Assessing synergy, extend, and impact of leveraging external control data in pediatric clinical trials using Bayesian dynamic borrowing

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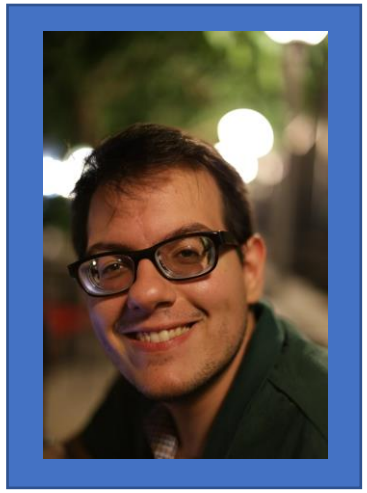

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- Saurabh Mukhopadhyay and Martina Kron are employees of AbbVie and Emmanouil Spanakis was an employee of Abbvie. They all may own AbbVie stocks.

Key challenges

- Conducting a well powered and adequately controlled clinical trial is often challenging
  - Ethical concerns
  - Patients' burden
  - Feasibility issue

- Particularly difficult in pediatric studies
  - Low incidence in children
  - Timing and course of the disease
  - Parents are reluctant

- Many of these issues are also present in rare diseases

Opportunity with Borrowing From Historical Data

- Often patients' data are available from historical trials across therapeutic areas and indications
  - In pediatric trials, opportunities could arise from existing knowledge from a reference population, usually from adults
  - General and clinical considerations of selection of historical trials presented by Pocock[1]
- Borrowing from such historical data to augment the control arm has huge motivations in drug development
  - Can overcome difficulties when placebo/control arms are difficult to enroll and at the same time reduces the chance of a patient being randomized to placebo/control
  - Can reduce size / risk of a new trial
  - Can save time and money
  - Can expedite drug development

[1]Pocock, S.J., 1976. The combination of randomized and historical controls in clinical trials. *Journal of chronic diseases*, *29*(3), pp.175-188.

Purpose of Borrowing

- The key idea behind borrowing
  - Synergistic borrowing should increase precision of the parameter estimate of interest

- Bayesian approaches are attractive for including historical data in current trials
  - Provides a quantitatively rigorous and flexible framework
  - Makes use of current control data to check and borrow information from historical control data
  - Many new approaches have been proposed using Bayesian framework over the last 20 years
  - A very active area of research

Bayesian Methods

- Notable and somewhat distinct approaches include
  - Naïve pooling
    - Does not allow discounting nor accounts for between trial heterogeneity
  - Power priors (Ibrahim and Chen[2])
  - Commensurate priors (Hobbs et al[3])
  - Meta-analytic predictive (MAP) priors (Neuenschwander et al[4])
    - Provides a very flexible and transparent implementation through hierarchical Bayesian model (HBM) structure
    - Allows to adjust for between trial heterogeneity
    - Relatively easy to explain and implement
    - Allows further discounting through robustification

[2] Ibrahim, J.G. and Chen, M.H., 2000. Power prior distributions for regression models. Statistical Science, pp.46-60

[3] Hobbs BP, et. al. 2011. Commensurate priors for incorporating historical information in clinical trials using general and generalized linear models. Bayesian Anal. pp 639–674

[4] Neuenschwander, B., et. al.., 2010. Summarizing historical information on controls in clinical trials. Clinical Trials, 7(1), pp.5-18.

Robustification of the MAP priors

- To further robustify the MAP priors Schmidli et al[5] proposed robustified MAP or rMAP priors by adding a vague or weakly informative component to form a mixture distribution

$$p_{rMAP}(\theta^*) = b \cdot p_{MAP}(\theta^*) + (1-b) \cdot p_V(\theta^*), \qquad (0 < b < 1)$$

  where b $(0 \leq b \leq 1)$ may be interpreted as the fraction of information used from the MAP prior to further downweigh the historical information

  - This can be useful if there are concerns that there is little synergy between current and historical control data and built-in protection of the MAP prior may not be enough to adequately downweigh undesirable influence of historical data in the current analysis
  - Such flexibility is useful, for example, when borrowing from adult data in a pediatric clinical trial

Question remains on how to determine the synergy to decide the mixing weight b.

[5] Schmidli, H., et. al. (2014), Robust meta-analytic-predictive priors in clinical trials with historical control information. Biometrics, 70: pp 1023-1032.

Illustration with a Binary Endpoint

- For historical control data:

$$Y_j \sim Binomial(n_j, p_j), j = 1,2, \cdots H$$

  - For the current control data

$$Y^* \sim Binomial(n^*, p^*);$$

  - Applying HBM on logit scale:

$$\theta_j = logit(p_j), j = 1,2, \cdots H, and\ \theta^* = logit(p^*)$$

$$\theta^*, \theta_1, \theta_2, \cdots, \theta_H \sim N(\mu, \tau^2)$$

$\mu \sim N(0, 2^2)$ and $\tau \sim HN(0,1)$

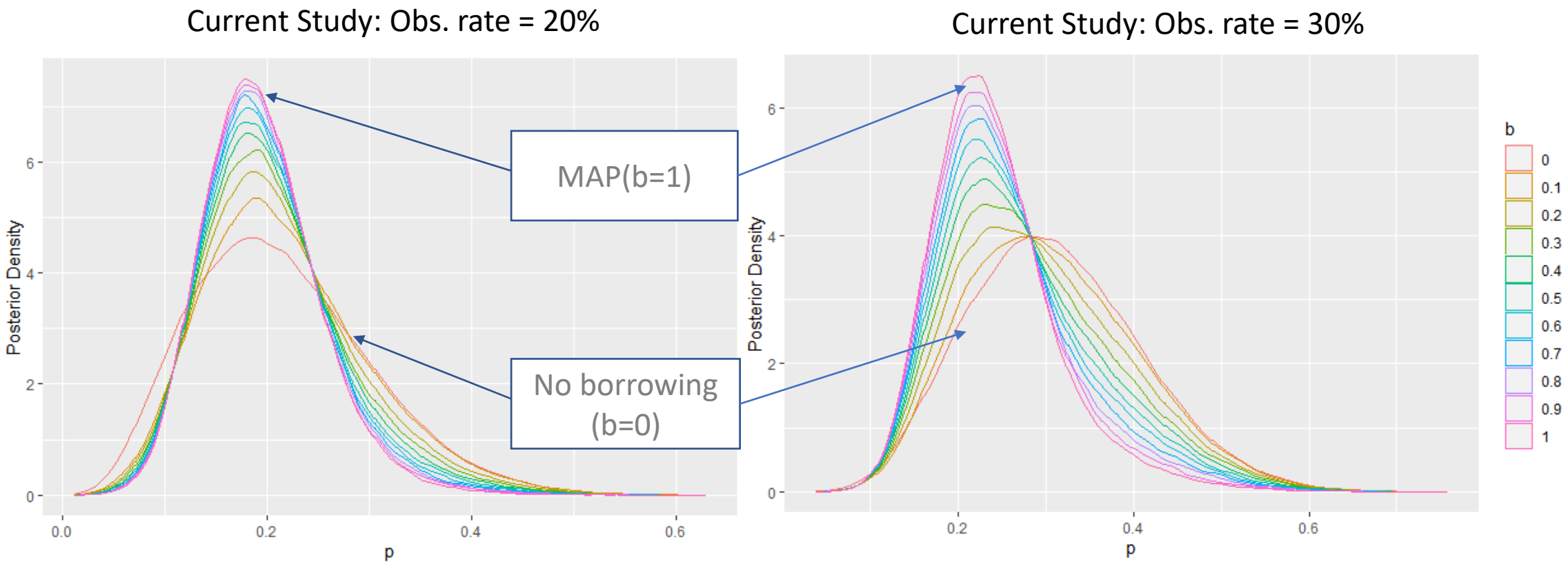
An appropriate choice of the prior for τ is crucial as it governs how much information will be shared from the historical trials (especially when $H < 5$, Gelman[6])

HN(0,1) gives conservative choice when response rate is in the range of 0.2 to 0.8 (Webber et al[7])

[6] Gelman, A., 2006. Prior distributions for variance parameters in hierarchical models. Bayesian analysis, 1(3), pp.515-534.

[7] Weber, S., et. al. 2021. Applying Meta-Analytic-Predictive Priors with the R Bayesian Evidence Synthesis Tools, Journal of Statistical Software, 100(19), pp. 1–32

Posterior Densities using MAP/rMAP framework



n0 = 20, historical data: 10/60, 12/60

Assessing Synergy and Impact of Borrowing Information

- We propose a Bayes Factor like quantity to formally measure whether borrowing improves the precision compared to any drift[8]

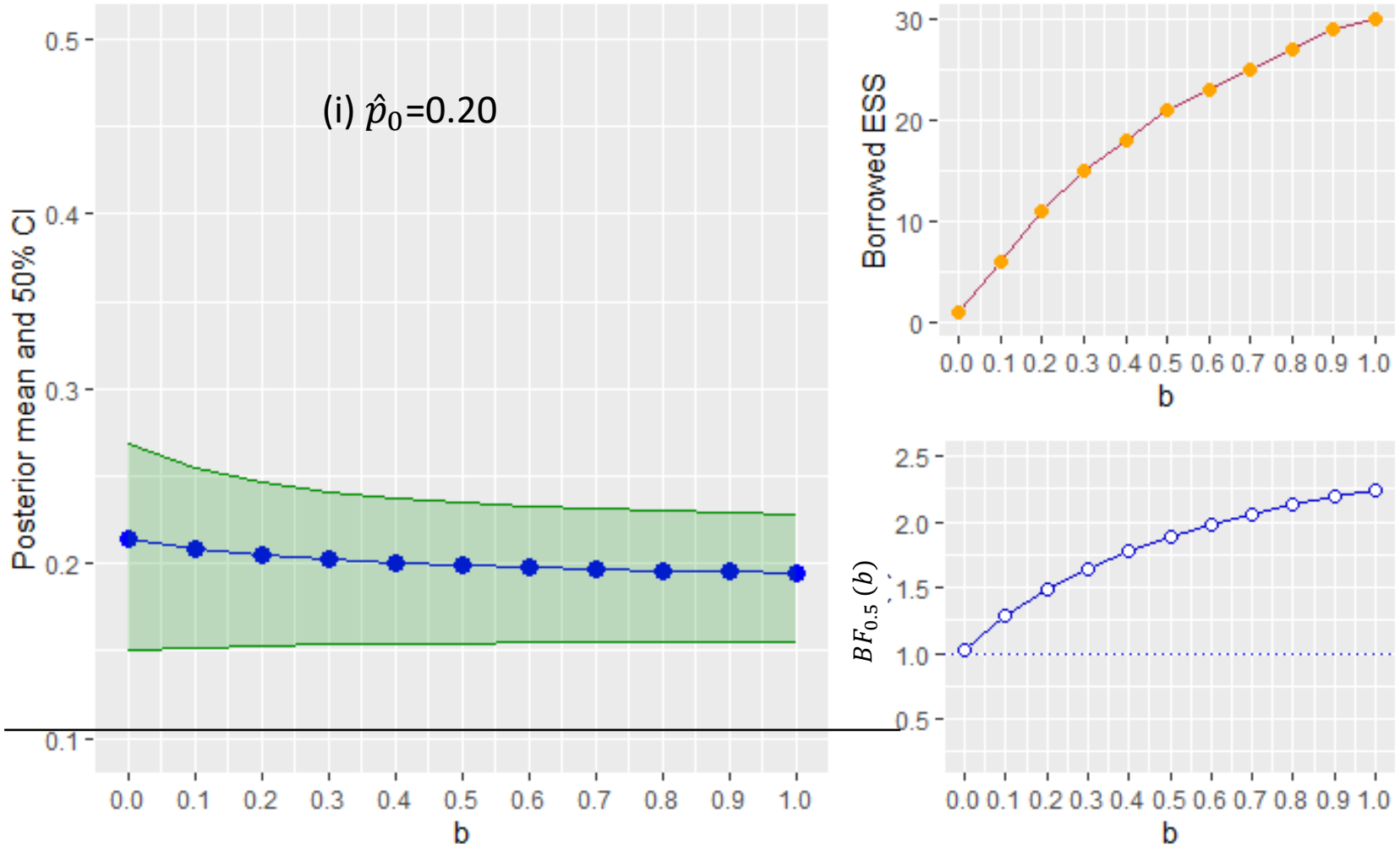
  - Specifically, it computes the ratio of odds that the true value of θ^* belongs to a set A under borrowing, as compared to that under no-borrowing as:

$$BF_\gamma(b) = \frac{\frac{P(A\,|b)}{1-P(A\,|b)}}{\frac{P(A\,|b=0)}{1-P(A\,|b=0)}} = \frac{P(A\,|b)}{1-P(A\,|b)} \cdot \frac{1-\gamma}{\gamma}$$

  - Where, A is a $\gamma * 100\%$ credible interval under *no-borrowing*
  - When there will be synergy, then we should expect the measure to be greater than 1

[8] Spanakis, E., Kron, M., Bereswill, M., and Mukhopadhyay, S. (2022). "Addressing statistical issues when leveraging external control data in pediatric clinical trials using Bayesian dynamic borrowing", Submitted for publication in *Journal of Biopharmaceutical Statistics*.

Observed rate is very similar to historical rates

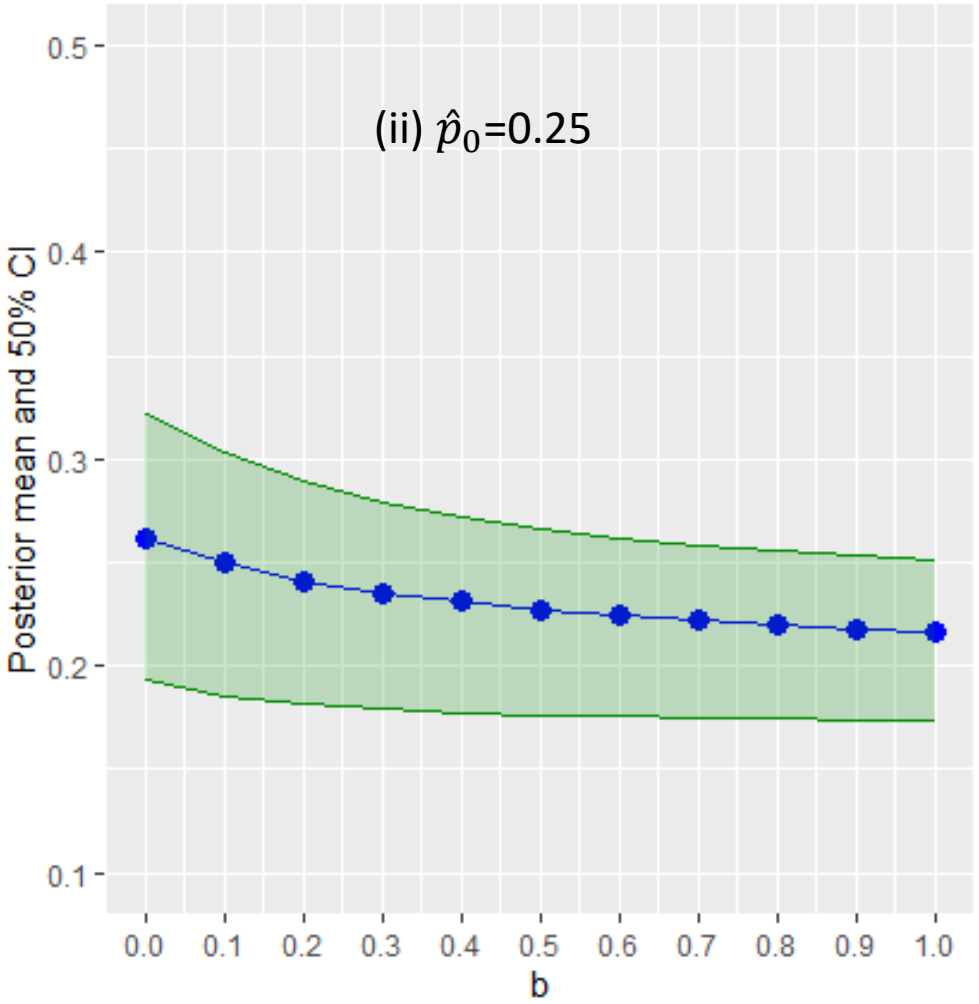


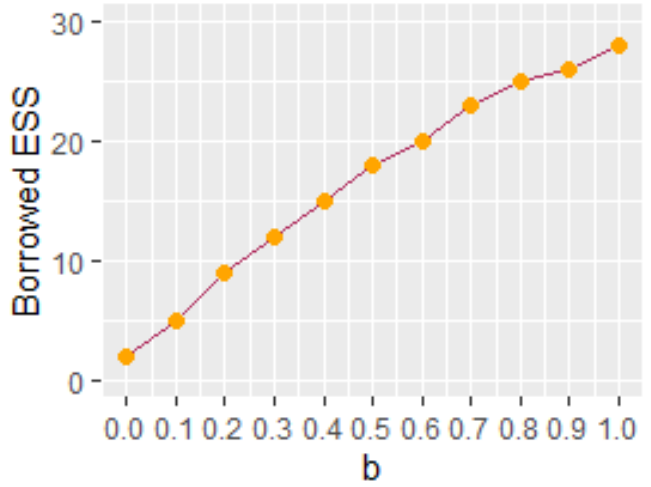
When observed rate in the current study (20%) is very similar to the overall rate in the historical studies (18.3%), we see $BF(b) > 1$ and kept increasing with b and the effective sample size (ESS[9]) borrowed from the historical data also kept increasing.

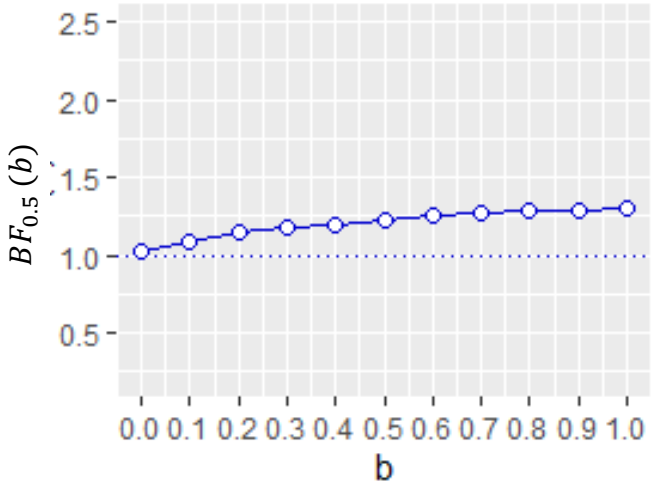
[9] Neuenschwander, B., et. a. 2020. Predictively consistent prior effective sample sizes. Biometrics, 76(2), pp.578-587.

n0 = 20, historical data: 10/60, 12/60

Observed rate is somewhat similar to historical rates



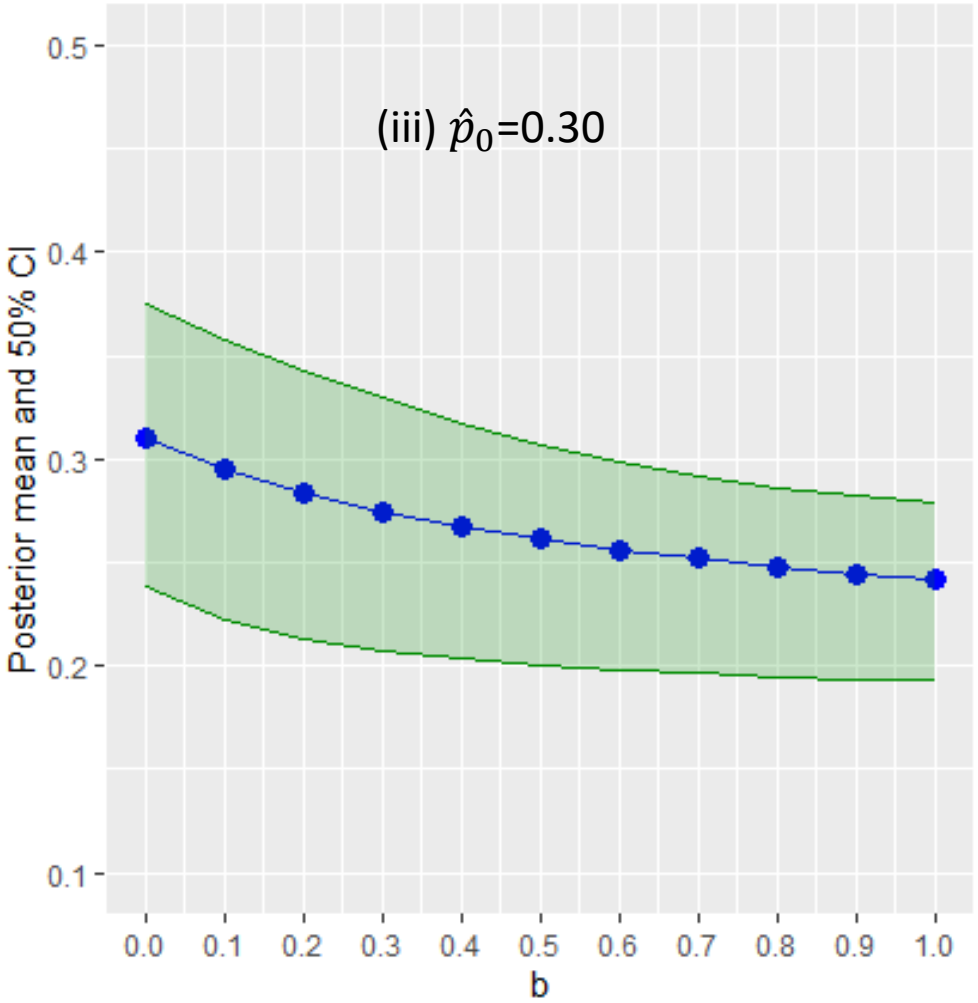


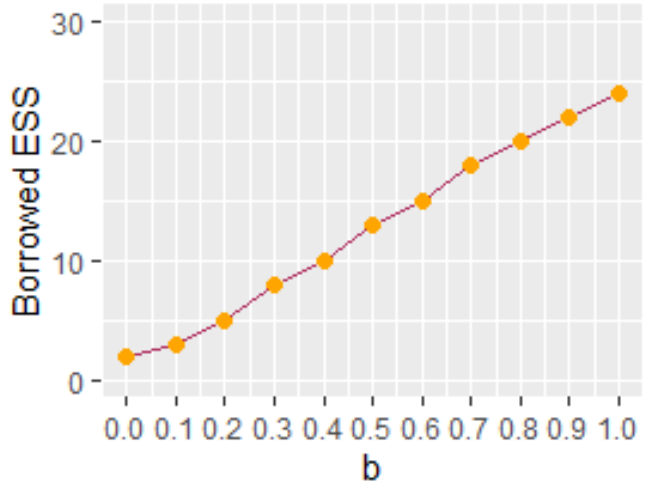


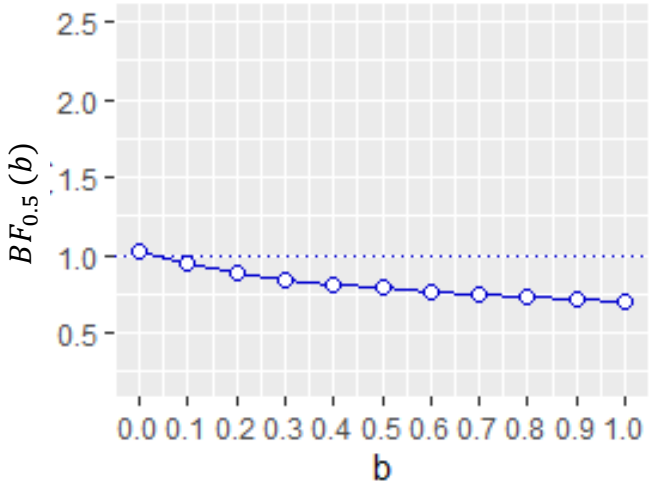
When observed rate in the current study (25%) is *somewhat similar* to the overall rate, we see BF(b) still increasing with b but at a much slower rate; whereas the ESS borrowed were similar to previous case.

n0 = 20, historical data: 10/60, 12/60

Observed rate is different from historical rates



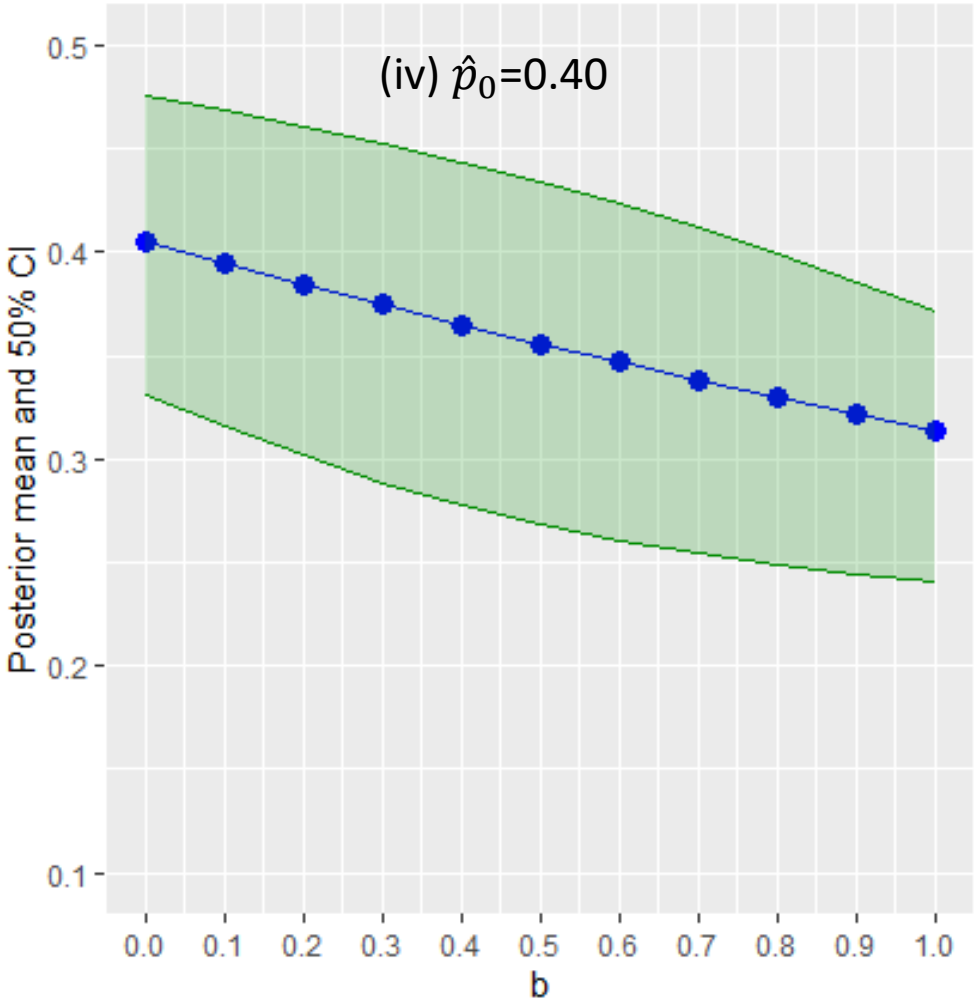


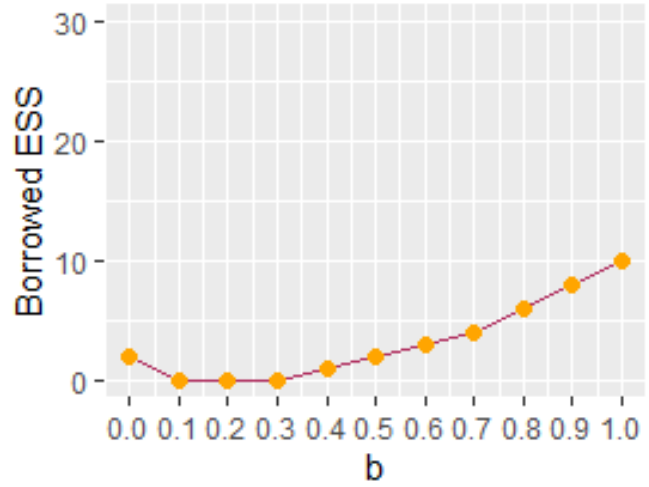


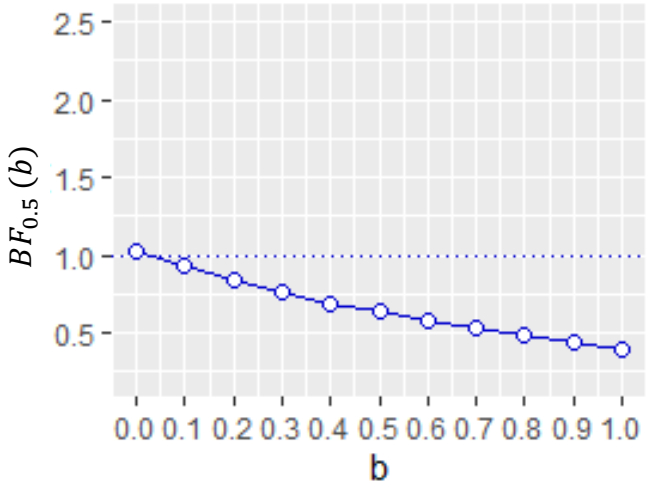
When observed rate in the current study (30%) is *different from* the overall rate, we see $BF(b) < 1$ and decreasing with $b > 0$. However, the ESS borrowed were still increasing considerably.

n0 = 20, historical data: 10/60, 12/60

Observed rate is very different from historical rates



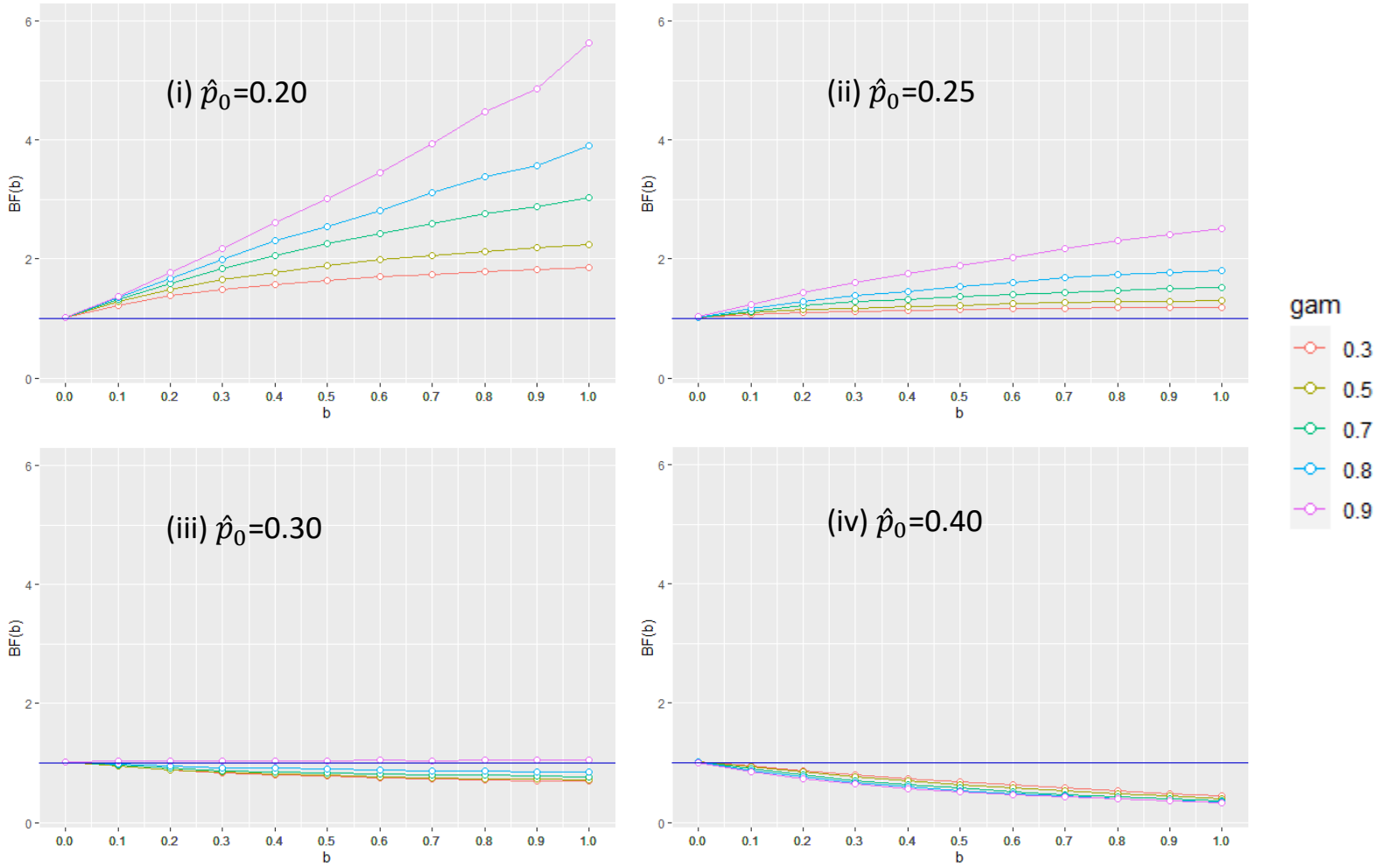




When observed rate in the current study (40%) is very *different from* the overall rate, we see $BF(b) < 1$ is decreasing with $b > 0$ at a higher rate. We also see the ESS borrowed have diminished considerably suggesting the HBM model was able to discount almost all information from the historical data

n0 = 20, historical data: 10/60, 12/60

Choosing γ



We do not want A to be too wide (for example, with γ=0.9) as this would emphasize more on CI width than the drift in location

Similarly, a very small value, say γ=0.3, would be too sensitive to minor drift in location which may be explained as adjustment to address between trial heterogeneity

We propose using $\gamma = 0.5$ as a reasonable choice

n0 = 20, historical data: 10/60, 12/60

Summary and Discussion

- Proposed a Bayes factor like measure to assess the synergy between current and historical data
  - This is not a Bayes factor in the traditional sense
  - Here, an inference (credible set) is compared under different models to see whether a specific amount of borrowing would increase precision to the current data with respect to no borrowing

- The measure is agnostic to underlying Bayes model
  - For example, it can be used to calibrate the power parameter in power prior model

- This measure, together with ESS, can assess the overall synergy and extent of borrowing
  - Gives a critical understanding of potential benefits and impact of borrowing *at the design stage*
  - Thus, a prospective planning with this framework can help to justify a specific amount of borrowing based on observed data to properly interpret the results *at the time of actual analysis and inference*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