Using historical data to inform extrapolation decisions in children

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Motivation

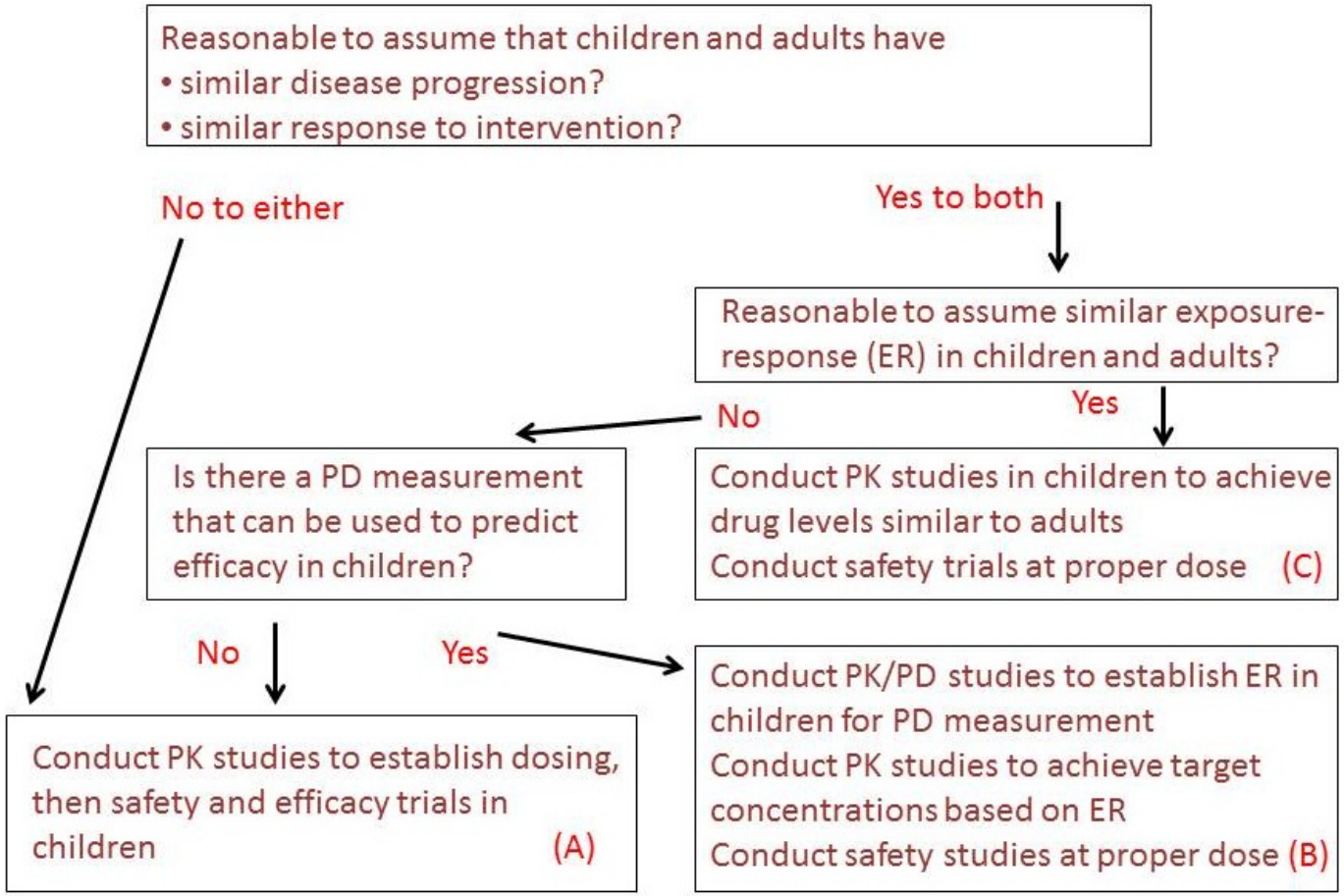
European Medicines Agency defines extrapolation as

'Extending information and conclusions available from studies in one or more subgroups of the patient population (source population) . . . to make inferences for another subgroup of the population (target population) . . . '

Strong assumptions are needed for extrapolations to be biologically plausible.

FDA paediatric decision tree

Source data can augment data from the target population or entirely substitute for it. Uncertainty determines whether extrapolations are 'partial' or 'complete'.



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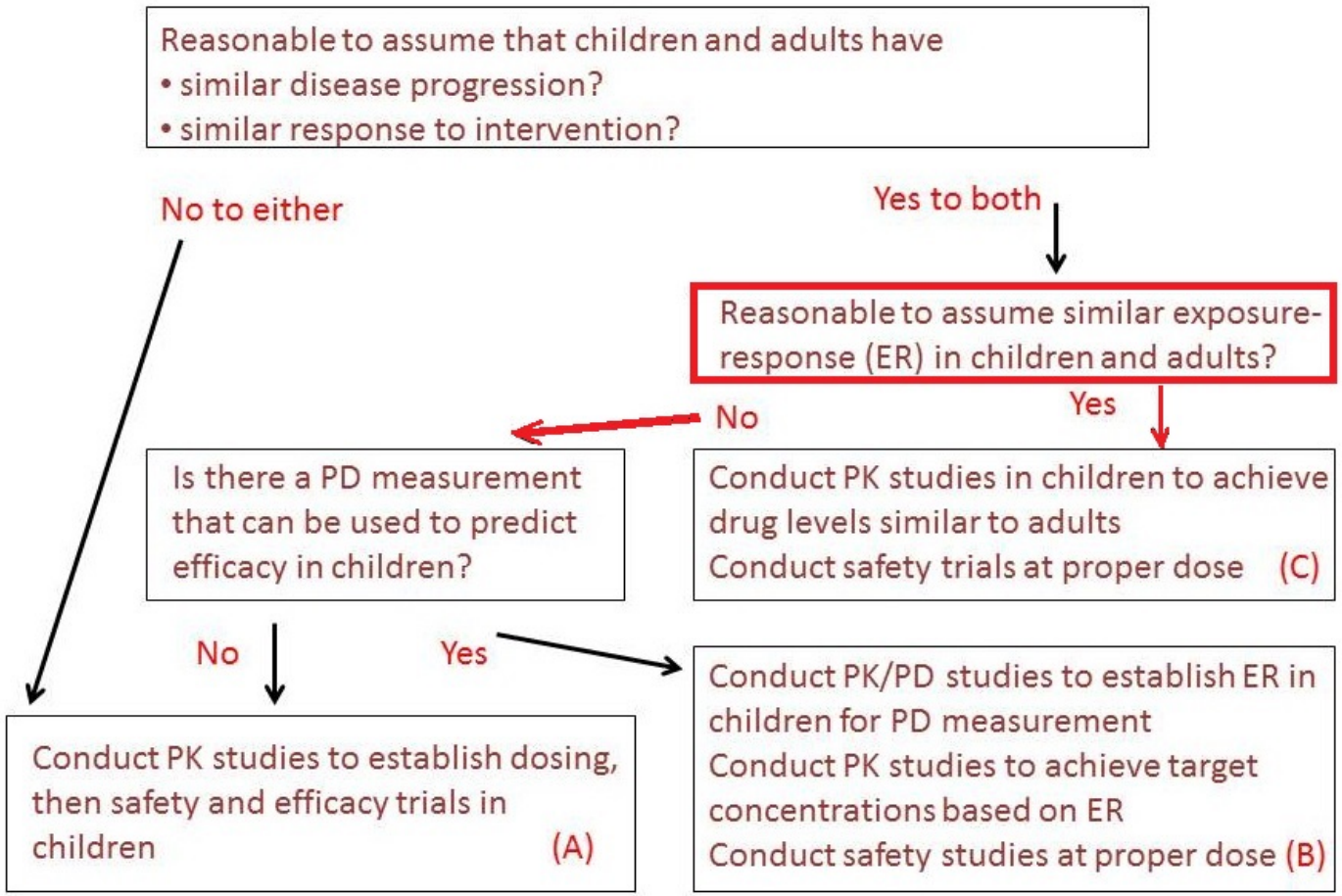

Aims

Existing data: PK-PD data from ≥ 1 study recruiting adults and adolescents.

Assumption: PK-PD relationships in adults and younger children are similar.

Q: How can we use the existing data to quantify our uncertainty about the extrapolation assumption and inform our choice of extrapolation strategy in younger children?

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Q: How can we use the existing data to quantify our uncertainty about the extrapolation assumption and inform our choice of extrapolation strategy in younger children?

1. Perform a meta-analysis of existing data.
2. Elicit opinion on whether differences between PK-PD relationships in adults and adolescents are representative of differences between adults and children.
3. Correct meta-analysis results for elicited biases.
4. Derive probability extrapolation assumption holds.

PK-PD models

Model existing data from J studies of adults and adolescents:

$$\mathbb{E}[y_{ij}] = \gamma_{0j} + \gamma_{Ej}\, E_{ij} + \gamma_{Aj}\, A_{ij} + \gamma_{\mathcal{I}j}\, E_{ij}\, A_{ij}$$

- y_{ij} is outcome for ith patient in jth study
- A is age (0 for adults; 1 for adolescents).

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Model data from future study enrolling adults and younger children:

$$\mathbb{E}[y_{iT}] = \beta_0 + \beta_E E_{iT} + \beta_A A_{iT} + \beta_{\mathcal{I}} E_{iT} A_{iT}$$

- A_{iT} is age (0 for adults; 1 for younger children)
- No difference between PK-PD relationships if $\beta_A = \beta_{\mathcal{I}} = 0$
- Use existing data to learn about β_A and $\beta_{\mathcal{I}}$.

Multivariate meta-analysis of existing data

Model existing data from jth completed study of adults and adolescents:

$$y_{ij} = \gamma_{0j} + \gamma_{Ej} E_{ij} + \gamma_{Aj} A_{ij} + \gamma_{\mathcal{I}j} E_{ij} A_{ij} + \epsilon_{ij}$$

where $\epsilon_{ij} \sim N(0, \sigma^2)$.

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At the second level of the meta-analytic model:

$$\gamma_{Aj} \sim N(\gamma_A, \xi_1^2) \qquad \text{and} \qquad \gamma_{\mathcal{I}j} \mid \gamma_{Aj} \sim N(\underbrace{\lambda_0 + \lambda_1(\gamma_A - \bar{\gamma}_{Aj})}_{=\gamma_{\mathcal{I}}}, \xi_2^2)$$

where $\bar{\gamma}_{Aj} = (1/J) \sum \gamma_{Aj}$, implying a joint bivariate Normal distribution for γ_{Aj} and $\gamma_{\mathcal{I}j}$.

Fitting the meta-analytic model using MCMC

Turner et al. (2009)

Bias parameters: Relate population means in source and target populations as:

$$\beta_A = \gamma_A + \delta_A \quad \text{and}$$
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Fit model using MCMC and approximate joint posterior distribution for $(\gamma_0, \gamma_E, \gamma_A, \gamma_{\mathcal{I}})$.

Generate samples for $(\beta_A, \beta_{\mathcal{I}})$ by simulating values of $(\delta_A, \delta_{\mathcal{I}})$ and $(\gamma_A, \gamma_{\mathcal{I}})$.

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Prior confidence in extrapolation assumption is

$$P\{-\epsilon \leq \mathcal{S}[f(Y_{0,\mathrm{A}})] - \mathcal{S}[f(Y_{0,\mathrm{C}})] \leq \epsilon,\ -\epsilon \leq \mathcal{S}[f(Y_{90,\mathrm{A}})] - \mathcal{S}[f(Y_{90,\mathrm{C}})] \leq \epsilon\}$$

where $\mathcal{S}$ is a chosen summary measure, and $f(Y_{0,\mathrm{Age}})$ and $f(Y_{90,\mathrm{Age}})$ are functions of the response for adults (Age = A) or younger children (Age = C) on placebo and EC_{90}.

Epilepsy drug development

Girgis et al. (2011); Nedelman et al. (2007); Pediatric News. (2016); Pollock et al. (2012)

Extrapolation from adults to children with partial onset seizures (POS) is accepted:

- Quantitative not qualitative differences between effects in adults and children;
- Some disagreement where boundary of certainty lies (2 years vs 4 years).

Commonly used endpoints and models:

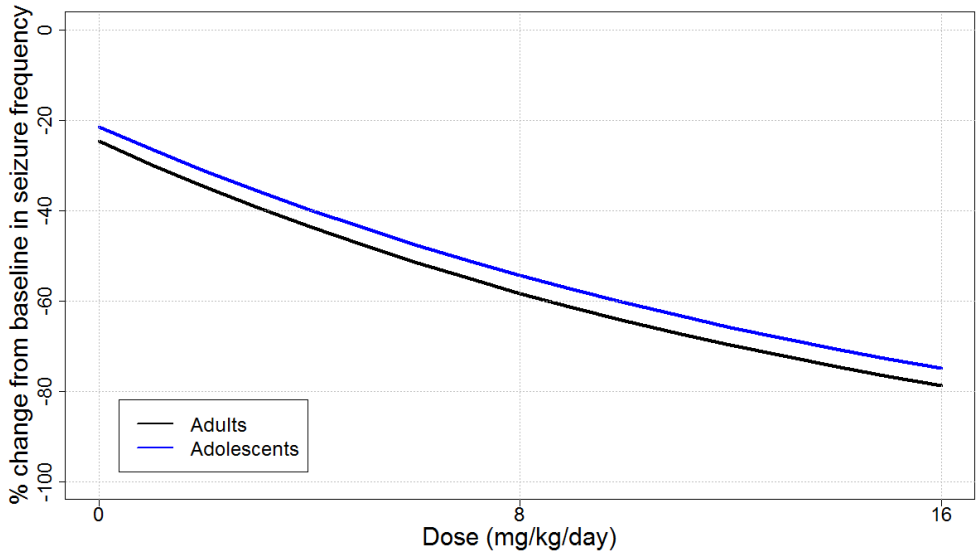
- Pharmacokinetics (PK): Average steady-state trough concentration (C_{min}).
- Pharmacodynamics (PD): Log of transformed percent change in seizure frequency from baseline, normally distributed.
- PK-PD model: Linear model

Eliciting opinion on biases

PK-PD relationship in younger children:

$$y_{iT} = \beta_0 + \beta_E C_{\min,iT} + \underbrace{(\gamma_A + \delta_A)}_{\beta_A} + \underbrace{(\gamma_{\mathcal{I}} + \delta_{\mathcal{I}})}_{\beta_{\mathcal{I}}} C_{\min,iT}$$

Difficult to elicit opinion on biases directly. Instead condition on the observed historical data and for placebo, a moderate dose and a high dose, ask for:



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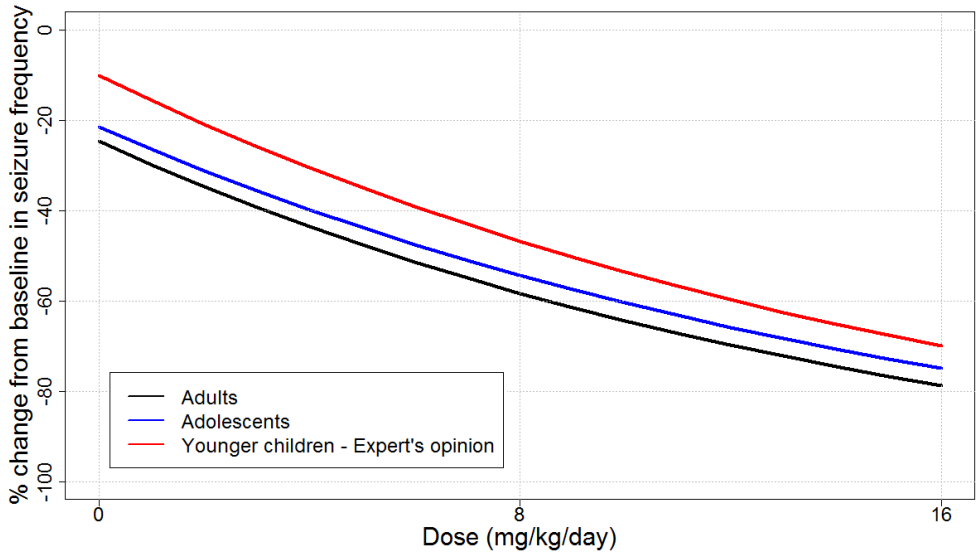

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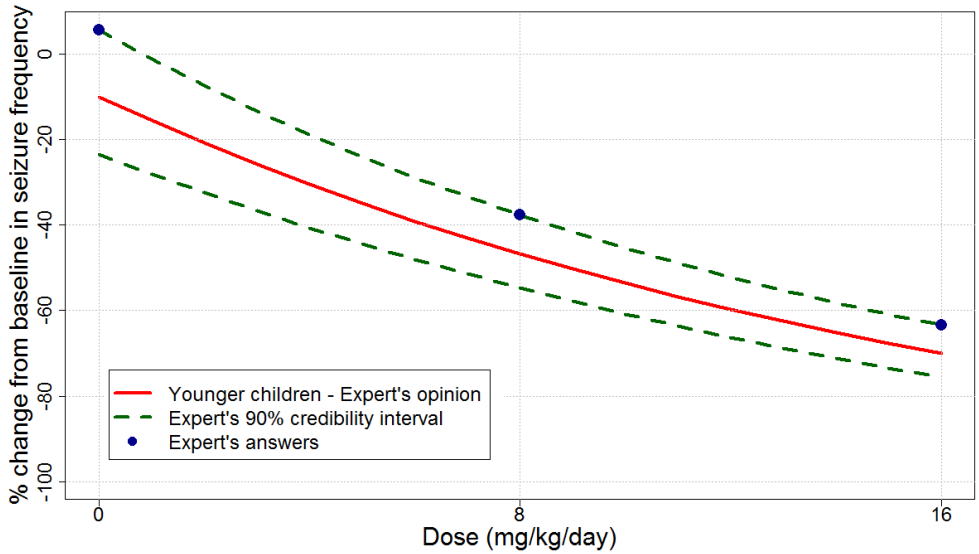

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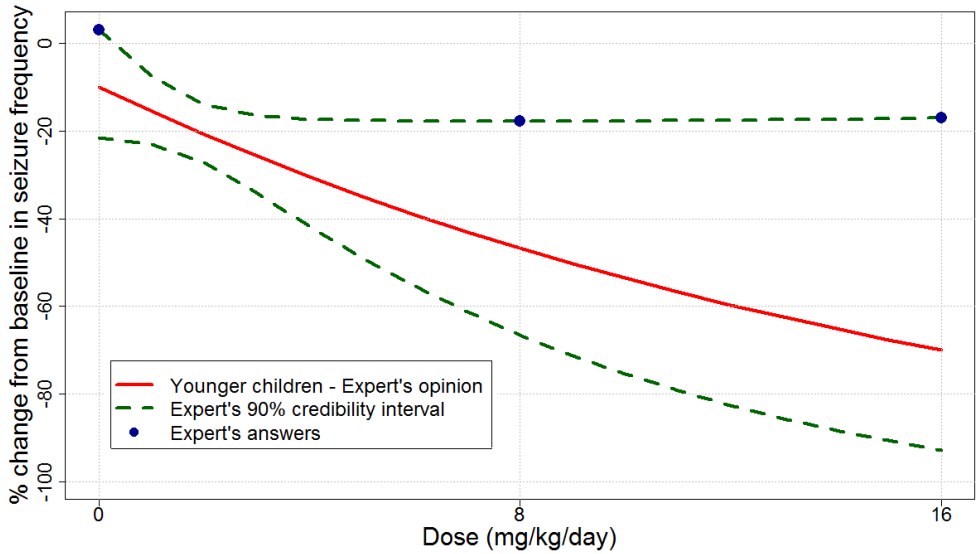

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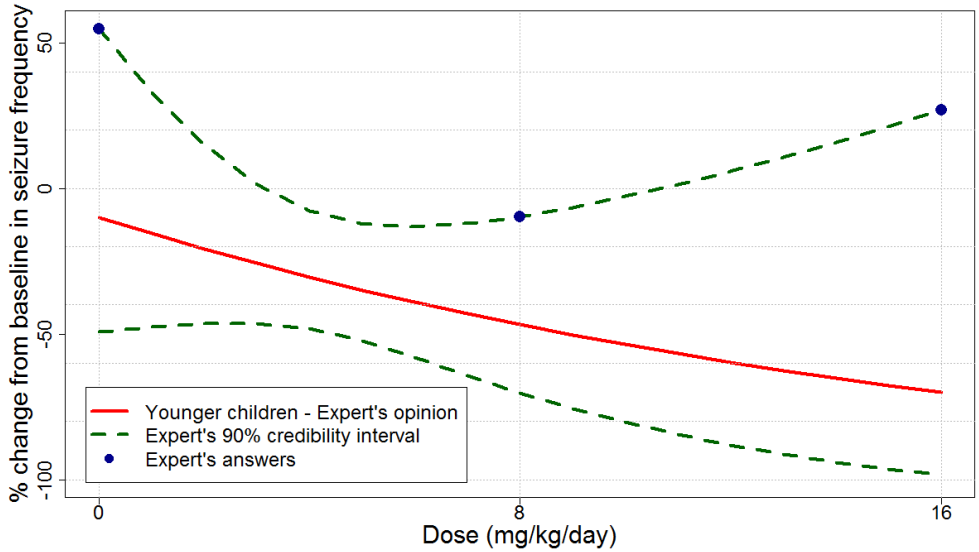

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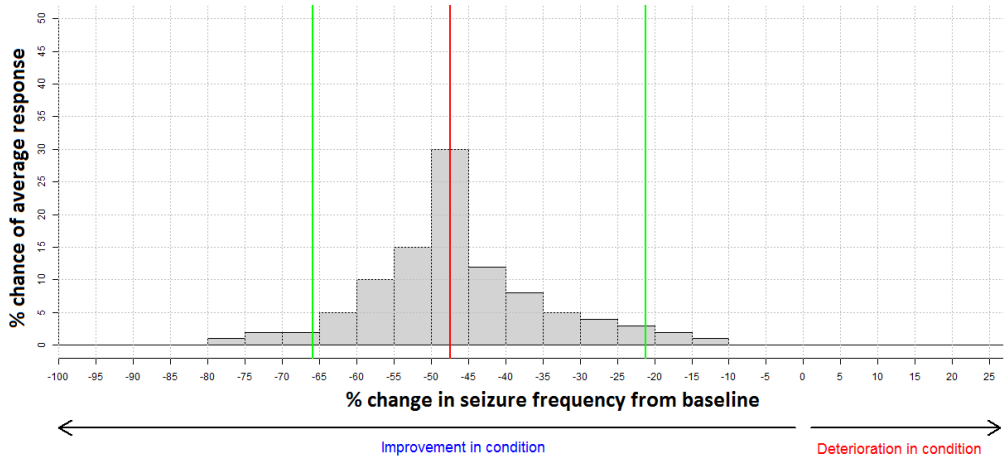
1. The most likely response *on average* for younger children.
2. A 90% credibility interval around the average response line.
3. Distribution for the average response, using histogram.



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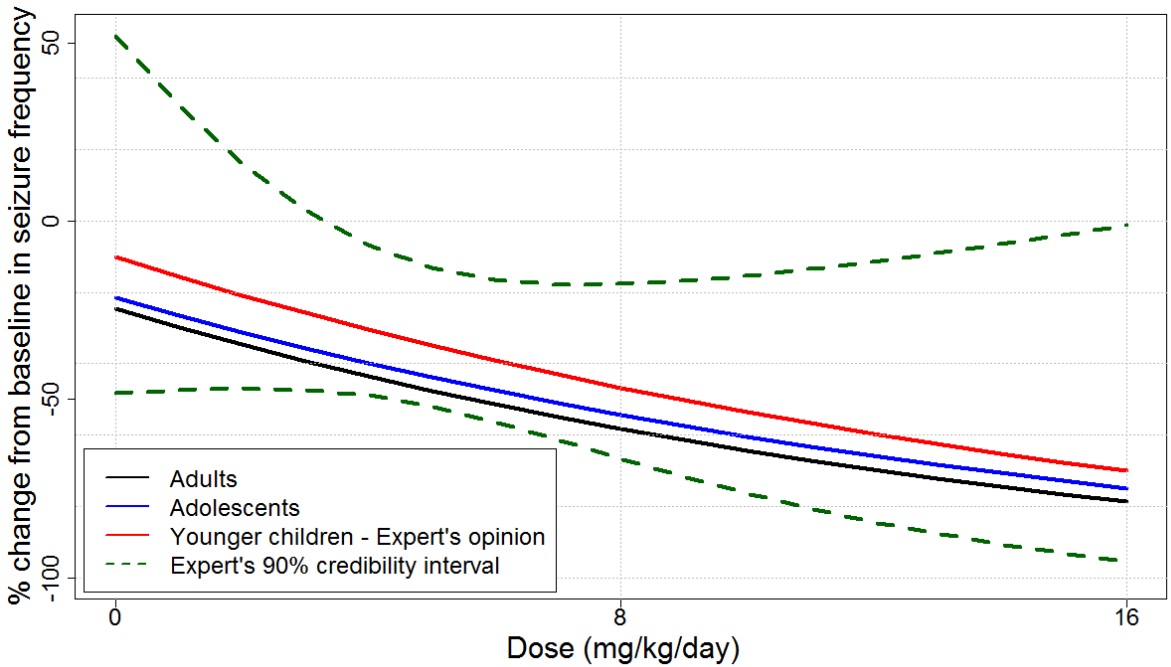


Clinicians think in terms of dose-response relationship. Assume exposure is directly proportional to dose.

Search to find the prior for $(\delta_A, \delta_{\mathcal{I}})$ which best captures the expert's answers.

Simulation study

Simulate data from n_H PK-PD studies in epilepsy recruiting adults and adolescents:

- Outcome: $Y = \log\{100(S - B)/B + 110\}$ (transformed % change from baseline);
- Exposures: $\log(C_{\min}) \sim \text{Normal}(\log(2.94), 0.921)$ truncated at $\log(17.27)$;
- Number of patients per trial: 30, 170;
- Proportion of adolescents: 15%.

Decision criterion for extrapolation:

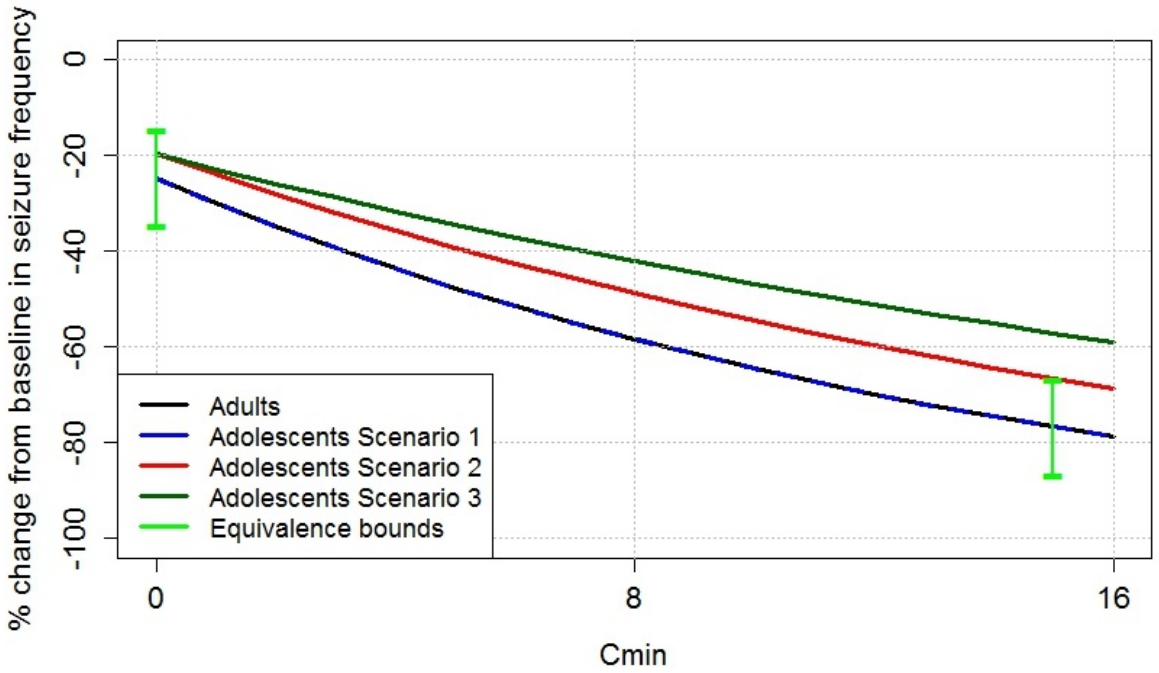
$$P\{-10 \leq \mathcal{M}[\exp(Y_{0,A}) - 110] - \mathcal{M}[\exp(Y_{0,C}) - 110] \leq 10,$$
$$-10 \leq \mathcal{M}[\exp(Y_{90,A}) - 110] - \mathcal{M}[\exp(Y_{90,C}) - 110] \leq 10\}$$

where $\mathcal{M}$ is the median.

Existing data: PK-PD relationships in adults and adolescents

Adult PK-PD: $y_{ij} = 4.45 - 0.06 C_{\text{min},ij} + \epsilon_{ij}$

- Scenario 1: E-R relationships in adolescents identical to adults
- Scenario 2: Lower response rate on placebo in adolescents; worse effect of exposure on response (just satisfies extrapolation criterion)
- Scenario 3: Lower response rate on placebo in adolescents; much worse effect of exposure on response (clearly do not satisfy extrapolation criterion)



Existing data: PK-PD relationships in adults and adolescents

For each scenario and variation considered we have simulated 1000 sets of existing studies, fitted the meta-analytic model and approximated the joint posterior distribution for $(\gamma_0, \gamma_E, \gamma_A, \gamma_{\mathcal{I}})$.

Next relate population means in existing studies and to future study using additive biases:

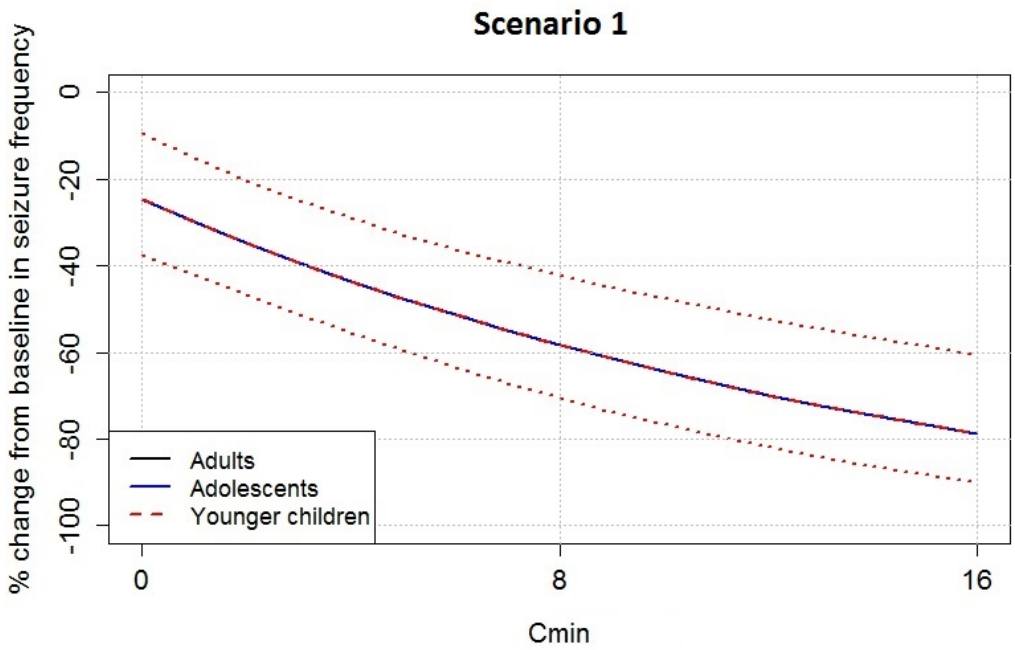
$$\beta_A = \gamma_A + \delta_A \quad \text{and}$$
$$\beta_{\mathcal{I}} = \gamma_{\mathcal{I}} + \delta_{\mathcal{I}}.$$

Relating existing data to target question

Bias prior:

$$\begin{pmatrix} \delta_A \\ \delta_{\mathcal{I}} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0.1^2 & 0.00004 \\ 0.00004 & 0.016^2 \end{pmatrix} \right)$$

Figures show the PK-PD relationship for younger children:



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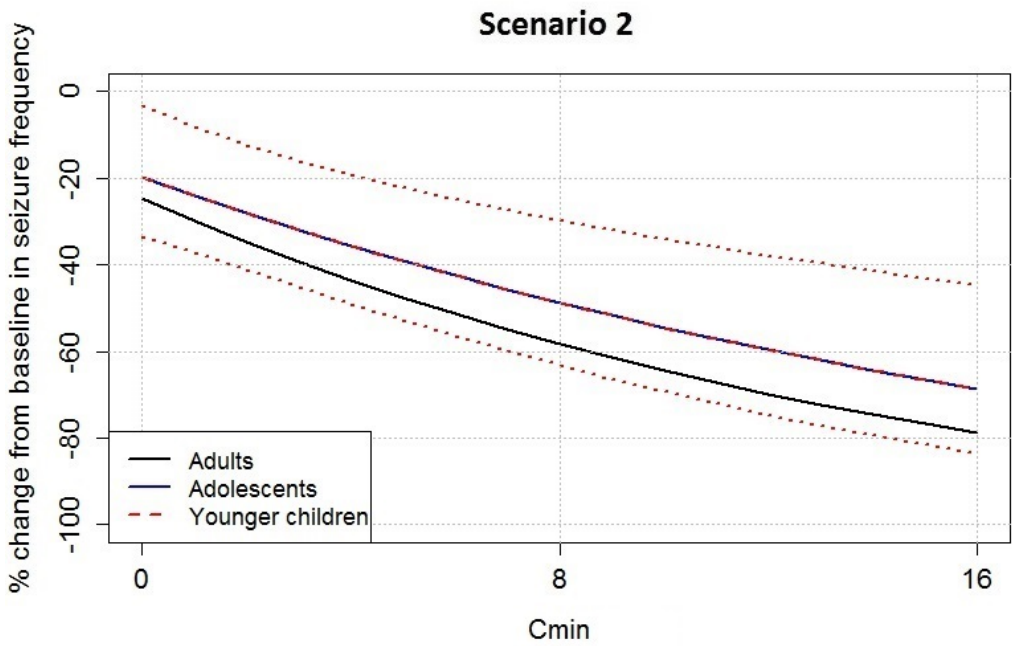

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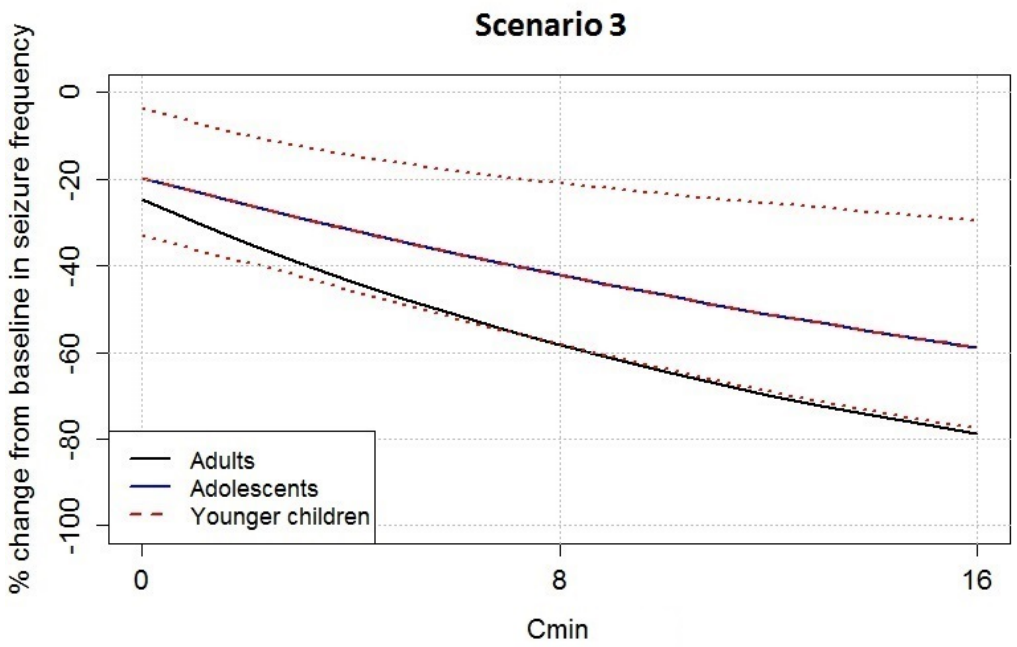
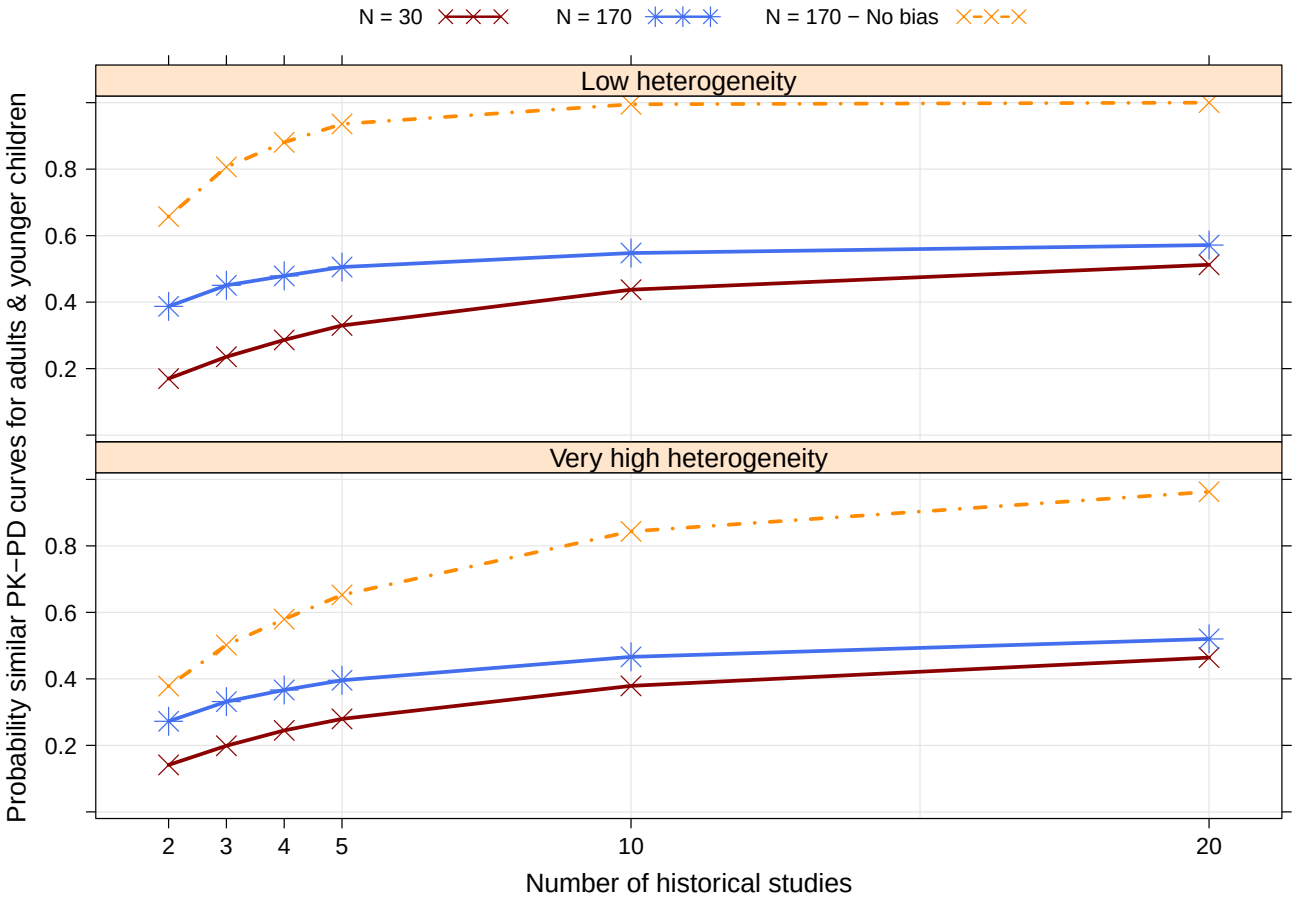
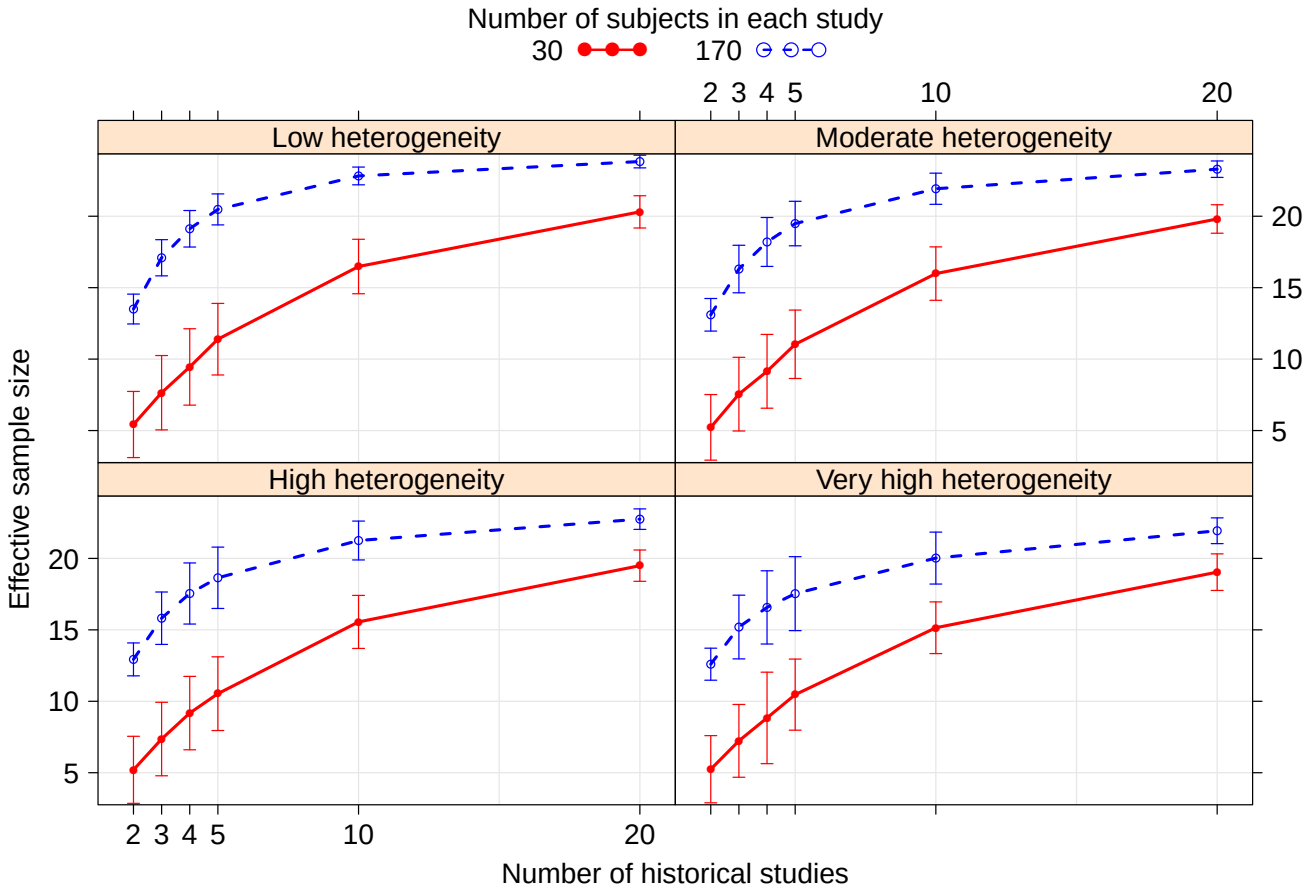


Results: Probability of the extrapolation assumption holding



(e) Scenario 1: Adult and adolescent PK-PD curves identical

Results: Effective sample size of the joint posterior of $(\beta_A, \beta_{\mathcal{I}})$



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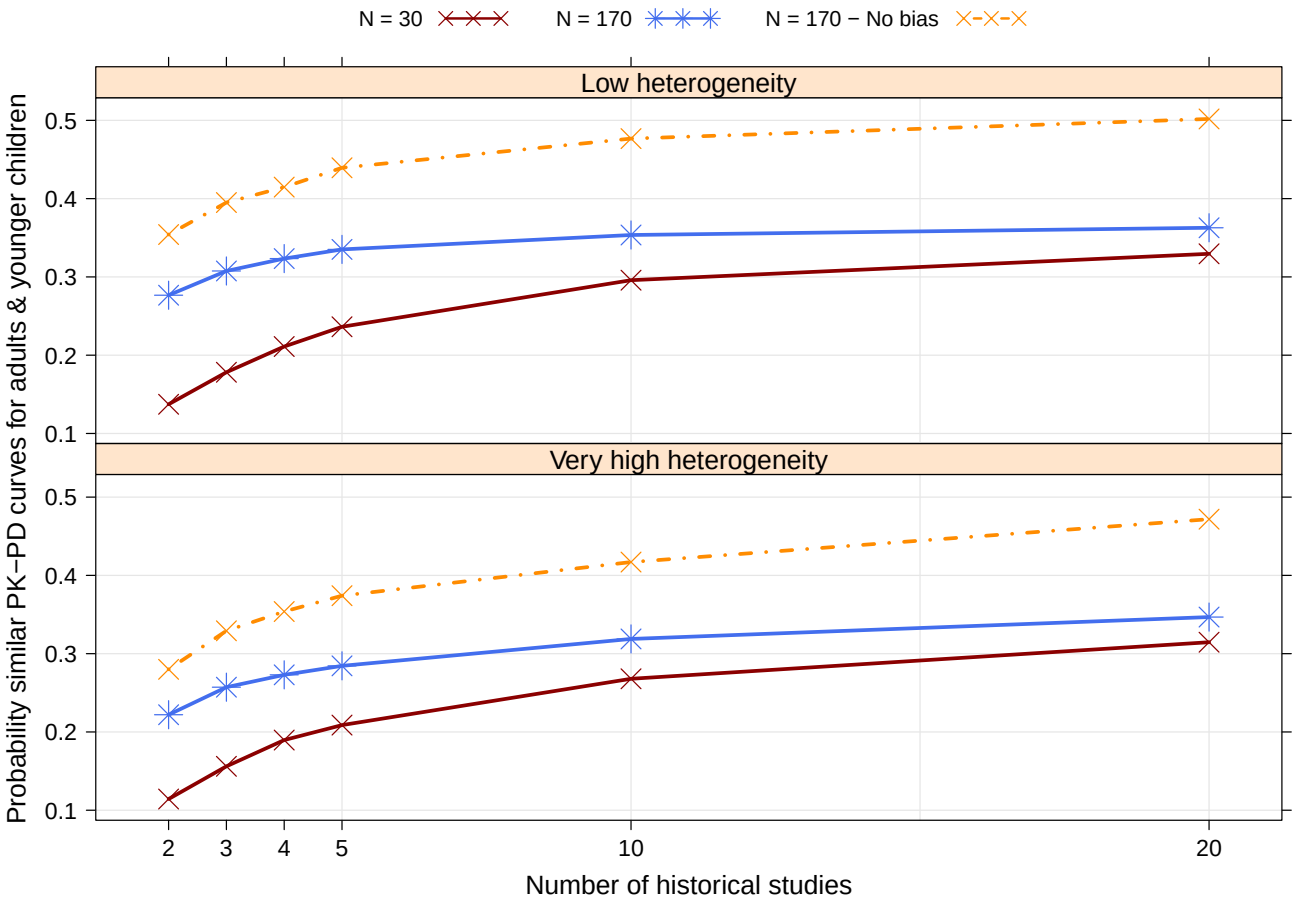
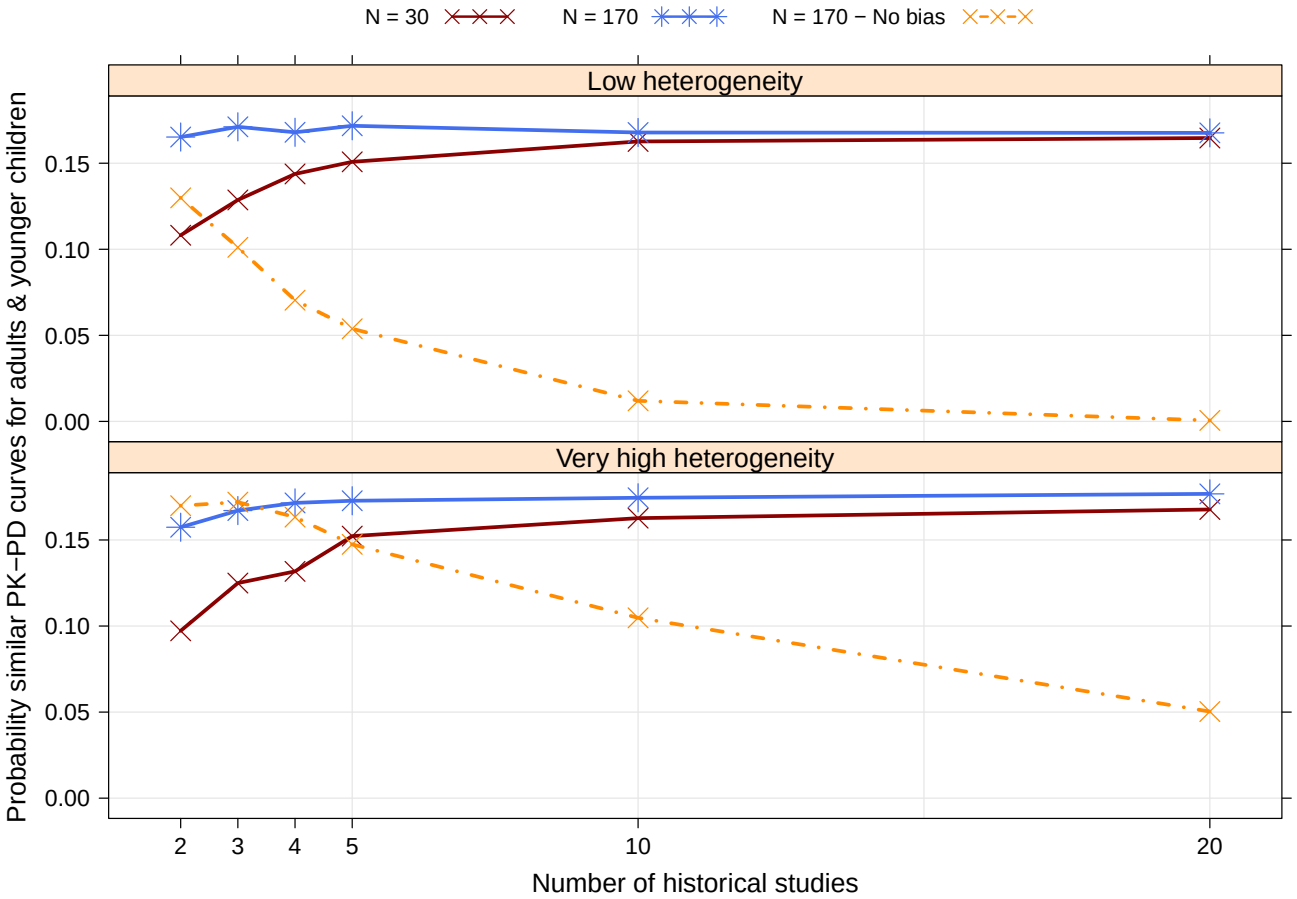


(g) Scenario 2: Adult and adolescent PK-PD curves different

Results: Probability of the extrapolation assumption holding



(h) Scenario 3: Adult and adolescent PK-PD curves very different

Conclusions

- Developed quantitative approach to using existing data to support extrapolation decisions.
- Prior elicitation Shiny app trialled at epilepsy conference with expert clinicians.
- Even in scenario where adults, adolescents and younger children identical on average, largest probability of extrapolation only 0.57 - Strong influence of expert uncertainty.
- Prior probability of an extrapolation assumption can be feed into Bayesian decision theoretic approach to determine whether additional data needed to verify assumption.

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