Basket and Umbrella Trial Design In Pediatric Chronic Inflammatory Airway Disease

Mohd Rashid Khan
PhD Student at University of Padova, Italy

Background

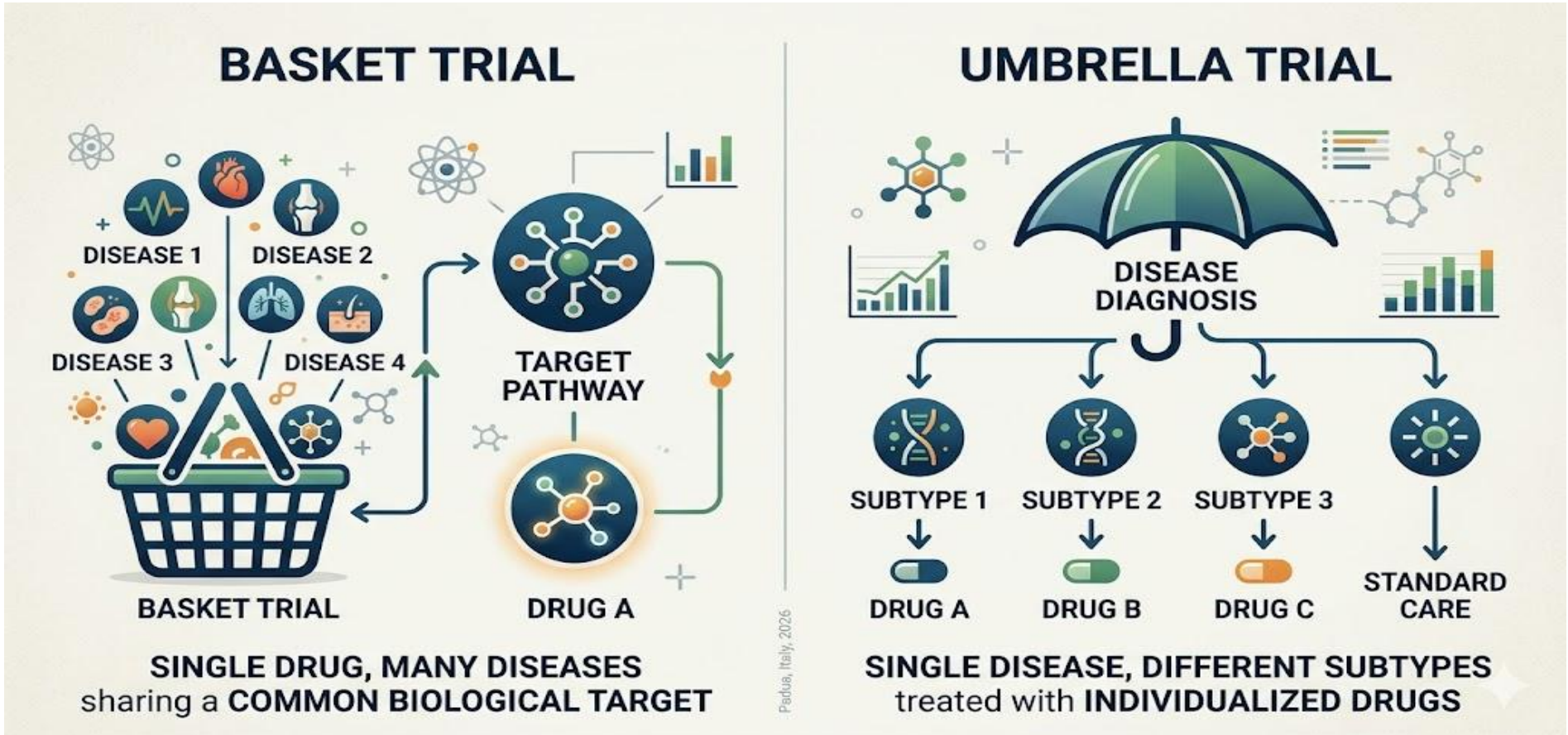
Pediatric chronic inflammatory airway disease is biologically heterogeneous despite similar clinical symptoms.

Nasal cytokine profiling routinely reveals five endotypes: eosinophilic, IL-5–high, IL-13–high, mixed, and pauci-inflammatory, each associated with differential response to targeted therapies with biologics.

Traditional RCTs would require massive, multi-center recruitment over many years for rare endotypes (e.g., prevalence <5%), which is often logistically impossible in pediatrics.

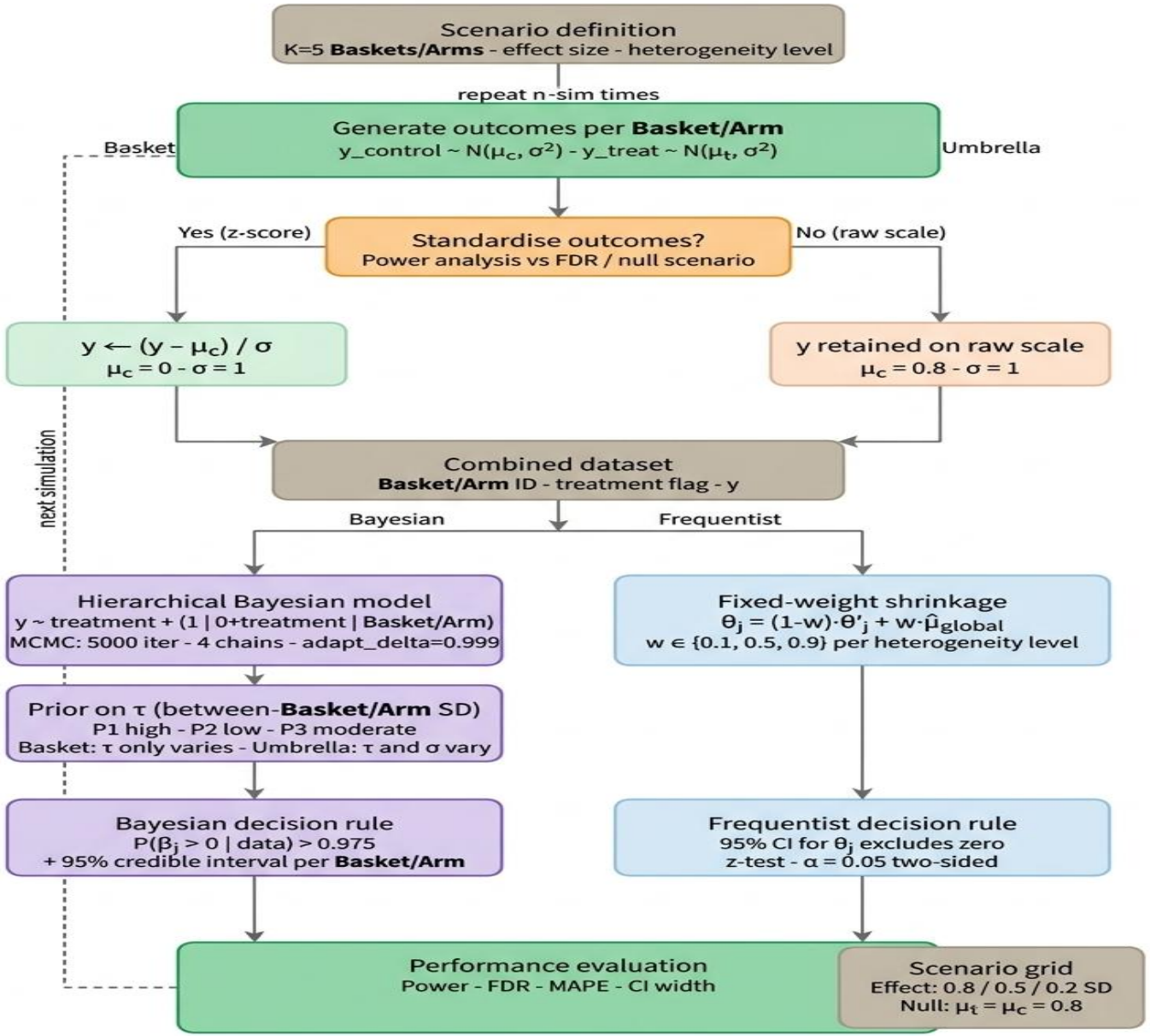
Given the requirement of targeted therapies matched to specific cytokine endotypes, a Bayesian basket-and-umbrella framework seems to be more appropriate choice

Basket and Umbrella Trial



Basically, it is for treating the mechanism, not the diagnosis.	It is more suitable to develop personalised treatment for complex conditions

Simulation Workflow



Data Generation Mechanism

	Basket Trial	Umbrella Trial
Unit	5 Basket	5 Arms
Sample size	(17-23)	(17-23)
Outcome	$y_0 \sim N(c,\sigma^2)$, $y_1 \sim N(\mu_{treat},\sigma^2)$ With $\mu_{control}=0$, and $\sigma=1$ throughout	$y_0 \sim N(\mu_{control},\sigma^2)$, $y_1 \sim N(\mu_{treat},\sigma^2)$ With $\mu_{control}=0$, and $\sigma=1$ throughout
Effect sizes	(0.8, 0.5, 0.2)	(0.8, 0.5, 0.2)
Heterogeneity level	P1 (0.23), P2 (0.19), P3 (0.15)	P1 (0.23), P2 (0.19), P3 (0.15)
Replication (n_sim)	2000	2000

5000 iter, 4 chains
adapt_delta=0.999, treedepth=18

Model Specifications

Basket Trial

$$\mu_{ij} = \alpha + b_{0j} + (\beta + b_{1j}) \cdot basket_{1j}$$

- α: global intercept
- β: global treatment effect
- b_{0j}: basket-specific intercept
- b_{1j}: basket-specific treatment effect

$$\begin{pmatrix} b_{0j} \\ b_{1j} \end{pmatrix} \sim \mathcal{N}(0, \Sigma)$$

Σ contains the whithin-basket heterogeneity variances, including:

$$\tau^2_{basket_{1j}}$$

Basket-specific treatment effect:

$$\text{eff}_{j_j} = \beta + b_{1j}$$

Decision Rule:

$$\boldsymbol{P(\text{eff}_j > 0) > 0.975}$$

Umbrella Trial

$$\mu_{ij} = \alpha + a_{0j} + (\beta + a_{1j}) \cdot treatment_{ij}$$

- α: global intercept
- β: global treatment effect
- a_{0j} :arm-specific intercept
- a_{1j} :arm-specific treatment effect

Random effects:

$$\begin{pmatrix} a_{0j} \\ a_{1j} \end{pmatrix} \sim \mathcal{N}(0, \Sigma)$$

where Σ contains the treatment heterogeneity variances, including:

$$\tau^2_{treatment_{ij}}$$

Arm-specific treatment effect:

$$\text{eff}_j = \beta + a_{1j}$$

Decision Rule:

$$\boldsymbol{P(eff_j > 0) > 0.975}$$

Priors Specifications

Parameter	Basket Trial	Umbrella Trial	Reasoning
Global intercept	$\alpha \sim t_3(0,10)$	$\alpha \sim t_3(0, s_\alpha), s_\alpha \in \{10,2,5\}$	Weakly informative baseline prior; umbrella varies by heterogeneity scenario
Global treatment effect	$\beta \sim \mathcal{N}(0,1)$ or $\mathcal{N}(0,1.5)$	$\beta \sim \mathcal{N}(0,1)$	Weakly informative treatment prior centered at no effect
Betweenbasket/arm SD	$\tau \sim t_5(0, s_\tau)$, $s_\tau \in \{0.6, 0.25, 0.4\}$	$\tau \sim$ Cauchy $(0, s_\tau)$, $s_\tau \in \{0.32, 0.4\}$	Controls adaptive borrowing and heterogeneity
Residual SD	$\sigma \sim$ Cauchy $(0,0.5)$	$\sigma \sim$ Cauchy $(0, s_\sigma)$ $s_\sigma \in \{0.1, 1.2, 0.6\}$	Models residual uncertainty and variability
Random effects	$(b_{0j}, b_{1j}) \sim \mathcal{N}(0, \Sigma)$	$(a_{0j}, a_{1j}) \sim \mathcal{N}(0, \Sigma)$	Partial pooling hierarchical structure

Frequentist Shrinkage estimator

- **Basket/Arm-Specific Effect Estimate**

$$\hat{\theta}_j = \bar{y}_{treat,j} - \bar{y}_{control,j}$$

- **Global Pooled Estimate**

$$\hat{\mu}_{global} = \frac{\sum_{j=1}^{J} \hat{\theta}_j / SE_j^2}{\sum_{j=1}^{J} 1/SE_j^2}$$

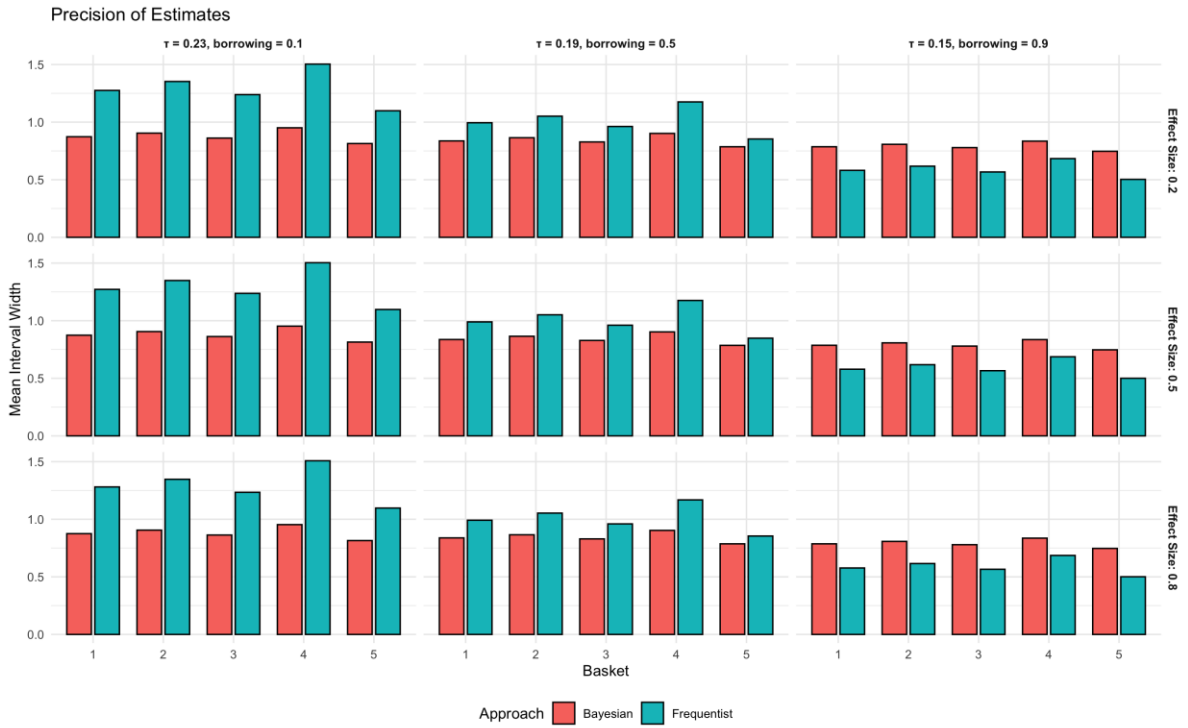
- **Shrinkage Estimator**
- $\tilde{\theta}_j = (1 - w)\hat{\theta}_j + w\hat{\mu}_{global}$
- $w \to 0$: low borrowing / high heterogeneity
- $w \to 1$: strong borrowing / low heterogeneity

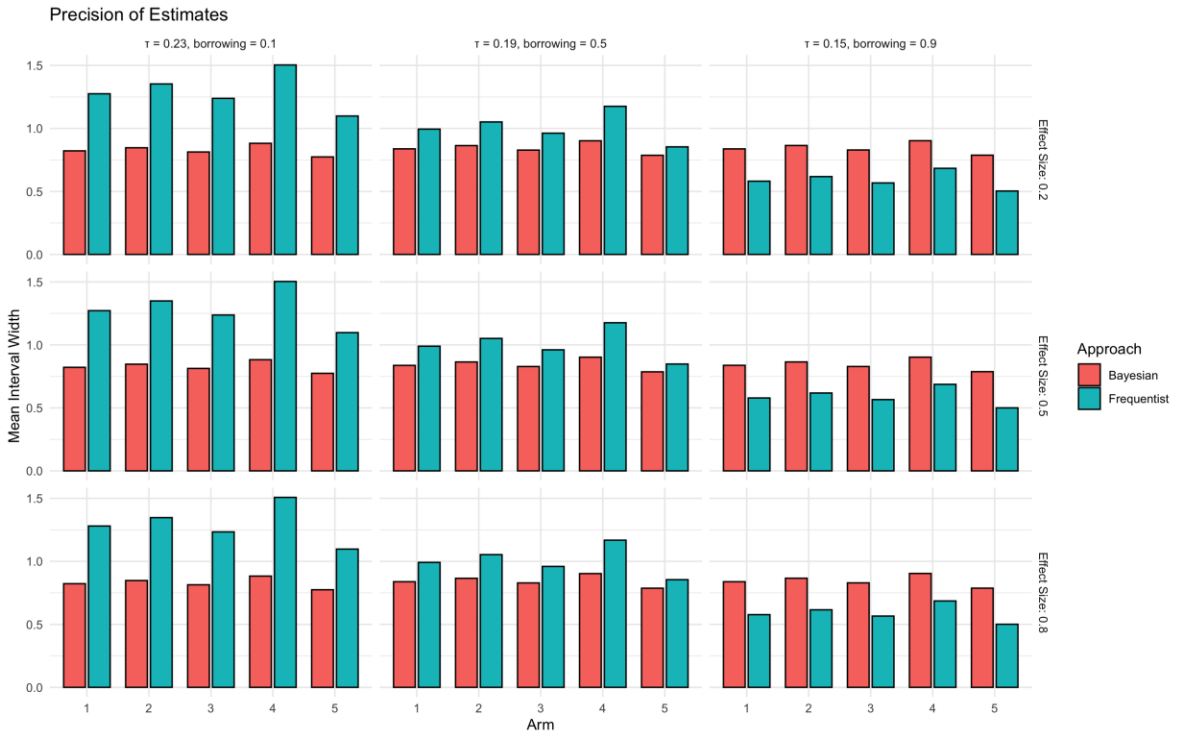
Decision Rule

- $CI_{95\%}(\tilde{\theta}_j) \ni 0$

Frequentist	Bayesian Hierarchical Model
Shrinkage weight (w) is externally specified or estimated separately	Borrowing is estimated directly from the posterior distribution
Produces a single shrinkage estimate	Produces a full posterior distribution for each basket/arm
Uncertainty in heterogeneity is not fully propagated	Heterogeneity uncertainty is fully integrated into inference
Borrowing is relatively rigid	Borrowing is adaptive and data-driven
Greater risk of over-shrinkage under high heterogeneity	Automatically reduces borrowing when heterogeneity increases
Inference based on confidence intervals	Inference based on posterior probabilities
Computationally simpler	Computationally more intensive (MCMC/posterior sampling)

Results –CI width

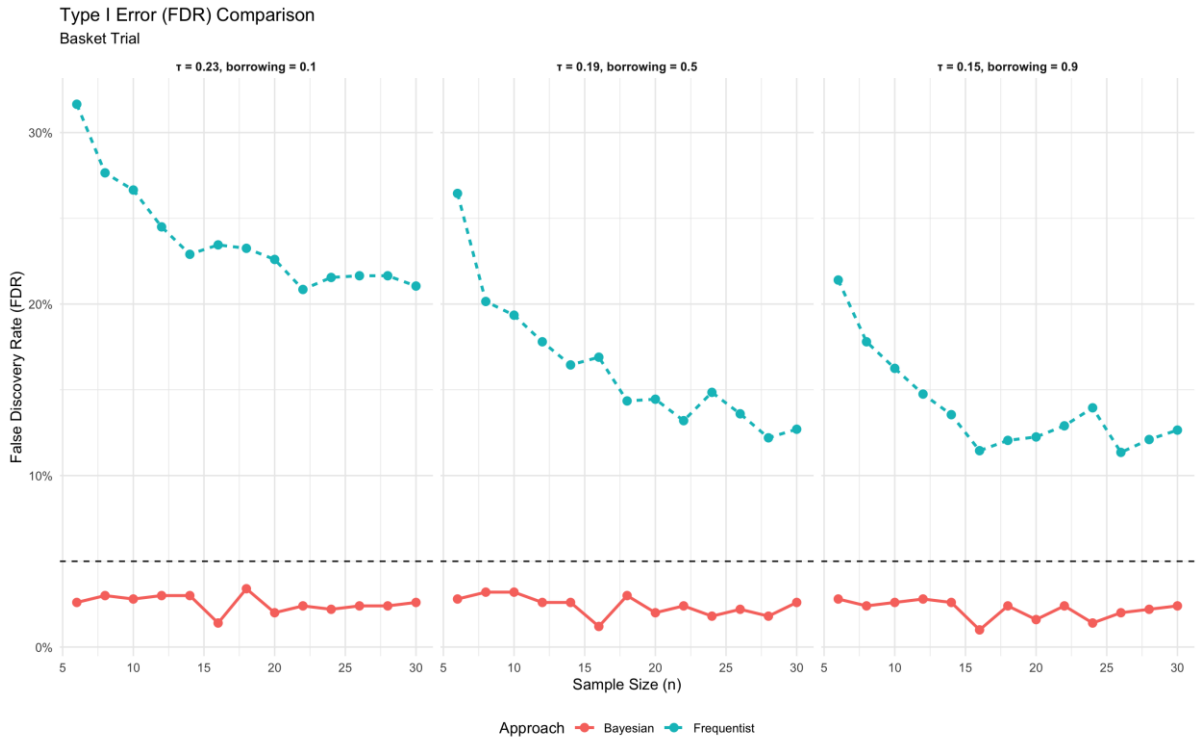


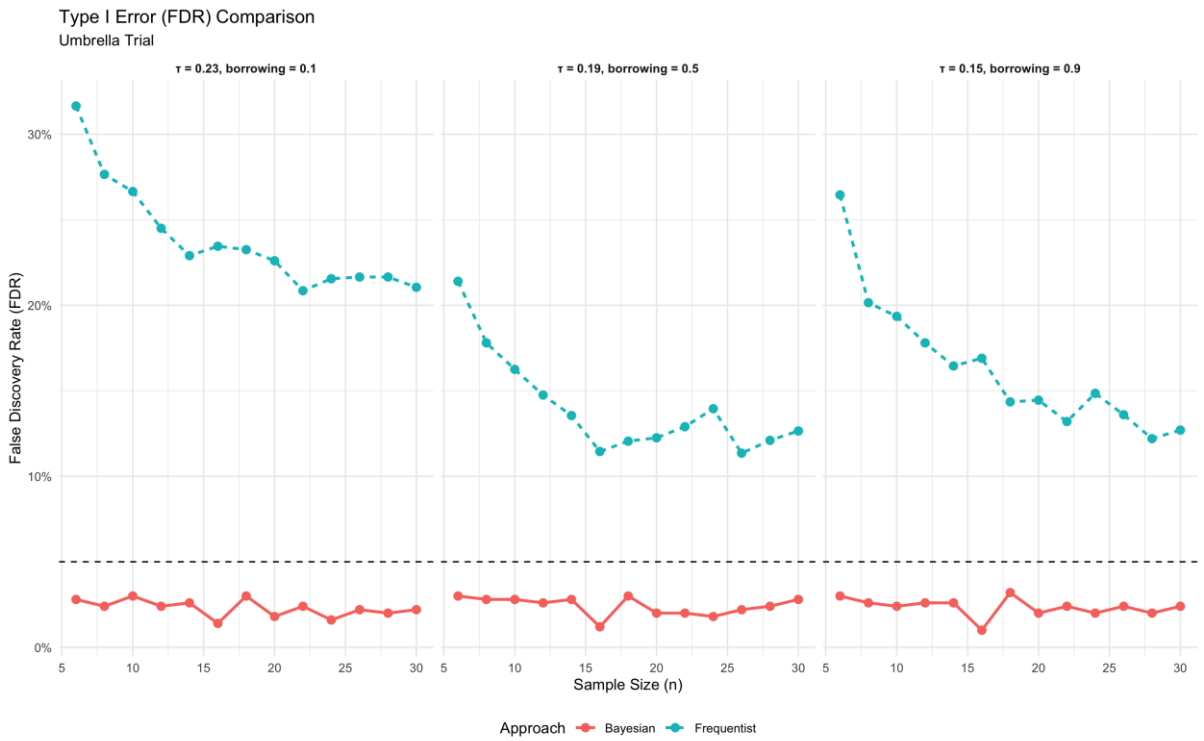


Basket

Umbrella

Results –FDR

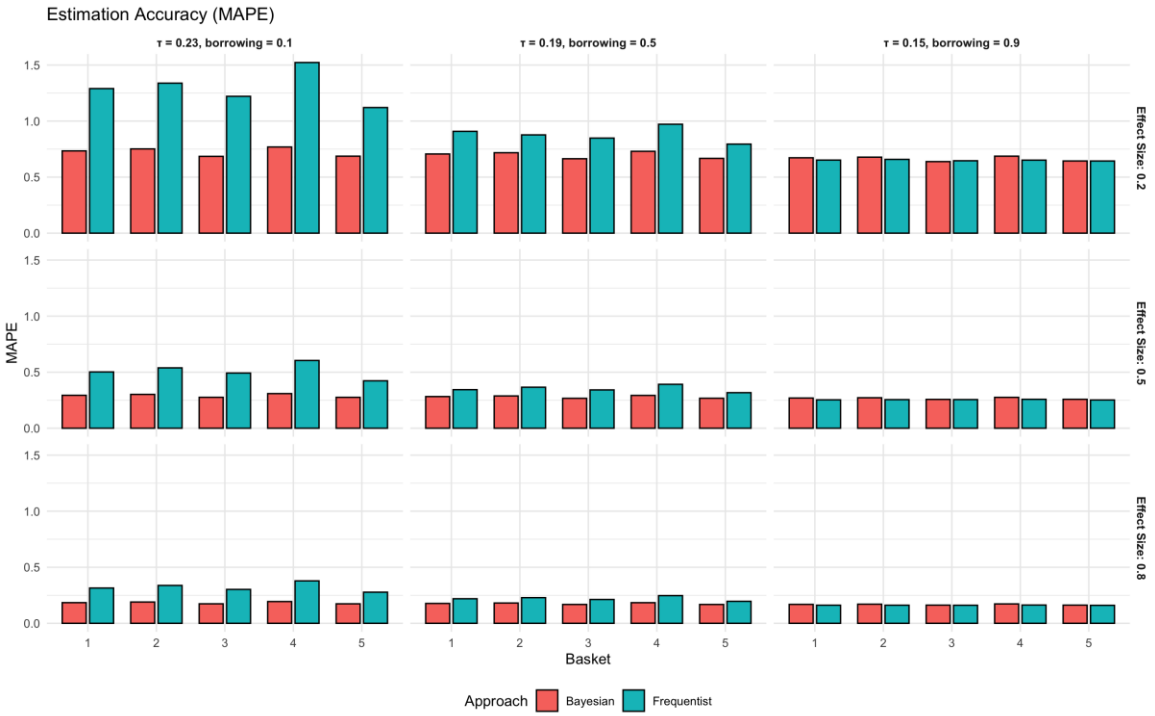




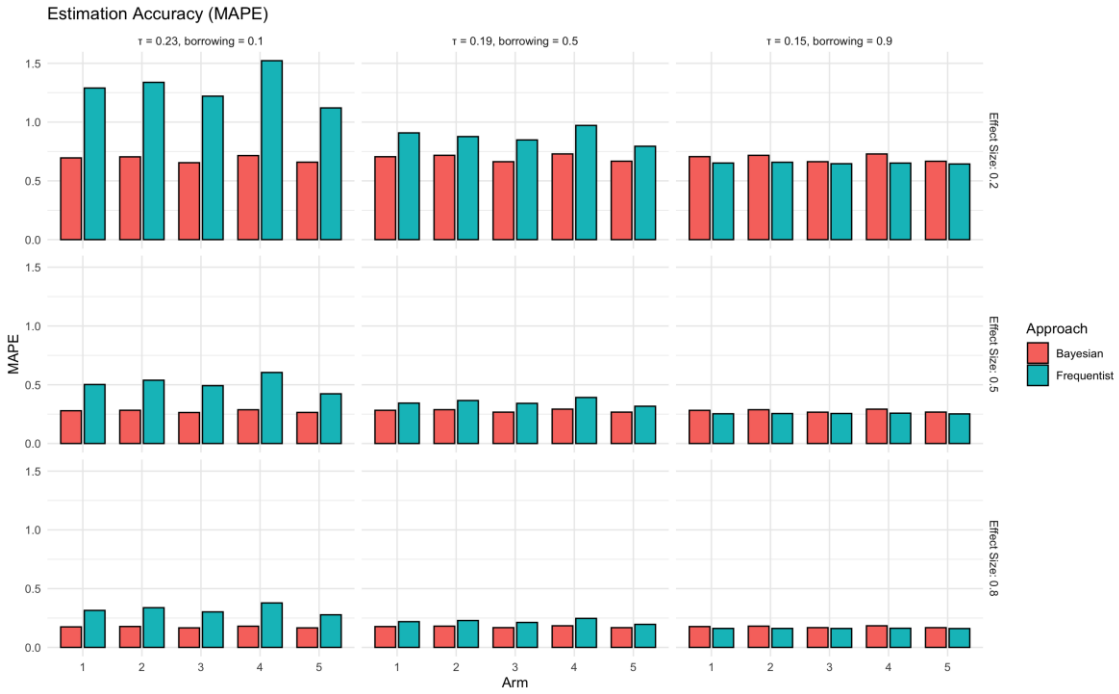
Basket

Umbrella

Results –MAPE

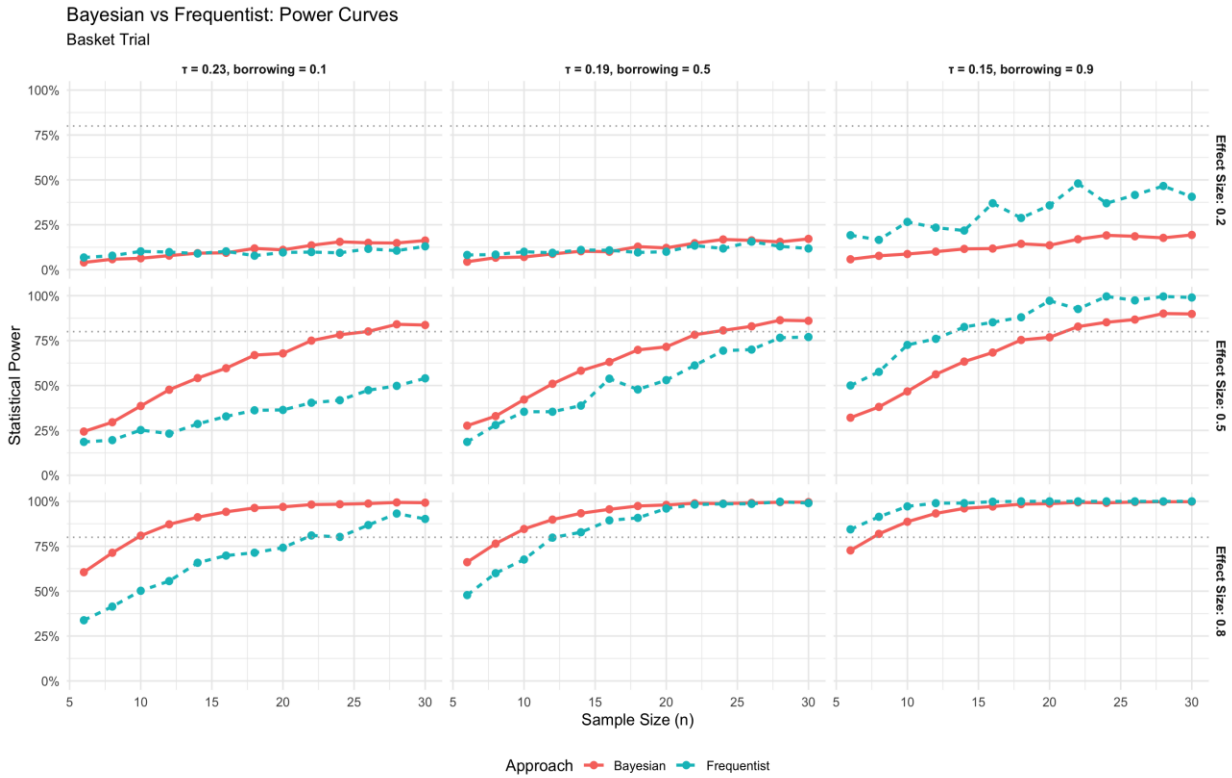


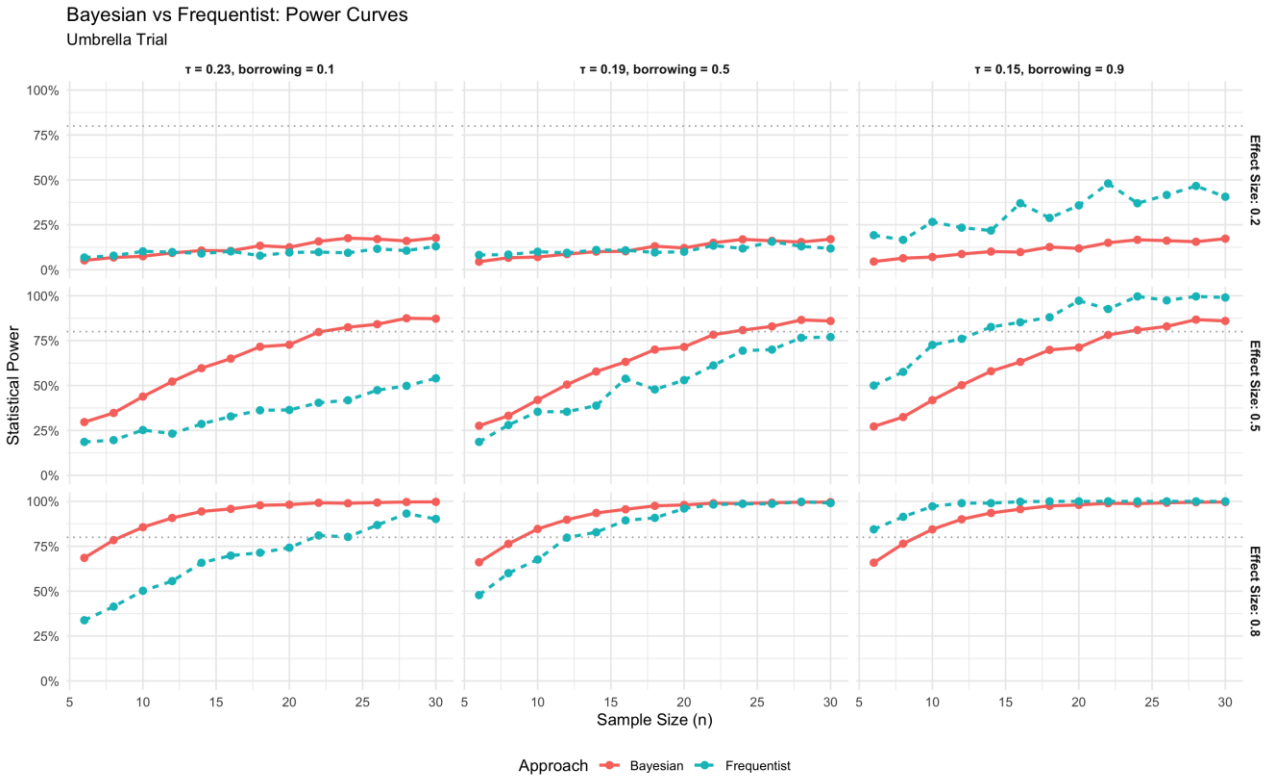
Basket



Umbrella

Results –Power





Basket

Umbrella

Findings

Bayesian hierarchical models showed more stable performance across basket and umbrella settings.

The heterogeneity parameter was the key mechanism controlling adaptive information borrowing.

In basket trials, stronger biological similarity improved borrowing, precision, and power.

In umbrella trials, greater treatment heterogeneity reduced borrowing, increasing uncertainty but limiting over-shrinkage.

Bayesian models maintained low FDR and better estimation accuracy, especially in small and heterogeneous pediatric populations.

Results highlight the importance of modeling heterogeneity explicitly.

Thanks to

Co-authors

- Angelo Capasso
- Mariateresa Russo
- Domenico Iervolino
- Pasquale Dolce
- Danila Azzolina

Affiliations

Thank you for the attention!

