

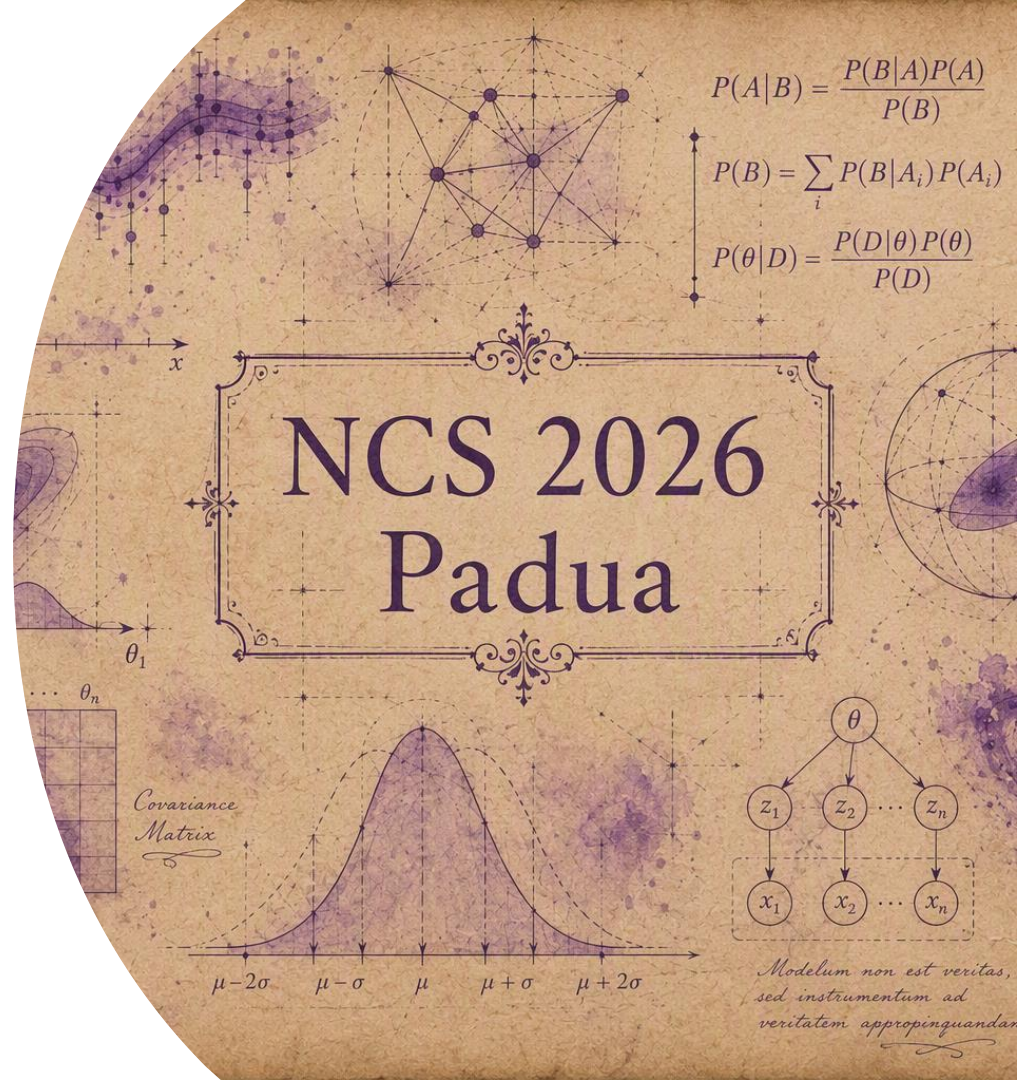


Dynamic Borrowing for Virtual Control Groups

Adapting Robust Meta-Analytic Priors to Reduce Control Size and Enhance Precision

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Virtual Control Group

Idea: Replacing the Concurrent Control Group (CCG), completely or partly, with a Virtual Control Group (VCG) generated from historical control data.

Following the 3R principle

– Replacement, Reduction, Refinement to minimize animal use in research.

Two major challenges arise:

- Between-study **heterogeneity** within historical data: Simple replacement is often not possible.
- Historical data **sparsity**: The number of historical studies is limited, and some variables are partially or completely missing.

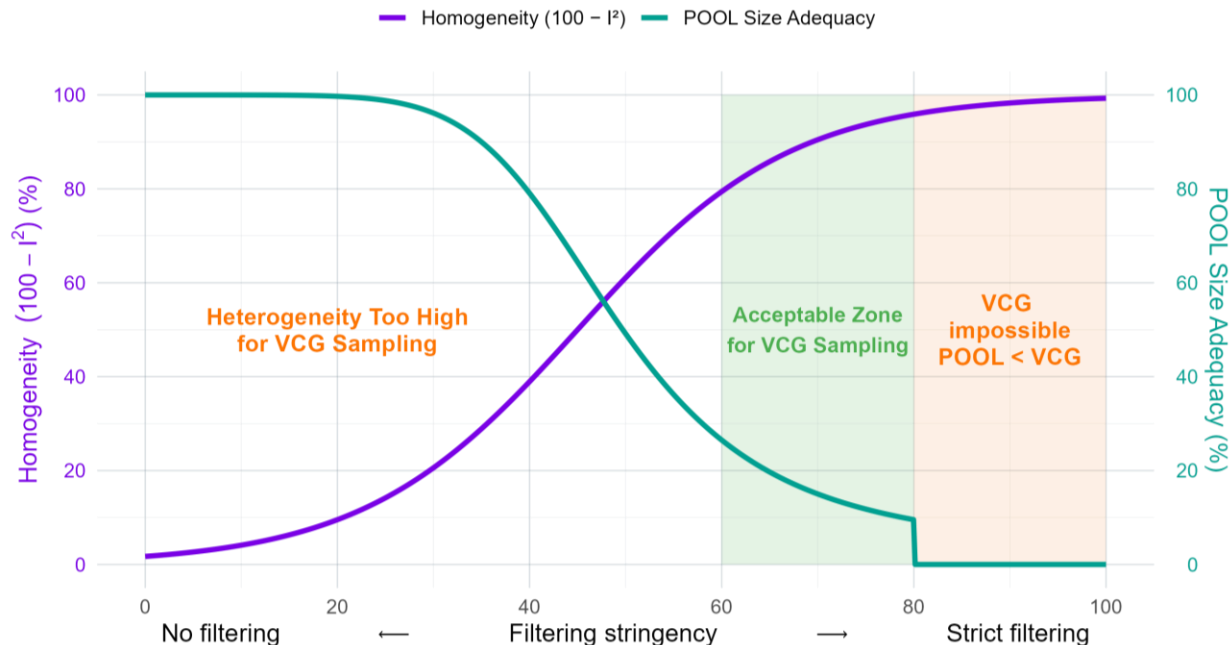
In this presentation, we propose a potential solution to address these challenges.

This work is part of the VICT3R consortium.



Trade-Off Between Homogeneity and Pool Size

A common solution for heterogeneity (I^2) is filtering the historical data to obtain a **POOL** of feasible, homogeneous historical studies (and sampling the VCG from this pool). However, reducing the POOL size decreases the likelihood of maintaining adequate pool size for VCG sampling.



If an acceptable balance can be achieved, my *eVCGsampler* R package can be used.



VCG Sampling Using Energy-Based Covariate Balancing
[CRAN: Package eVCGsampler](#)

Proposed Approach

We propose a unified solution to address both heterogeneity and sparsity challenges.

The **Meta-Analytic-Predictive (MAP)** method is a Bayesian approach that synthesizes evidence from multiple historical studies to generate a predictive prior for future studies.

A key advantage of the MAP framework is its capacity to account for between-study **heterogeneity** via a random-effects model. By explicitly modeling variability across studies, the resulting prior appropriately captures uncertainty.

Additionally, direct modeling of outcome variables eliminates the need for baseline covariates and auxiliary information, effectively mitigating data **sparsity** issues, strongly reduces the impact of missing values.

MAP is implemented in **RBeST** R package.

Weber S, Li Y, Seaman JW, Kakizume T, Schmidli H (2021). "Applying Meta-Analytic-Predictive Priors with the R Bayesian Evidence Synthesis Tools." *Journal of Statistical Software*, **100**(19), 1–32.

Mixture Prior

rMAP mixture Prior:

$$\text{rMAP} = (1 - w) \cdot \text{MAP} + w \cdot \text{vague}$$

Robustness weight

Historical studies

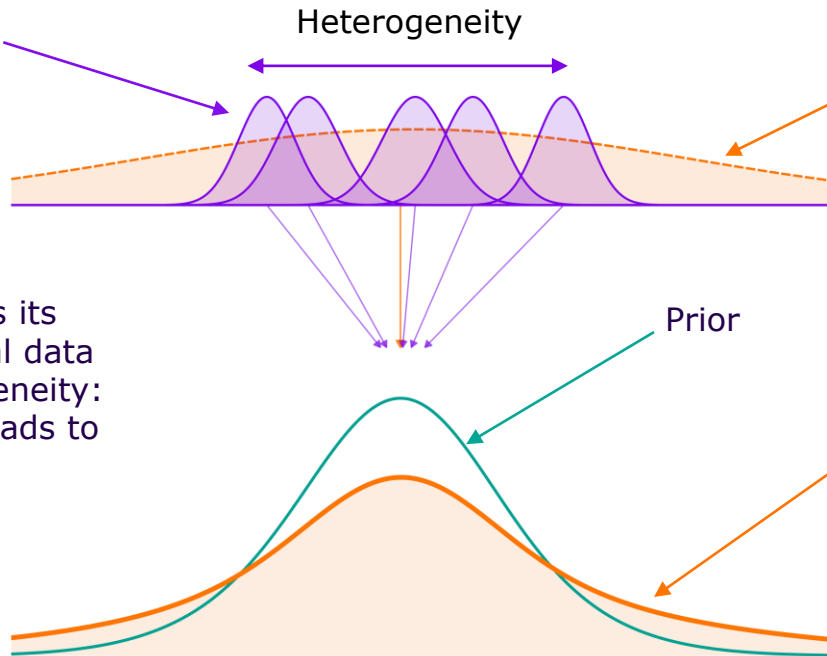
Heterogeneity

Non-informative (vague)
component for robustness

MAP dynamically adjusts its borrowing from historical data based on study heterogeneity: greater heterogeneity leads to less borrowing.

Prior

Robust Prior



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Simulation study

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Evaluating the performance in a real-setting

Simulation study using real historical data

- Randomly select one historical study control group and partition it into two groups to represent the treatment group (TG) and the corresponding control arm (CCG).
- Apply the rMAP method to borrow information from the remaining historical studies.
- Assess the performance in a realistic setting.

Data used:

- 3 Strains by sex (mice and rats - )
- 42 different outcome variables
- Number of possible unique combinations ~ 15000
- 1000 Monte Carlo simulations for each scenario

Median heterogeneity $I^2 = 88\%$

Median study size (min - max) = **5 (3 - 128)**

Median number of studies per outcome (min - max) = **7 (3 - 17)**



Thanks!

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Co-funded by
the European Union

This project is supported by the Innovative Health Initiative Joint Undertaking (IHI JU) under grant agreement No 101172693.

The JU receives support from the European Union's Horizon Europe research and innovation programme and COCIR, EFPIA, Europa Bio, MedTech Europe, and Vaccines Europe and Instem Scientific Limited.

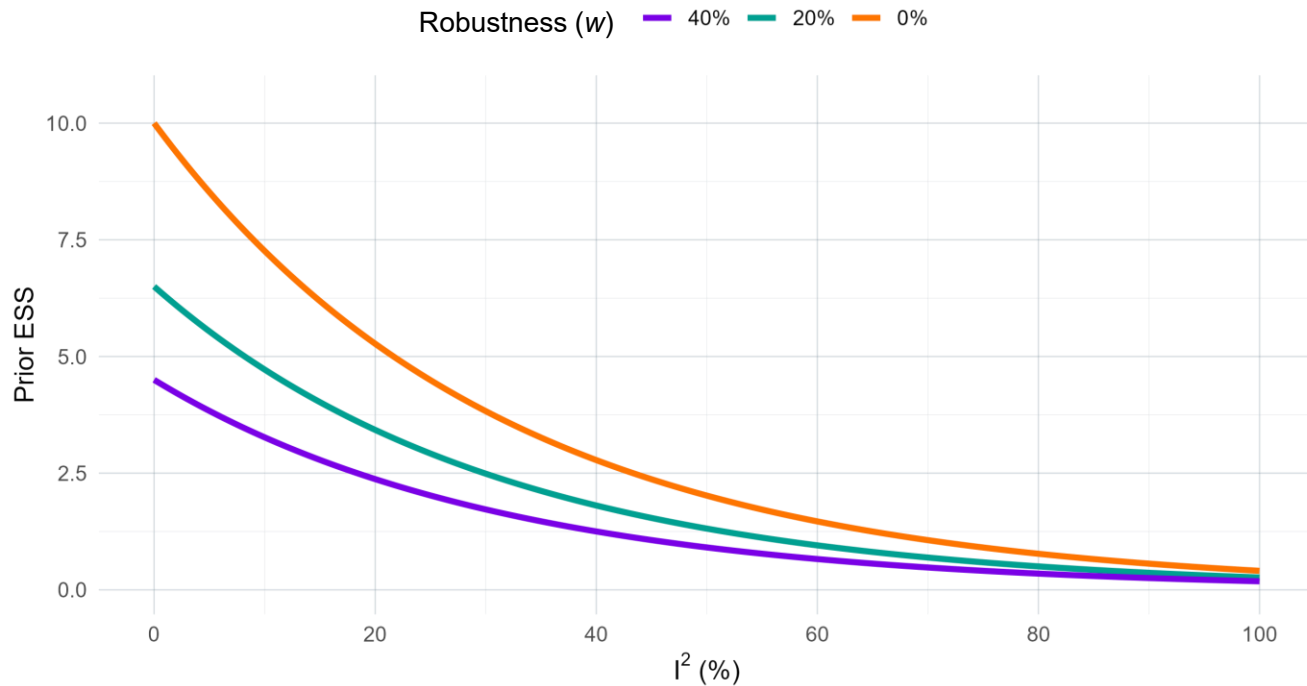
Funded by the European Union, the private members, and those contributing partners of the IHI JU. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the aforementioned parties.

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Proof of simulation concept

Prior Effective Sample Size (ESS) and observed heterogeneity represented as I^2



Robustification ✓

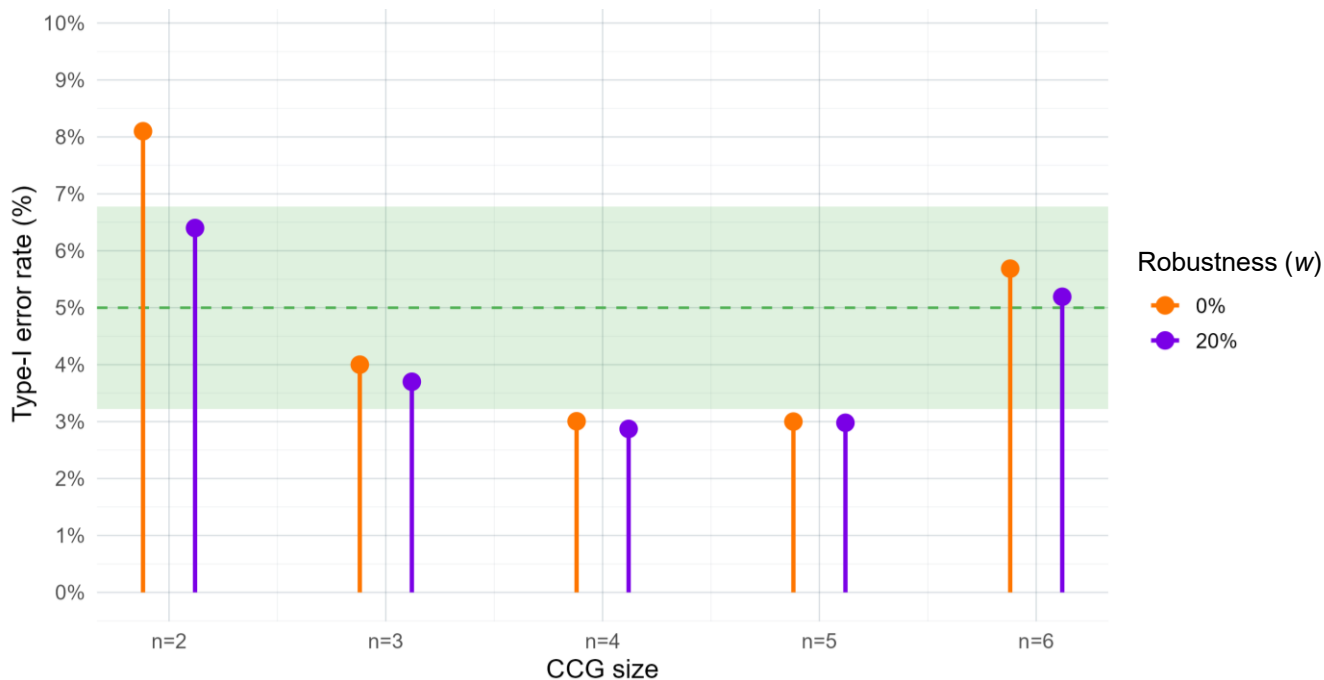
Heterogeneity ✓

Type-I error rate (false positives)

Proof that the method effectively guards against possible bias.

Proportion of 95% Credible Intervals that include 0 (no effect).

As CCG and TG are coming from the same historical study group → no effect is expected





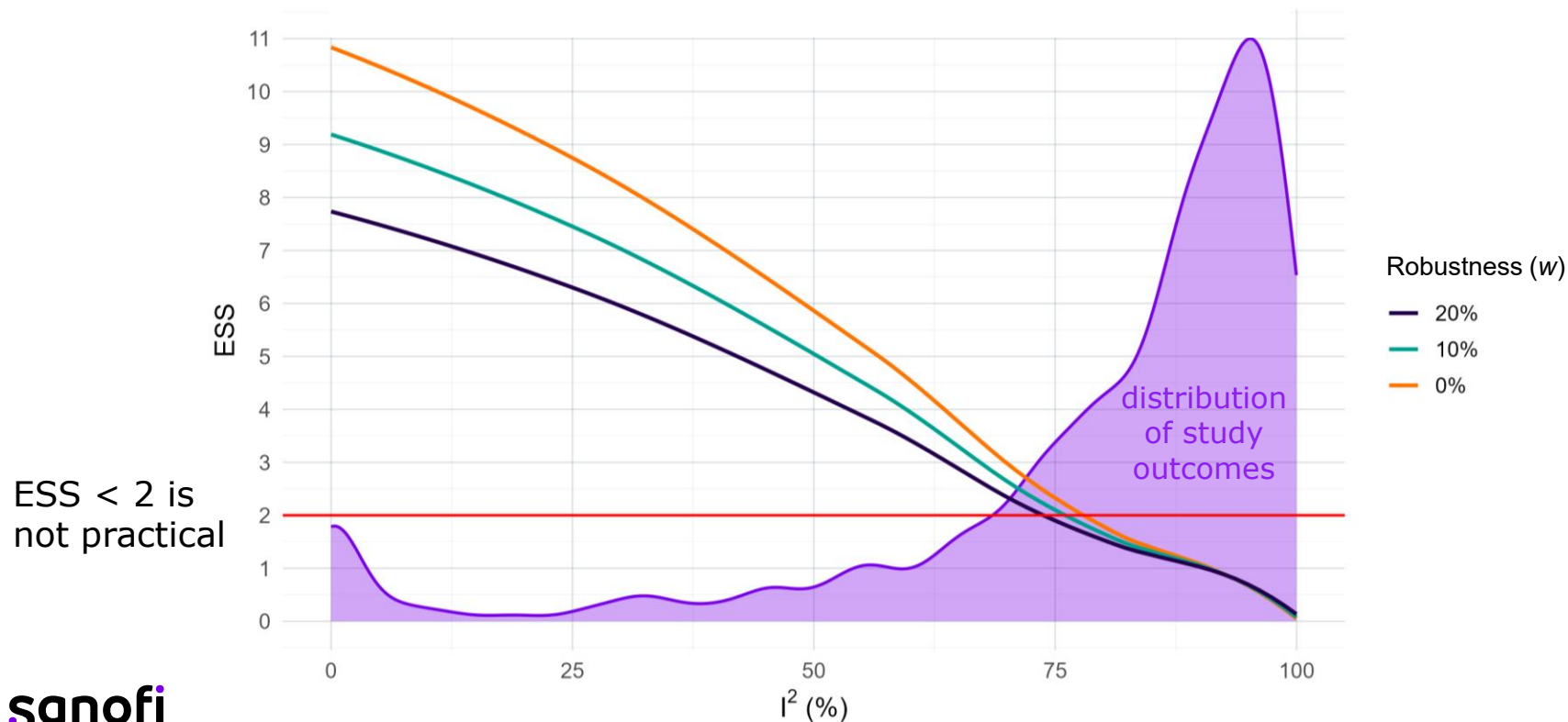
Results



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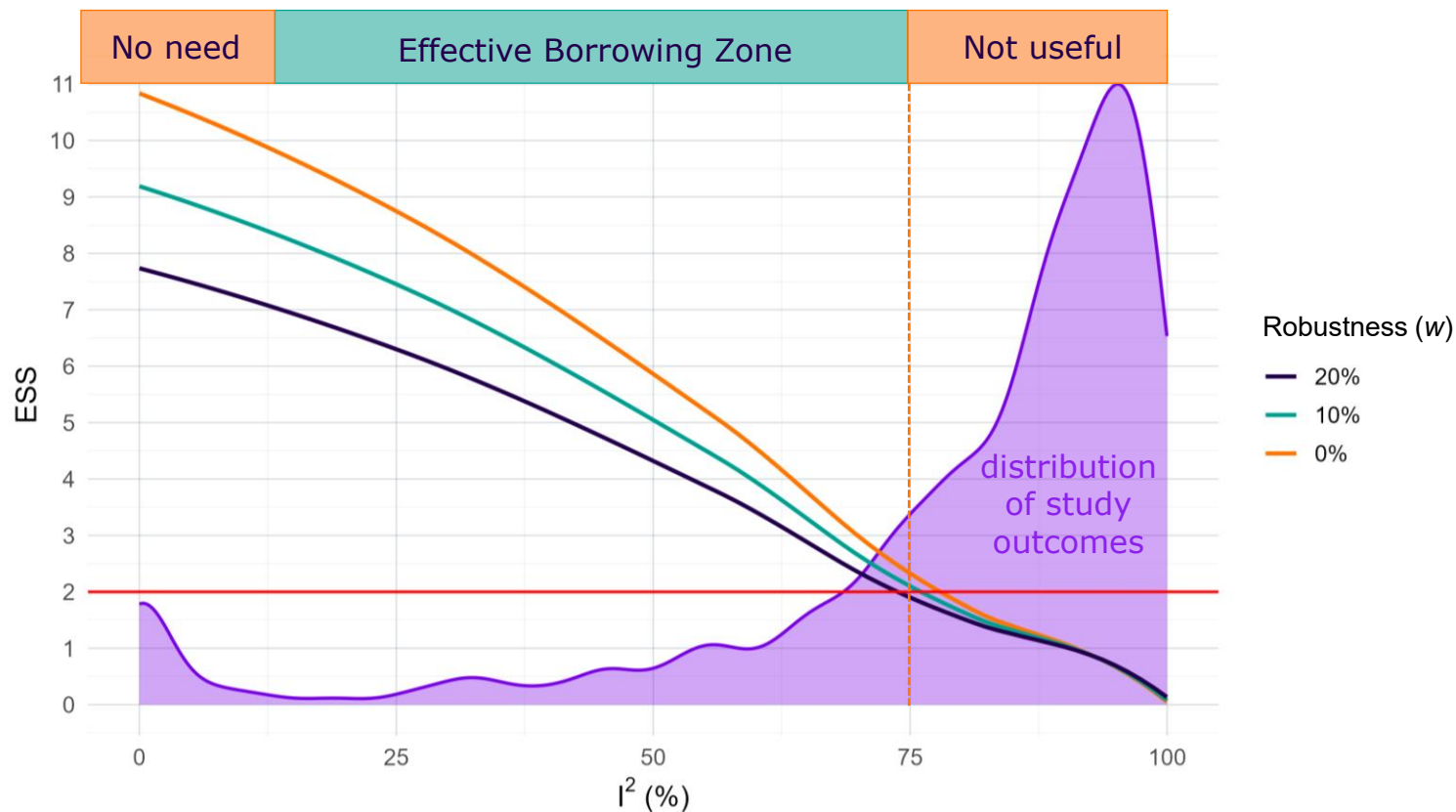
Simulation study results

Between-Study Heterogeneity vs Effective Sample Size



Simulation study results

Between-Study Heterogeneity vs Effective Sample Size



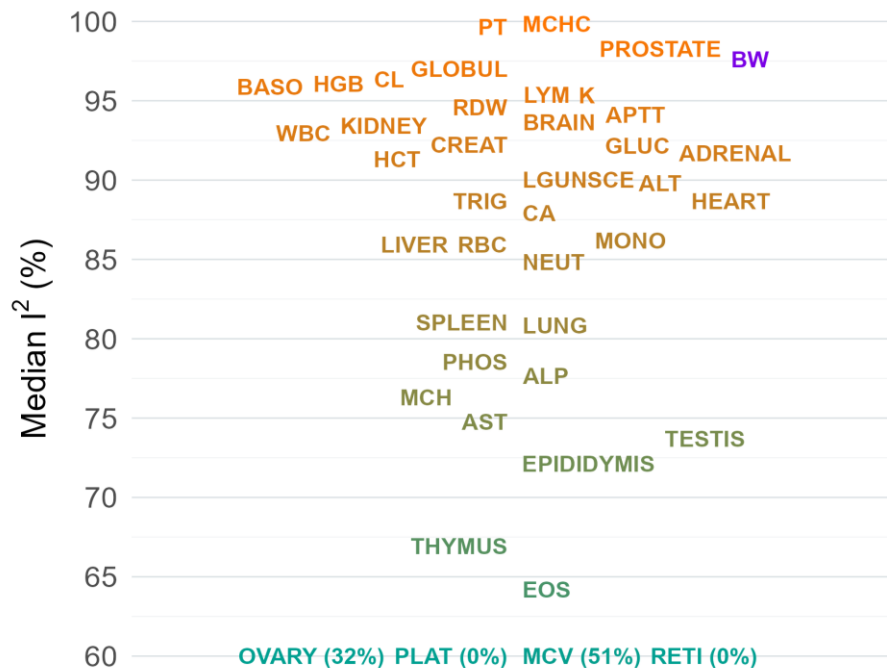
Simulation study results

Even body weight (BW) shows considerable heterogeneity.

Keep in mind that the pre-filtering of historical data was intentionally kept simple to represent a worst-case scenario in the simulation.

While more stringent filtering could reduce the initial heterogeneity to some extent, this quickly leads to a trade-off between reducing heterogeneity and maintaining an adequate pool size.

Between-Study Heterogeneity per outcome





Conclusion



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Conclusion

Overall, the simulation study has demonstrated the applicability of the proposed method in real setting.

However, heterogeneity must be reduced beforehand for the approach to be truly applicable.

Key Properties:

- Accounts for study heterogeneity naturally
- Addresses sparse historical data challenges
- Provides robust protection against bias
- Works effectively with real historical data
- Retains all Bayesian method advantages

Limitations:

- Pre-filtering or other methods to reduce heterogeneity remain necessary
- May not be applicable or practical in all settings
- Requires considerable extra analysis effort per outcome
- Small CCG requirement ($n=3$) limits reduction potential
- Cannot capture individual virtual animal characteristics, rare events, or histology findings

Ideas for Next Steps

Next Steps:

- Investigate covariate-adjusted meta-regression as a strategy to reduce heterogeneity.
- Integrate Elastic Prior methodology for better type I error control, accounting for agreement between VCG and CCG (e.g. SAM: Self-Adapting Mixture Prior).
- Perform large-scale simulations with synthetic data.
- Create an accessible implementation pipeline for wider use (R-Package?).

Thank you!

Questions?

