitions of non-inferiority: $P(\text{declare treatment NI} \mid HR_{\text{true}})$
- (Expected) posterior probability: $E[\pi(HR < \delta^*_{HR} | \mathcal{D}_n)]$
- Coverage and precision of ETI and HDI credible interval (CrI)

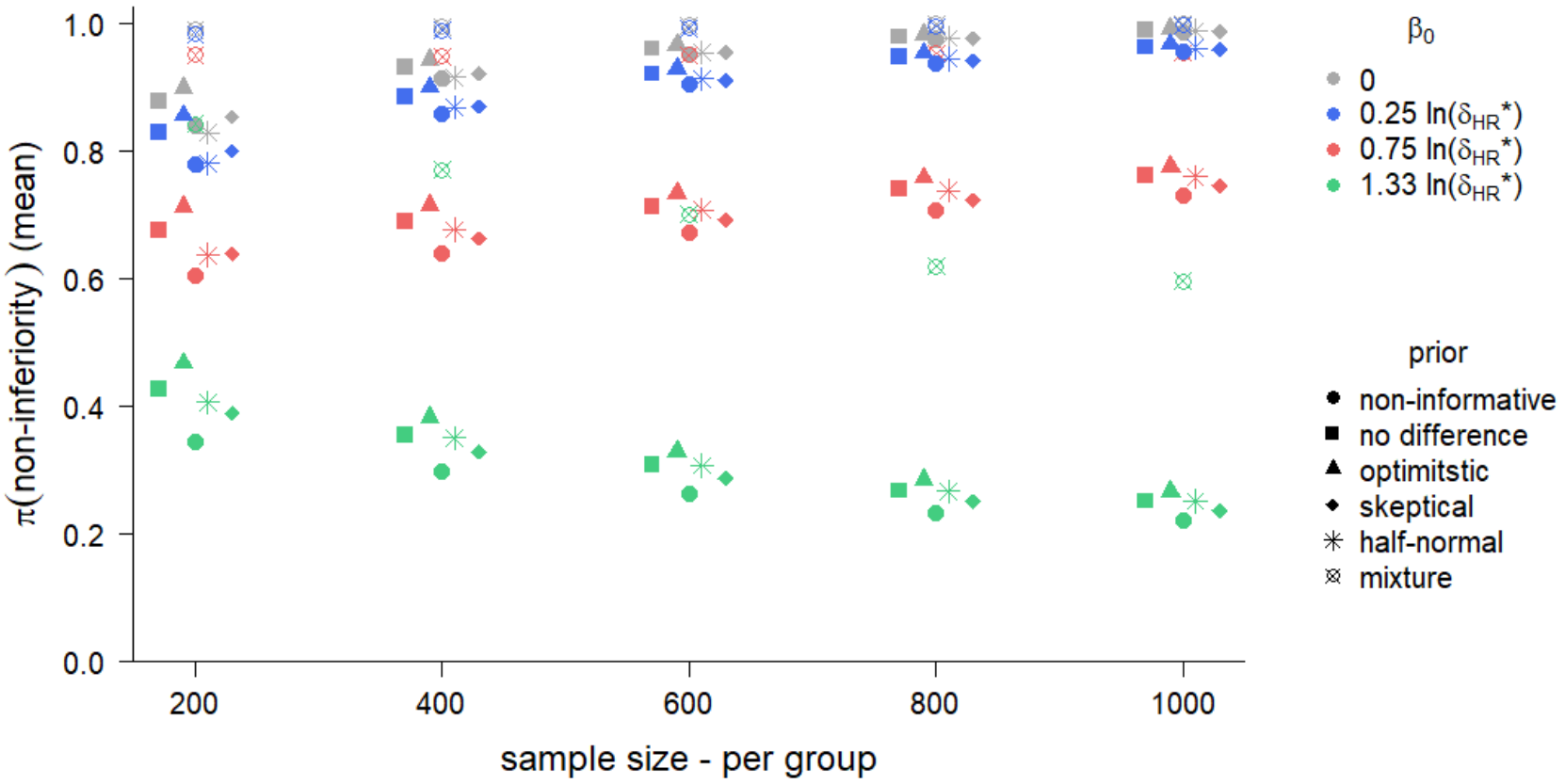
Compared with frequentist type I and II errors, coverage and precision of confidence interval (CI)

Predictive power



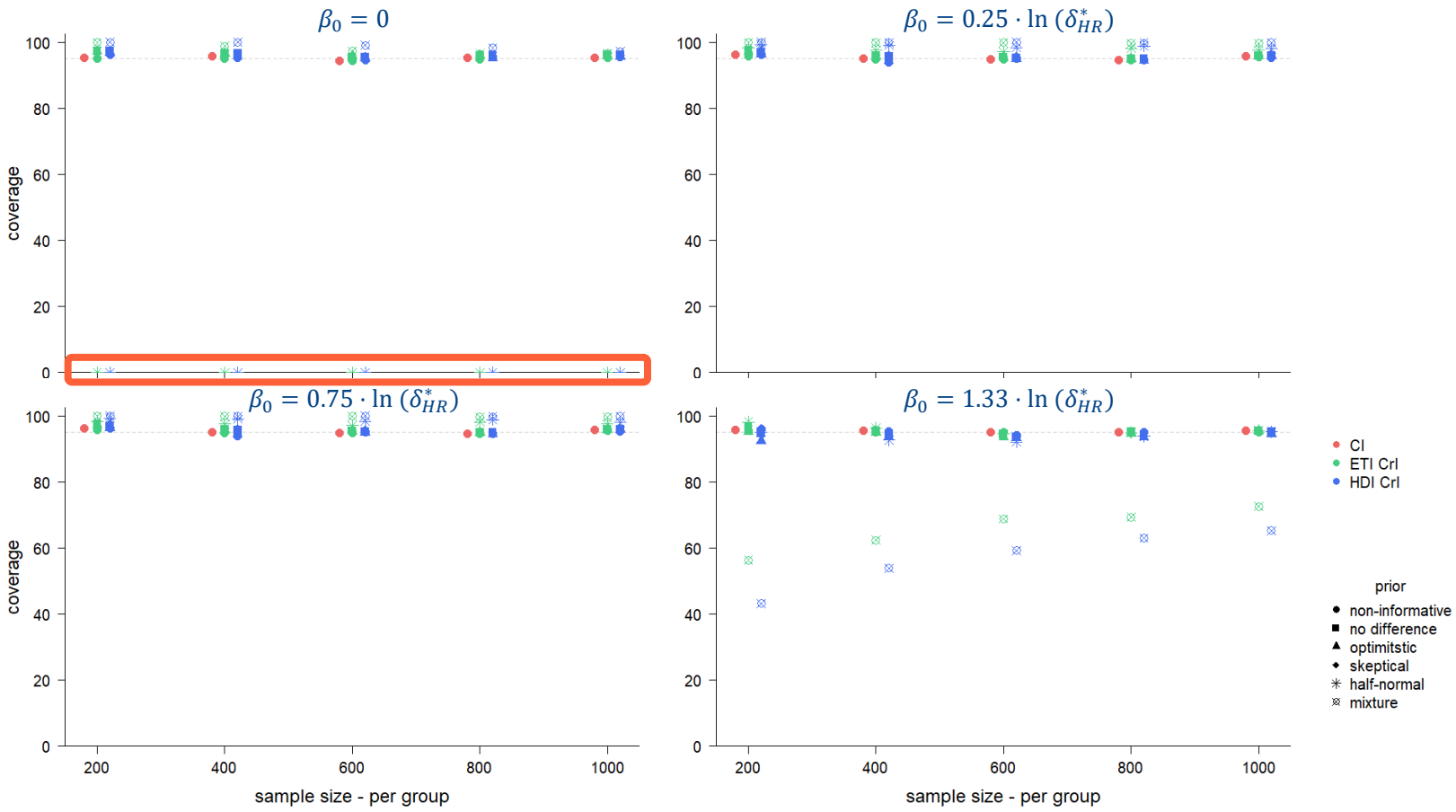
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Expected posterior probability of non-inferiority



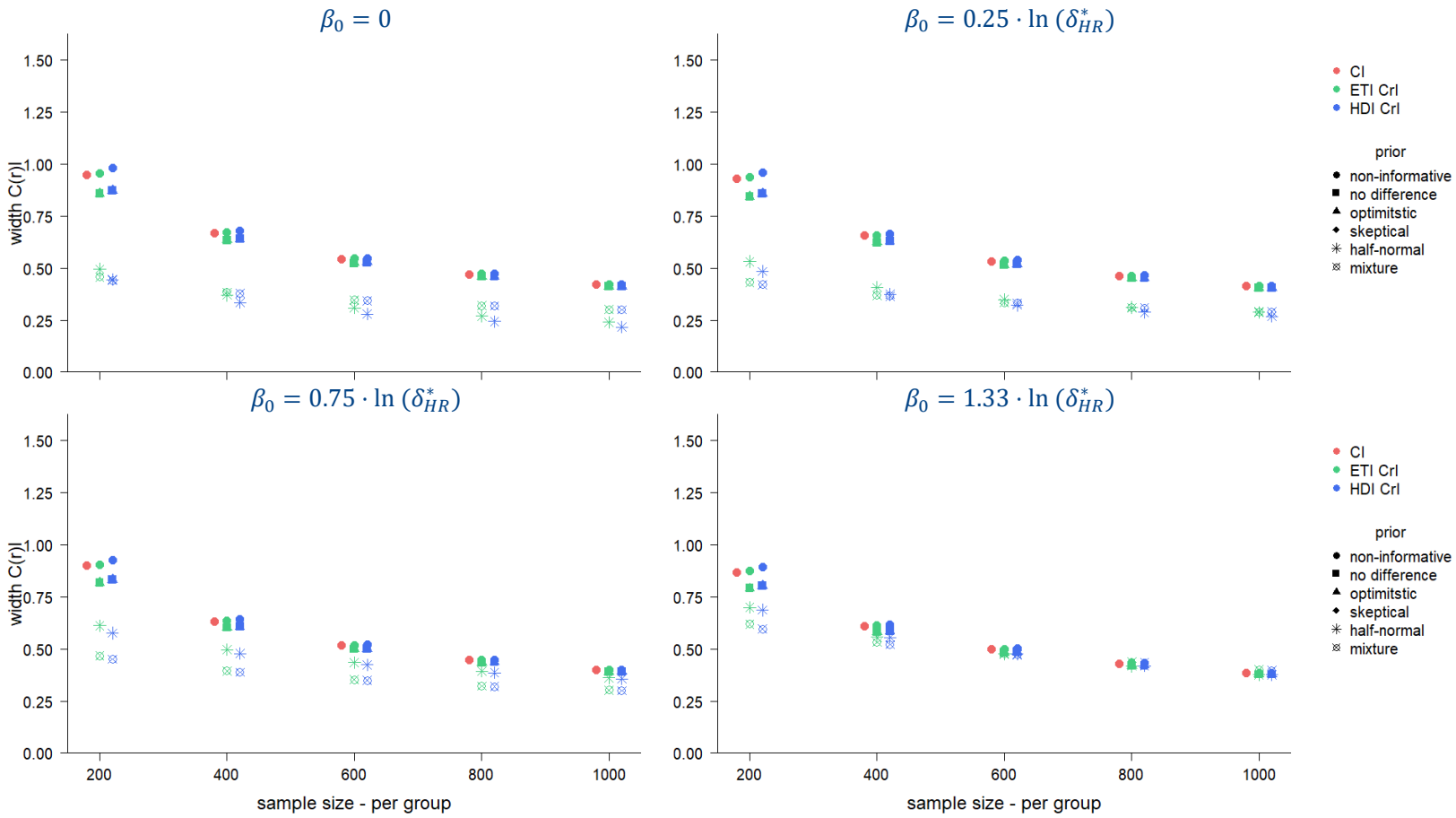
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Coverage



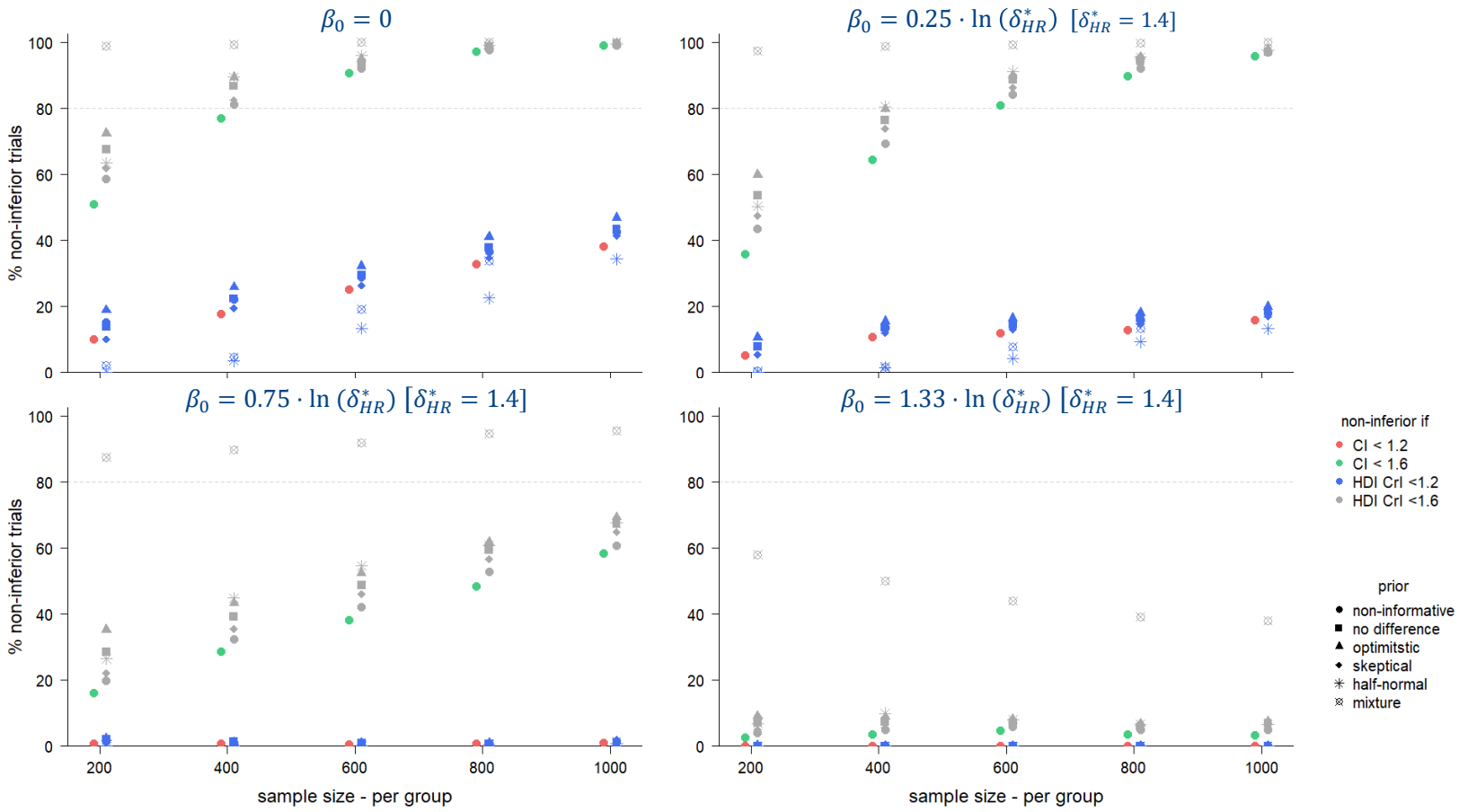
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Precision



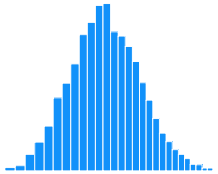
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Predictive power – influence of NIM

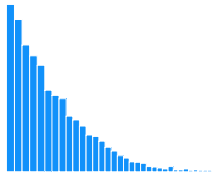


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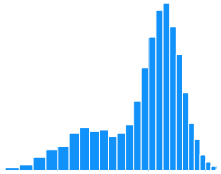
Conclusions and future directions



Small differences between non-informative, no difference, optimistic and skeptical priors



Markedly lower predictive power, except for larger NIMs



High predictive power in case of no to small true effect also for small sample sizes, except for smaller NIMs

Worse performance in case of truly inferior effect



Study effect of including design prior

Extend to non-constant hazard and competing events

Add external controls

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Thank you for your attention!



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