Bayesian methods for borrowing information in clinical drug development

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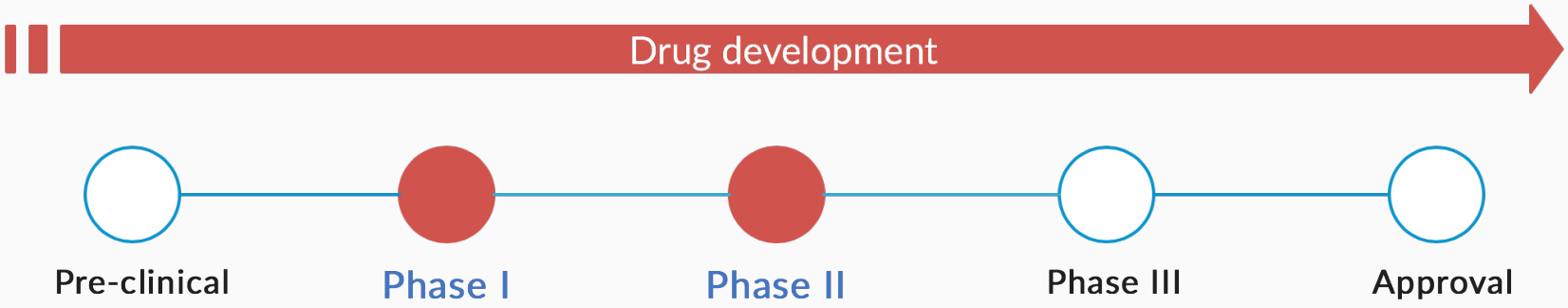
Introduction

Early phases of clinical drug development



Phase I

- First-in-man trials
- Conducted through dose-escalation steps
- Investigates safety profile

Phase II

- Usually randomized controlled trials
- Aims:

1) Establishing dose-response signal

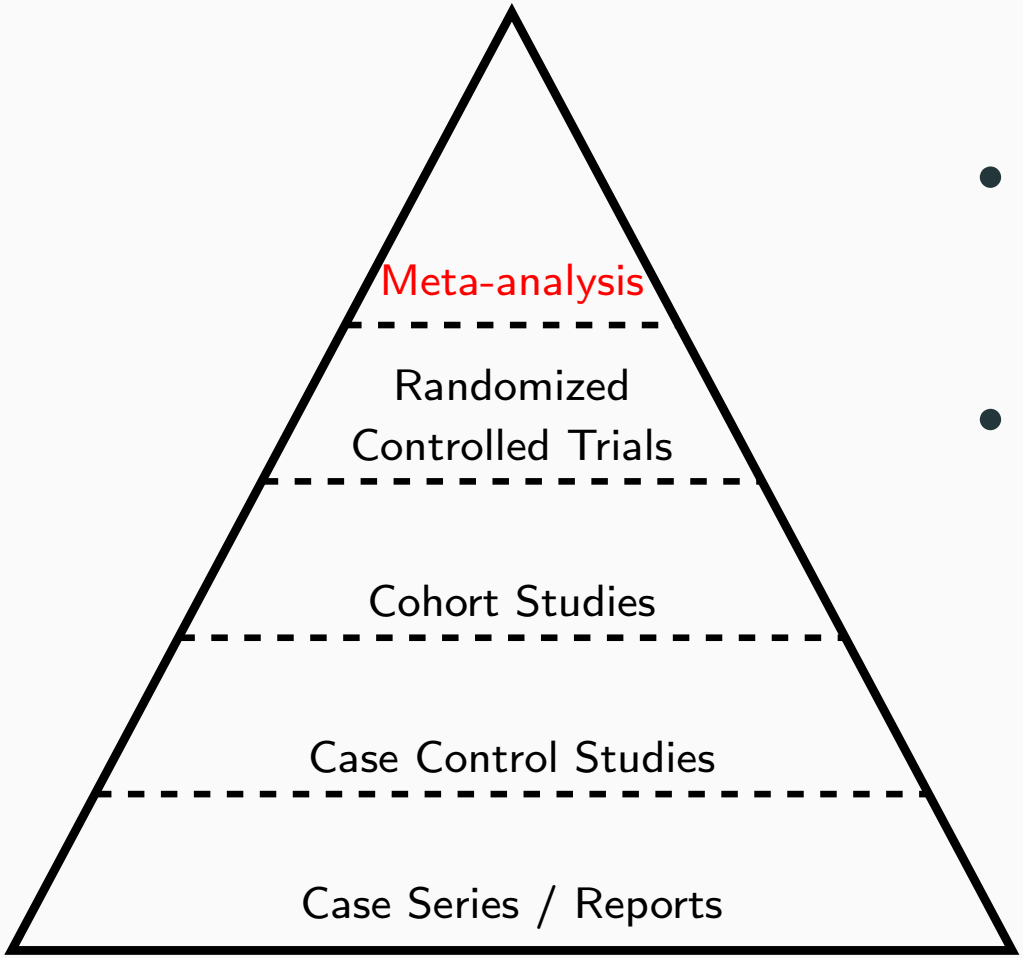
2) Estimating dose-response function

Multiple treatment schedules in phase I and II trials

- **Treatment schedule**: Frequency of administration, e.g. a daily or a weekly schedule
- Recently, phase I or II trials investigating multiple schedules have become more popular, for instance:
  - In oncology (de Lima et al., 2010)
  - In atopic dermatitis (Thaçi et al., 2016)
  - In hypercholesterolemia (Pfizer, 2017)
- Limited literature exists on statistical methods to analyze data from such trials (Guo et al., 2016)

Meta-analysis of clinical trials

- Hierarchy of evidence (Greenhalgh, 1997)

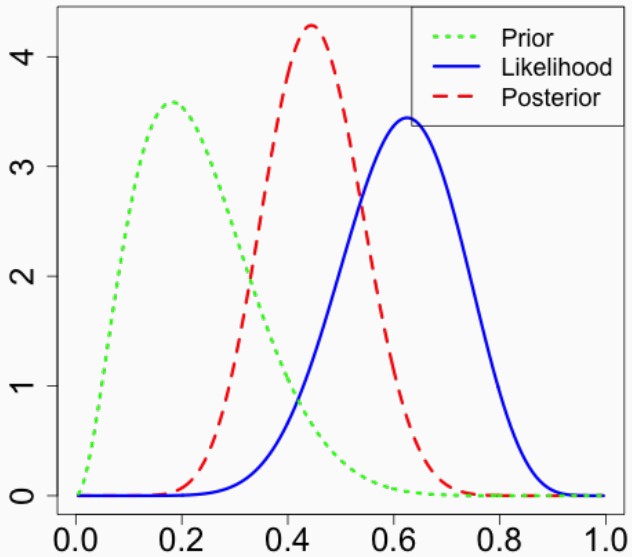


- Statistical methods to combine multiple trials to address a question of interest
- Common methods
  - Fixed-effects meta-analysis
  - Random-effects meta-analysis
- Challenges to conduct a meta-analysis
  - **Rare events**, outcomes with very low event probabilities
  - **Few trials**, e.g. five or fewer trials

Bayesian methods in clinical drug development

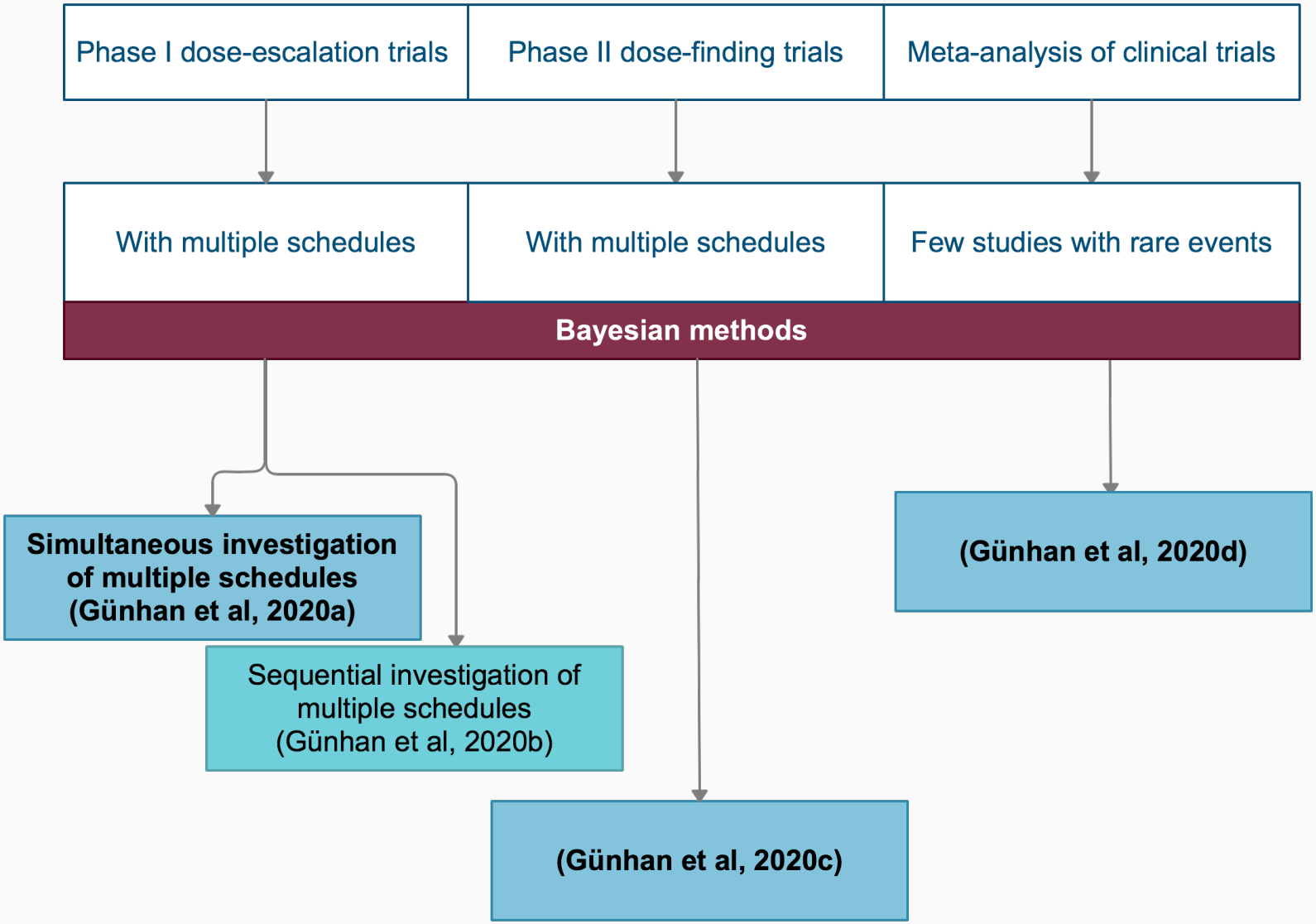
- A particular approach to solve statistical problems
- Bayes' theorem:

$$f(\theta|x) \propto f(x|\theta)\, f(\theta)$$



  - $f(\theta|x)$ the posterior
  - $f(x|\theta)$ the likelihood
  - $f(\theta)$ the prior
  - Bayesian methods used, for example:
    - In phase I dose-escalation trials, Continual Reassessment Method (O'Quigley et al., 1990)
    - In phase II trials (Thomas, 2006)
    - In meta-analysis of clinical trials (Smith et al., 1995)

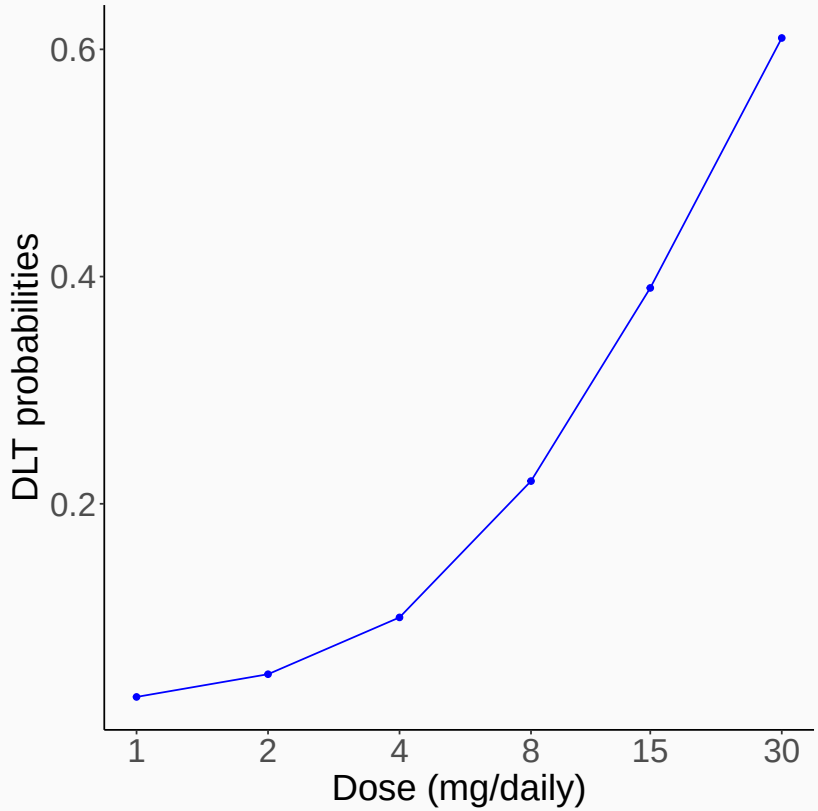
Three major focus areas of the dissertation



Phase I dose-escalation trials with multiple schedules (Günhan et al, 2020a and Günhan et al, 2020b)

Phase I dose-escalation trials

- Small cohorts of patients are treated in treatment cycles
- Relationship between dose and probability of dose-limiting-toxicities (DLTs)
- Aim: Informing dose-escalation decisions and finding the **m**aximum **t**olerated **d**ose (MTD)
- With multiple schedules, two types of designs possible



1) Simultaneous investigation of multiple schedules

- Dose and schedule are varied within the same trial
- Finding **m**aximum **t**olerated dose and schedule **c**ombination (MTC)

Cohort	Frequency (hrs)	Dose (mg)	Number of pats	Number of DLTs	MTC
1	192	8	1	0	No
2	96	16	1	0	No
3	96	24	1	0	No
⋮	⋮	⋮	⋮	⋮	⋮
30	24	24	1	0	Yes!

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30	24	24	1	0	Yes!

2) Sequential investigation of multiple schedules

Cohort	Frequency (hrs)	Dose (mg)	Number of pats	Number of DLTs	MTD
1	48	2.5	3	0	No
2	48	5	3	0	No
⋮	⋮	⋮	⋮	⋮	⋮
7	48	15	3	1	Yes!

Cohort	Frequency (hrs)	Dose (mg)	Number of pats	Number of DLTs	MTD
8	24	10	3	1	No
9	24	7.5	3	1	No
⋮	⋮	⋮	⋮	⋮	⋮
14	24	7.5	3	0	Yes!

2) Sequential investigation of multiple schedules

Cohort	Frequency (hrs)	Dose (mg)	Number of pats	Number of DLTs	MTD
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7	48	15	3	1	Yes!

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⋮	⋮	⋮	⋮	⋮	⋮
14	24	7.5	3	0	Yes!

A Bayesian time-to-event pharmacokinetic model (TITE-PK)

- Modelling time to first DLTs, depends on an **exposure** measure $E(t)$
- Exposure measure based on drug **pharmacokinetics** (PK), treated as fixed
- Use of planned schedule and known PK parameter elimination rate constant
- A time-varying Poisson process
- Hazard $h(t)$ and cumulative hazard $H(t)$ given by

$$h(t) = \beta\, E(t) \implies H(t) = \beta\, \mathrm{AUC}_E(t)$$

Time-to-event pharmacokinetic model (TITE-PK) (cont.)

- Metric to inform dose-escalation decisions:
  End-of-cycle 1 DLT probability

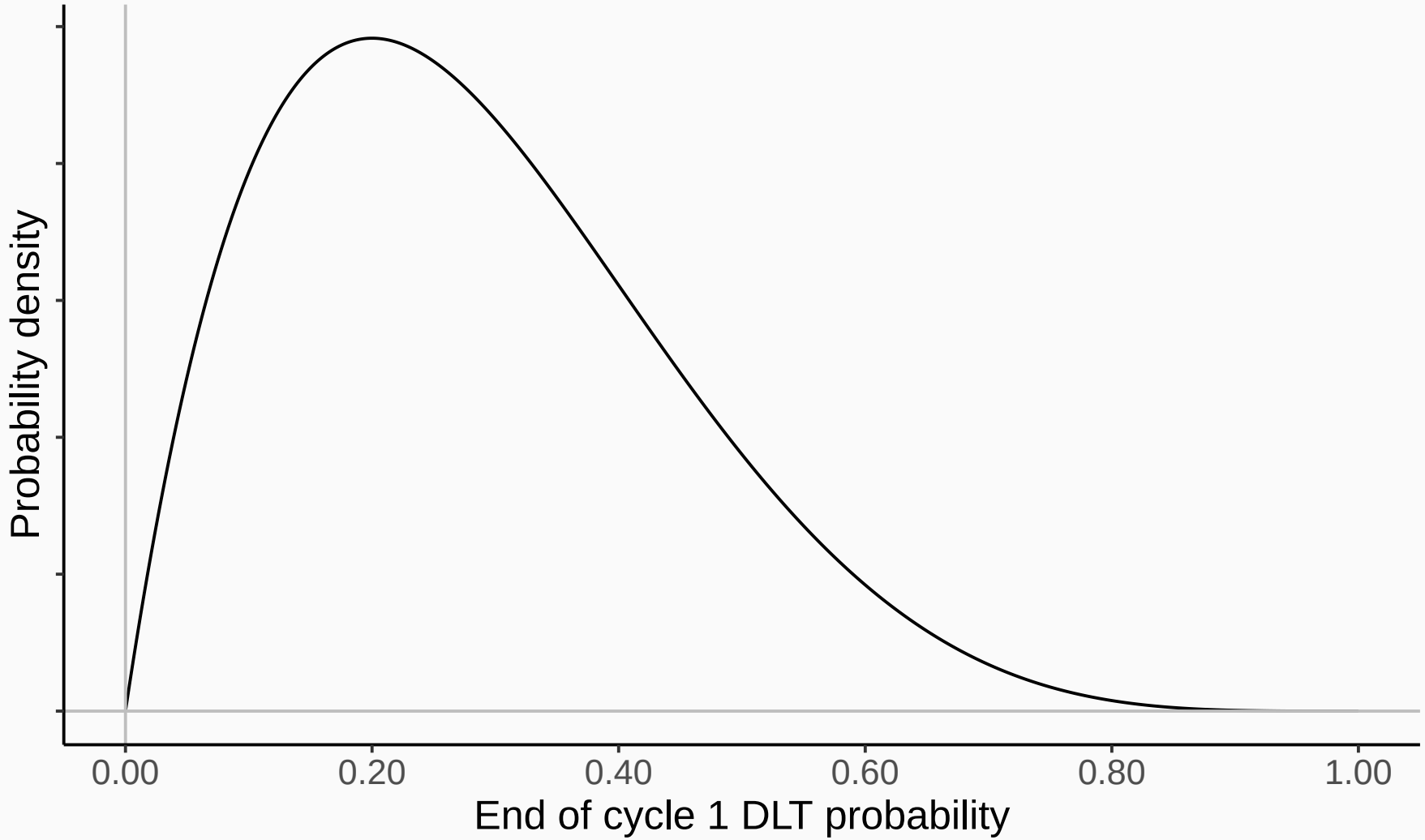
$$P(T \leq t^* | d, f) = 1 - \exp(-H(t^* | d, f))$$

- Three categories for $P(T \leq t^* | d, f)$

(i)	$P(T \leq t^* \mid d, f) < 0.20$	Underdosing (UD)
(ii)	$0.20 \leq P(T \leq t^* \mid d, f) \leq 0.40$	Targeted toxicity (TT)
(iii)	$P(T \leq t^* \mid d, f) > 0.40$	Overdosing (OD)

- **Escalation with overdose control** (EWOC) (Babb et al., 1998)
  - $P(P(T \leq t^* | d, f) \geq 0.40)$ should not exceed 0.25

Visualization of the dose-schedule decisions



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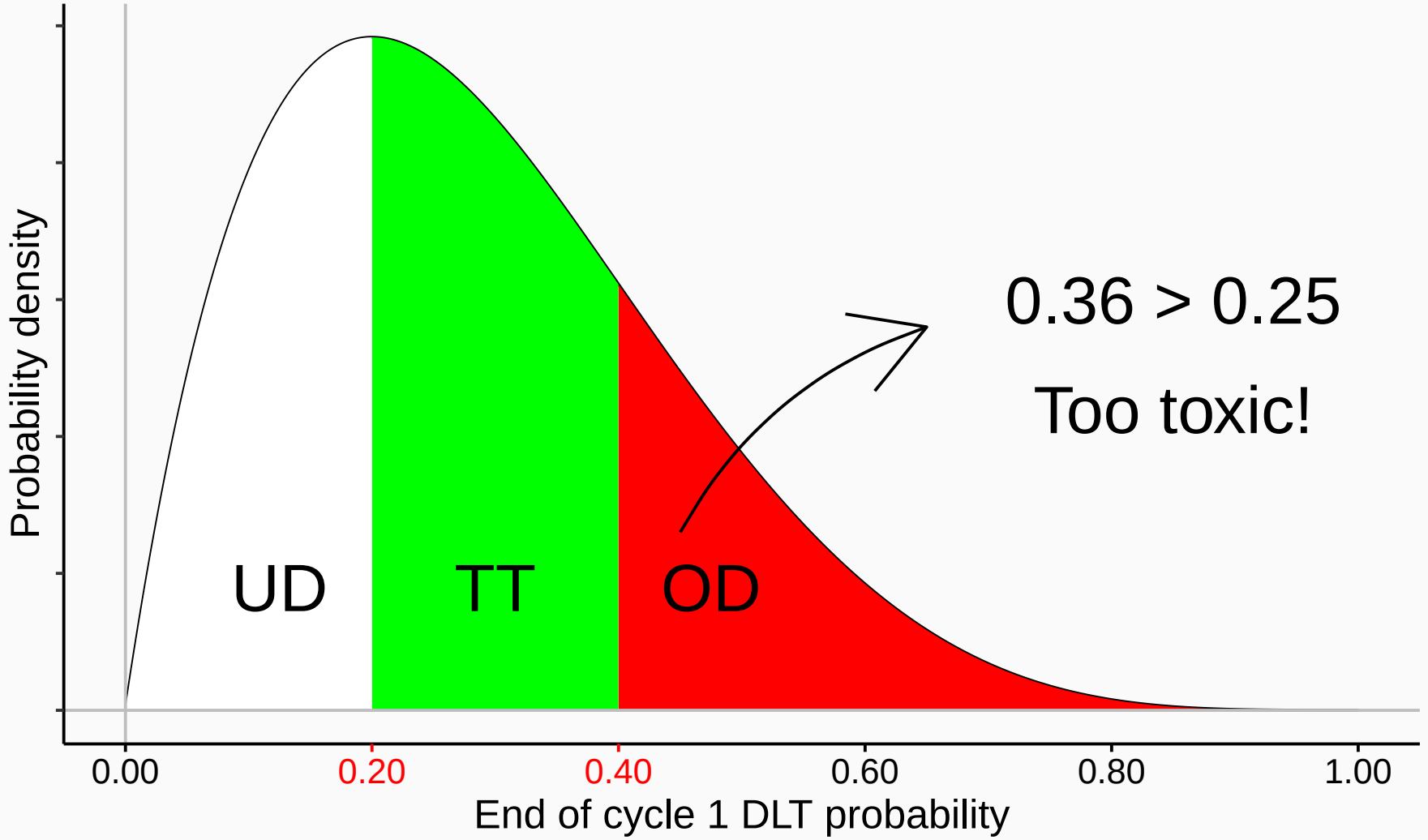


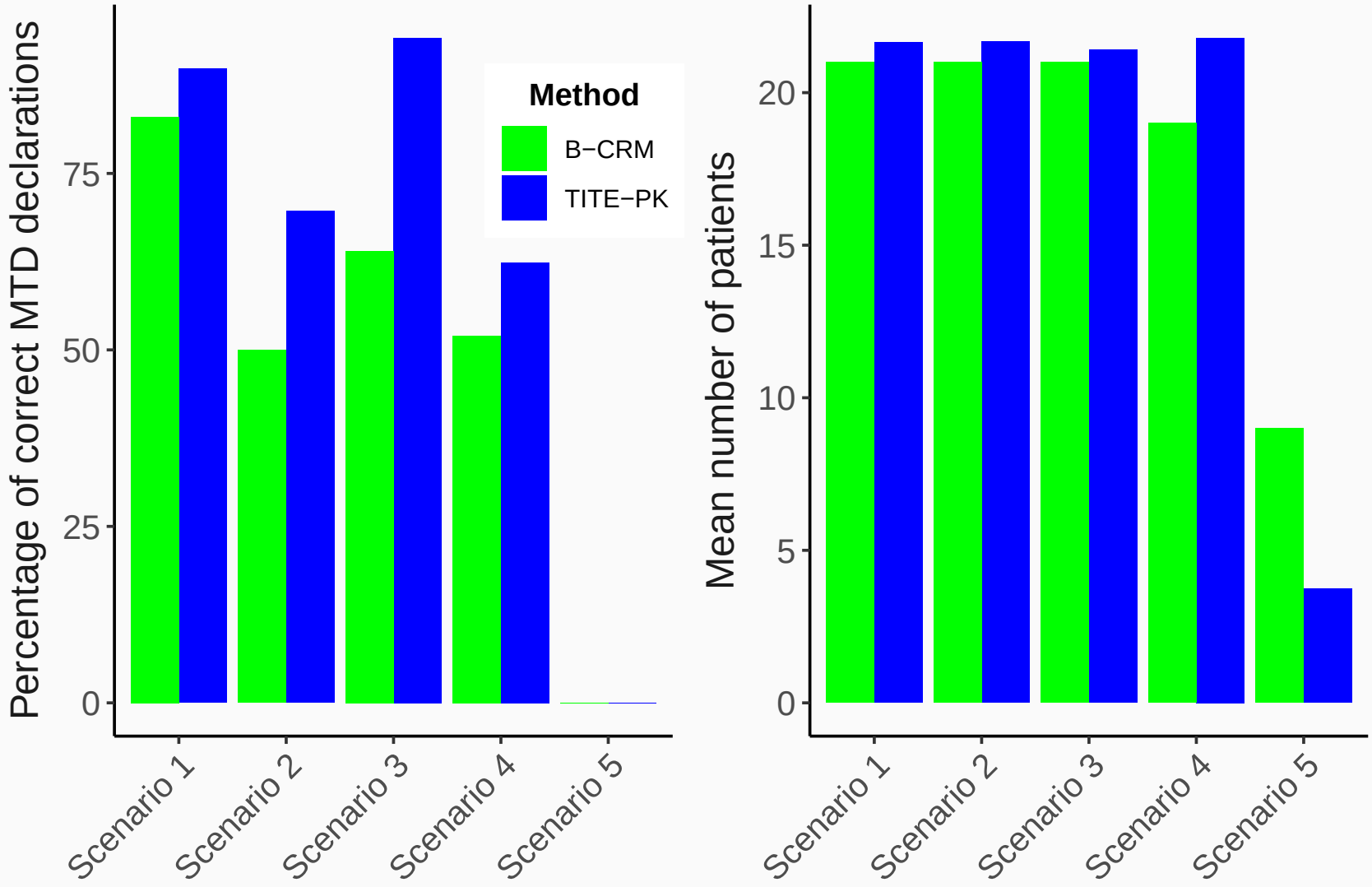
Simulation setup (Sequential design)

- Comparison of performances: TITE-PK vs Bridging Continual Reassessment Method (B-CRM) (Liu et al., 2015)
- B-CRM: Extension of CRM to analyze bridging trials
- Simulations are motivated by the Everolimus trial (NCT00466466)
- Sequential design:
  - S_1: Once every two days
  - S_2: Daily
- Performance measures:
  - The percentage of correct MTD declarations
  - Mean number of patients required in the trial

Toxicity probabilities of simulation scenarios

Scenario	Schedule	Doses in mg					
		2.5	5	7.5	10	12.5	15
1	S_1	0.05	0.07	0.09	0.10	0.13	0.18
	S_2	0.08	0.12	0.16	0.18	**0.23**	**0.27**
2	S_1	0.08	0.12	0.16	**0.20**	**0.23**	**0.27**
	S_2	0.18	**0.26**	**0.34**	0.45	0.49	0.55
3	S_1	0.03	0.12	**0.28**	**0.40**	0.54	0.62
	S_2	**0.20**	**0.30**	0.45	0.50	0.60	0.75
4	S_1	0.05	0.07	0.09	0.15	**0.22**	**0.28**
	S_2	**0.30**	**0.35**	0.48	0.52	0.61	0.70
5	S_1	0.45	0.50	0.55	0.65	0.75	0.85
	S_2	0.48	0.56	0.62	0.70	0.80	0.88

Simulation results



Further results for the proposed method TITE-PK

- Sequential investigation of multiple schedules (Günhan et al., 2020b)
    - The Everolimus application is reanalyzed to illustrate TITE-PK
- Simultaneous investigation of multiple schedules (Günhan et al., 2020a)
    - TITE-PK was shown to improve correct MTC declarations with lower sample sizes in simulation studies

Conclusions and outlook

- A time-to-event PK model to analyze phase I trials with multiple schedules
    - Displays better performance in terms of the correct MTD declarations in simulations
- Possible extensions include
    - Modelling multiple compounds (possible interactions must be taken into account)
    - Considering long-term safety events, not only time-to-first DLTs

Phase II dose-finding trials with multiple schedules (Günhan et al., 2020c)

MOR106 trial: NCT03568071

- A phase II dose-finding trial: MOR106 investigated for the treatment of atopic dermatitis
- Primary outcome: The percentage change from baseline in Eczema Area and Severity Index at Day 85

Arm	Schedule	Dose (mg/kg)
1	Bi-weekly	0
2	Bi-weekly	1
3	Bi-weekly	3
4	Bi-weekly	10
5	Monthly	1
6	Monthly	3

The general model

- For schedule i, dose j, and patient k

$$y_{ijk} = f(d_j^{(i)}, \boldsymbol{\theta}) + \epsilon_{ijk}, \quad \epsilon_{ijk} \sim \mathcal{N}(0, \sigma_i^2)$$

- The Emax model for dose-response relationship:

$$f(d_j^{(i)}, \boldsymbol{\theta}) = \mathrm{E}_0^{(i)} + \mathrm{E}_{\max}^{(i)} \frac{d_j^{(i)}}{\mathrm{ED}_{50}^{(i)} + d_j^{(i)}}$$

  - $\mathrm{E}_0^{(i)}$ placebo effect
  - $\mathrm{E}_{\max}^{(i)}$ maximum effect
  - $\mathrm{ED}_{50}^{(i)}$ dose providing half of the maximum effect

Different ways to estimate dose-response functions

- Estimating separate curves for each schedule (**stratification**)
  - Ignores the potential similarity in the dose-response functions
- Scaling doses to a common unit and pooling doses from different schedules (**complete pooling**; CP)
  - Ignores the potential heterogeneity in the dose-response functions
- **Partial pooling with fixed-effects** (PP - FE) (Feller et al., 2017)
  - $E_0^{(i)}$ are shared between schedules: $E_0^{(1)} = E_0^{(2)} = \ldots$
  - For some situations also $E_{max}^{(i)}$, but perhaps not $ED_{50}^{(i)}$
  - Using schedule specific fixed-effects for $E_{max}^{(i)}$ and/or $ED_{50}^{(i)}$

Proposed method: Partial pooling with random-effects

- Schedule specific random-effects for $E_{max}^{(i)}$ and/or $ED_{50}^{(i)}$ (PP - RE)
- **Exchangeable** around an overall mean
  - $ED_{50}^{(i)}$: Re-scaling and log transformation
  - $ED_{50}^{*(i)} = ED_{50}^{(i)} \frac{f^{(i)}}{f^{(i_{\mathbf{ref}})}}$, $f^{(i)}$ frequency of administration in hours
  - $\log(ED_{50}^{*(i)}) \sim \mathcal{N}(\mu_{ED_{\mathbf{50}}}, \tau^2_{ED_{\mathbf{50}}})$

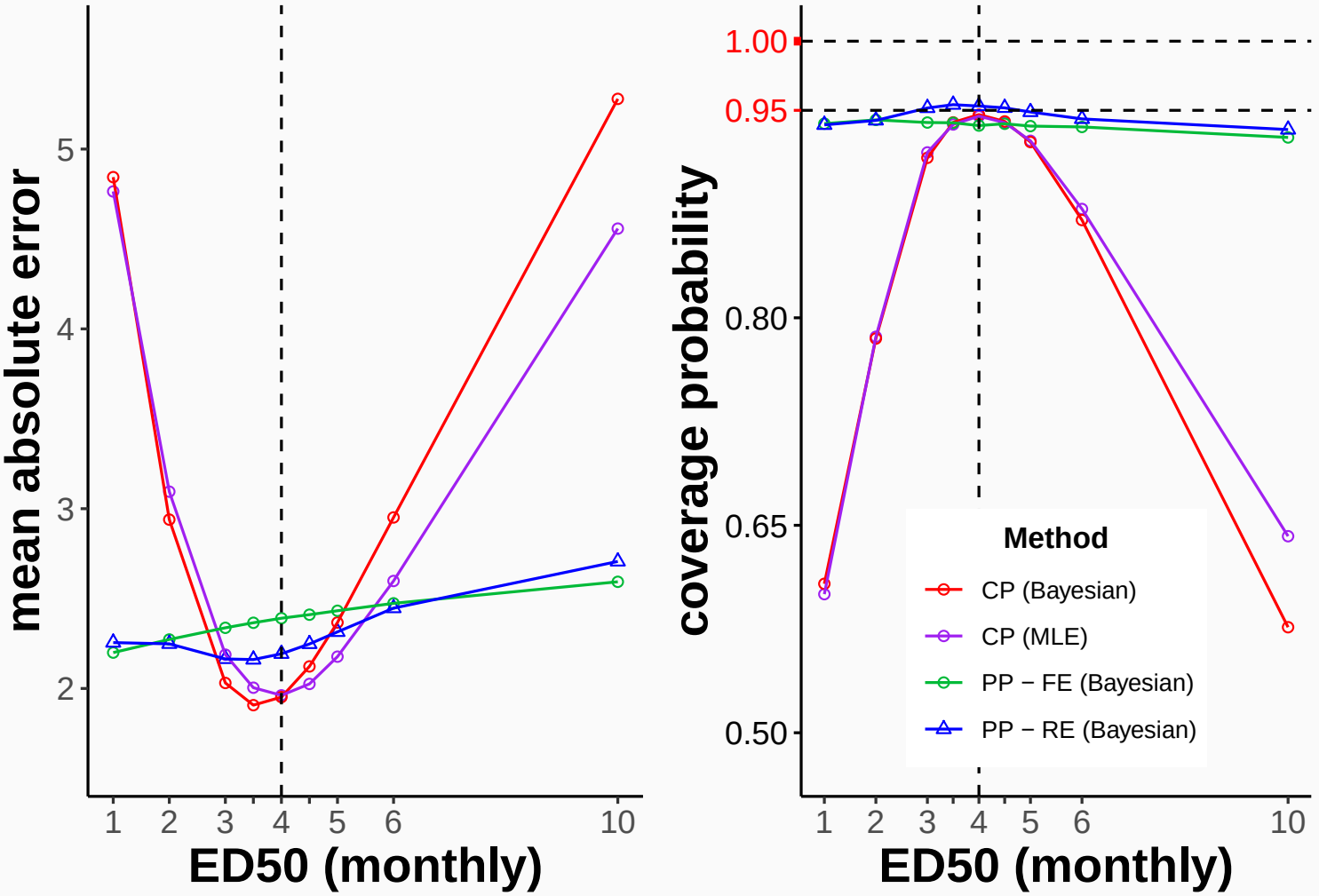
Prior distributions

- Vague priors: $\mathcal{N}(0, 100^2)$ for E_0 and $E_{max}^{(i)}$ and $\mathcal{HN}(100)$ for σ_i
- Weakly informative prior (WIP) for τ_{ED50}: $\mathcal{HN}(1)$ (Friede et al., 2017)
- In the frequentist framework, usually bounds are imposed on ED_{50} to ensure convergence, e.g. $[0, 1.5 \times \max(d_j^{(i)})]$
- Functional uniform priors for $ED_{50}^{(i)}$ (Bornkamp, 2014): Uniformly distributed on the potential different shapes of the underlying Emax model

Simulation setup

- The design of each trial and true values for the model parameters are motivated by the MOR106 trial
  - $ED_{50}^{\text{bi-weekly}}$ is 2 mg/kg
  - 9 scenarios: $ED_{50}^{\text{monthly}} \in \{1, 2, 3, 3.5, 4, 4.5, 5, 6, 10 \text{ (mg/kg)}\}$
- Performance measures:
  - Mean absolute error of the point estimates for the dose-response function evaluated at each dose level of a grid
  - Mean coverage probability of the interval estimates evaluated at each dose level of a grid

Simulation results



Conclusions and outlook

- Partial pooling with schedule specific random-effects:
  - yields more robust mean absolute error and higher coverage compared to the alternatives
  - R package which implements the proposed method, `ModStan`, is publicly available: `https://github.com/gunhanb/ModStan`
- Possible extensions:
  - Taking into account model uncertainty, considering other dose-response models
  - Meta-analysis of dose-response models

Meta-analysis of few studies involving rare events (Günhan et al., 2020d)

Cochrane Database of Systematic Reviews

- The richest resource of meta-analyses of randomized controlled trials in the world
- I analysed:
  - All datasets available in March 2018
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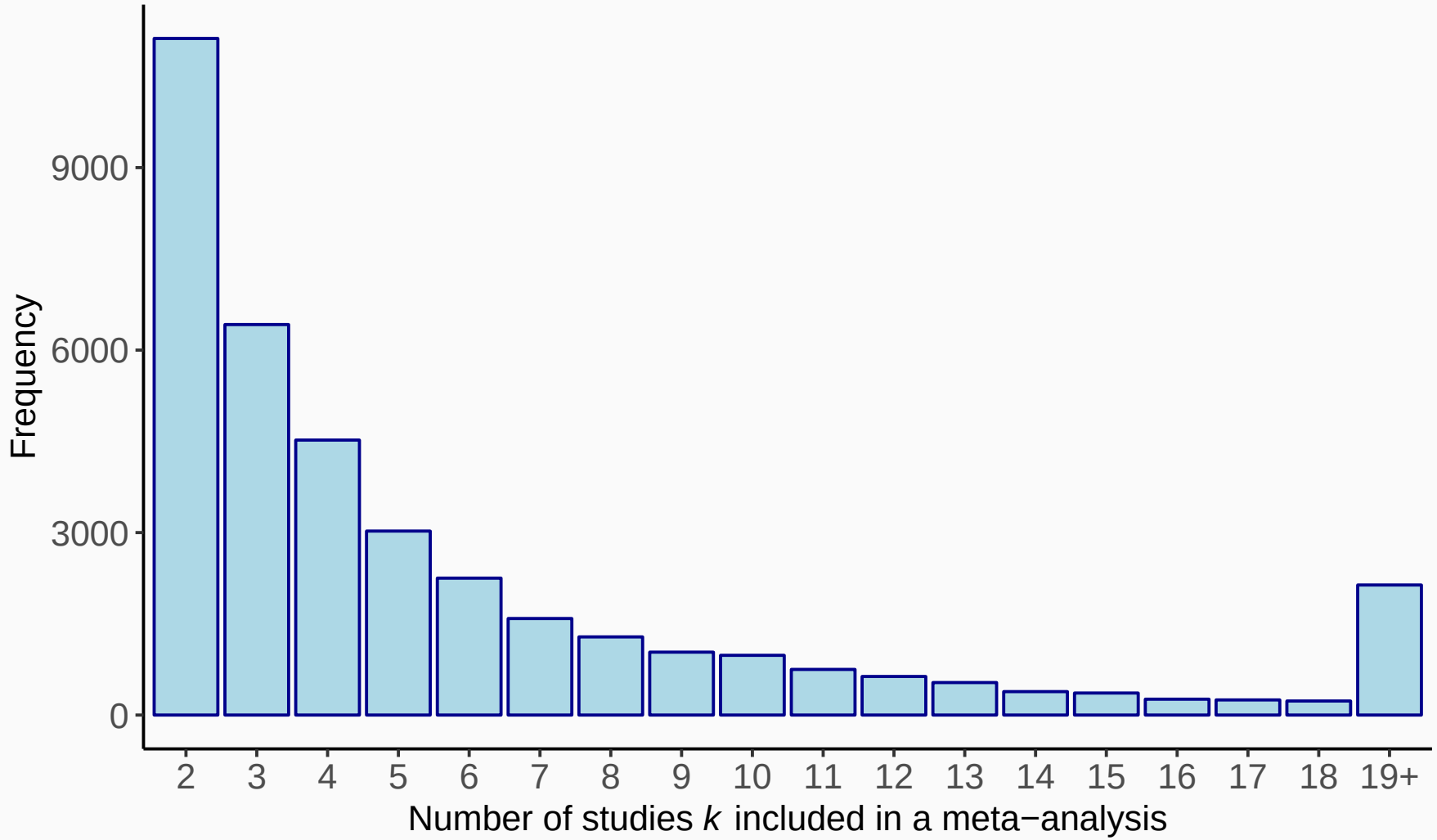
Cochrane Database: Number of studies



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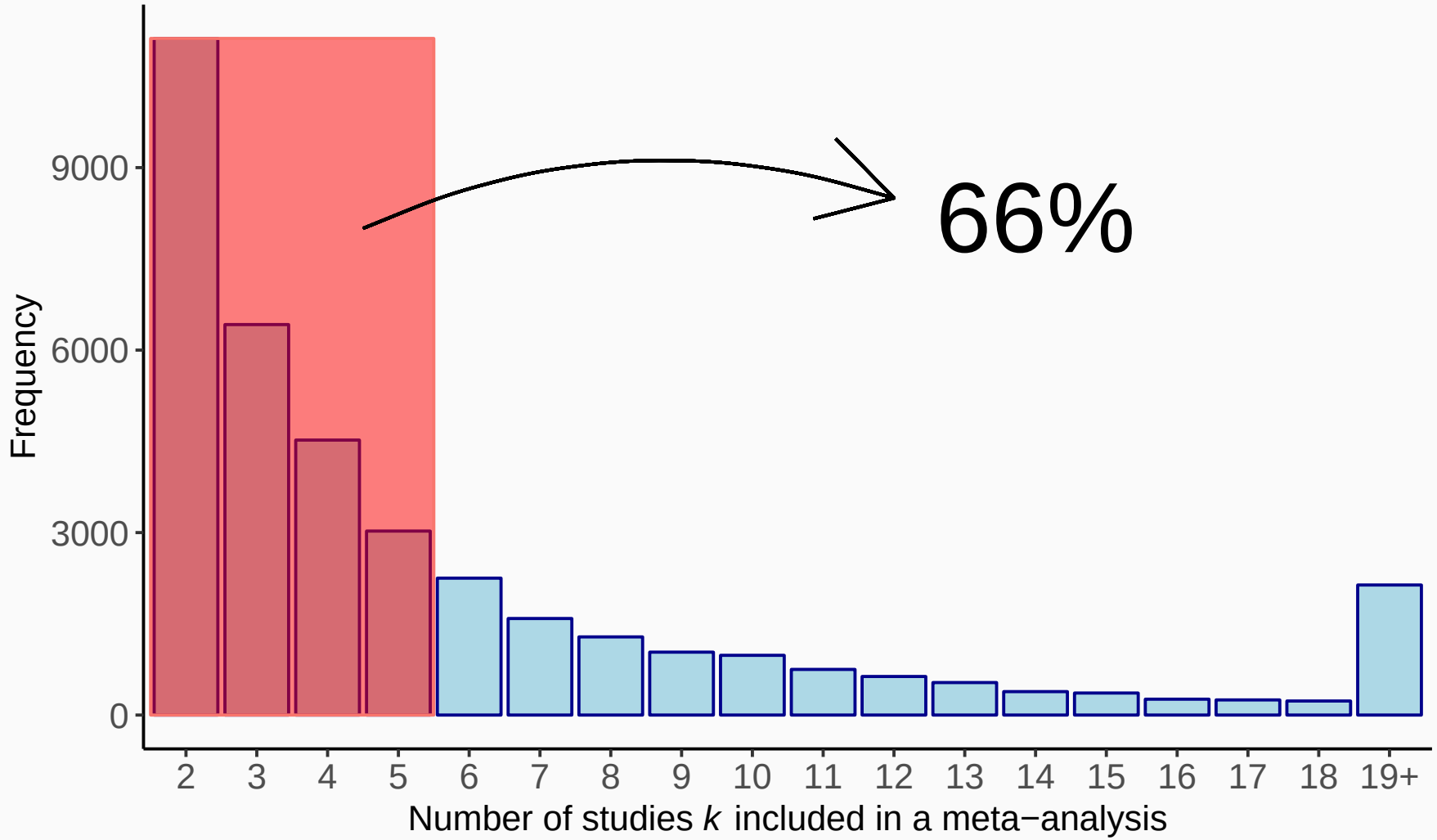

Cochrane Database: Rare events

Arm	Event		Sample size
	Yes	No	
Treatment	a	b	a + b
Control	c	d	c + d

- Percentage of meta-analyses with at least
  - one single-zero study: 38%
  - one double-zero study: 1%

- Standard meta-analysis methods rely on large sample properties (Bradburn et al., 2007)

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The statistical model (Smith et al., 1995)

- For trial i, number of events $r_i \sim \text{Bin}(\pi_i, n_i)$

$$\text{logit}(\pi_i) = \begin{cases} \mu_i - 0.5 \cdot \theta_i & \text{(control arm)} \\ \mu_i + 0.5 \cdot \theta_i & \text{(treatment arm)} \end{cases}$$

- Random treatment effects: $\theta_i \sim \mathcal{N}(\theta, \tau^2)$

- θ on the log-odds ratio scale

- Baseline risks (μ_i) trial-specific fixed-effects

A weakly informative prior (WIP) for θ

- A WIP for heterogeneity parameter τ, e.g. a half-normal prior

- A priori the odds ratio is with 95% probability confined to a certain range:

$$P(1/\delta < \exp(\theta) < \delta) = 95\%$$

- Normal prior: $\sigma = \frac{\log(\delta)}{1.96}$

- Say, conservatively, $\delta = 250$ implies $\theta \sim \mathcal{N}(0, 2.82^2)$

- The use of a WIP may be interpreted as a **penalizing** approach (Greenland and Mansournia, 2015)

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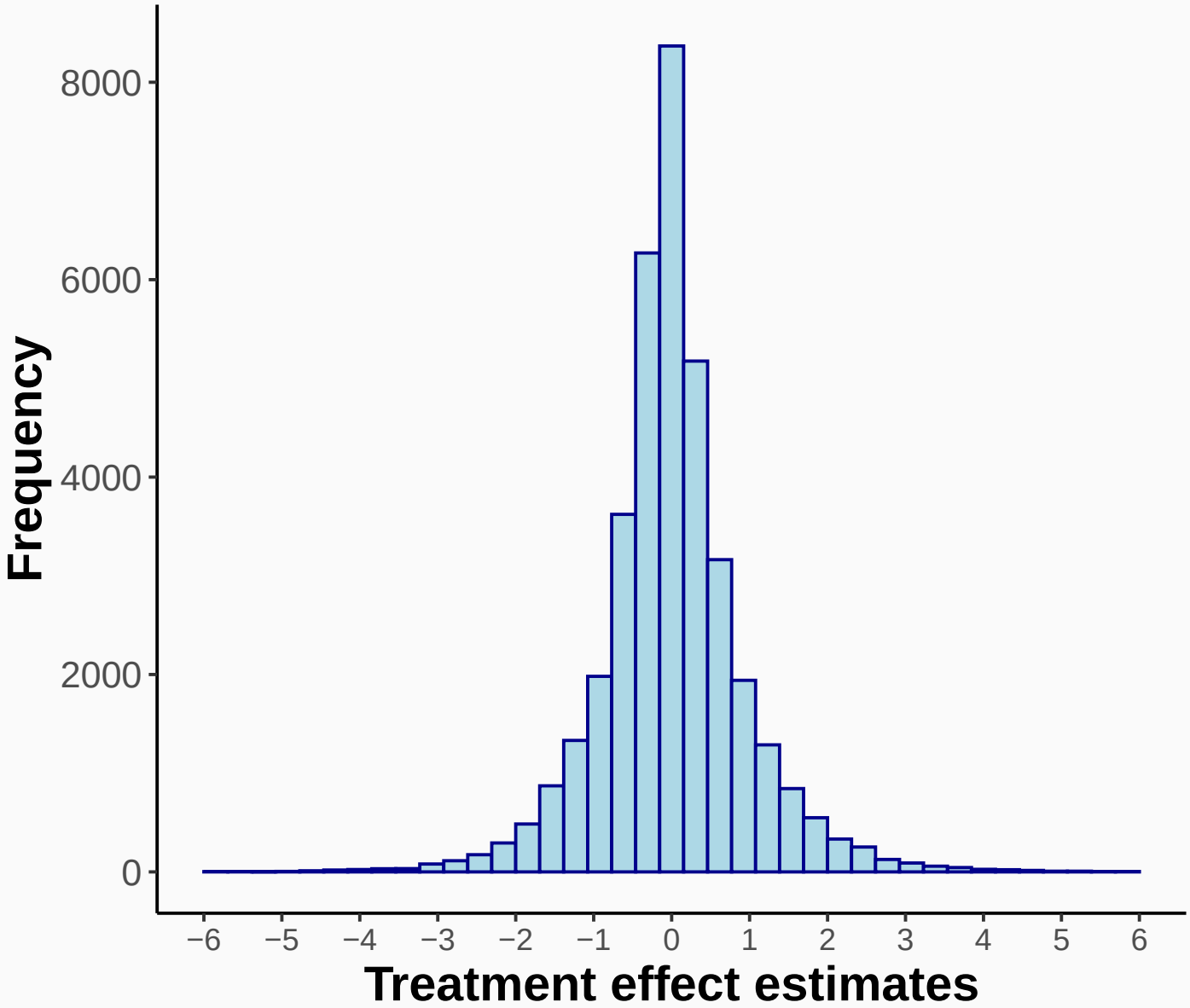
Cochrane Database: The distribution of the estimates of θ



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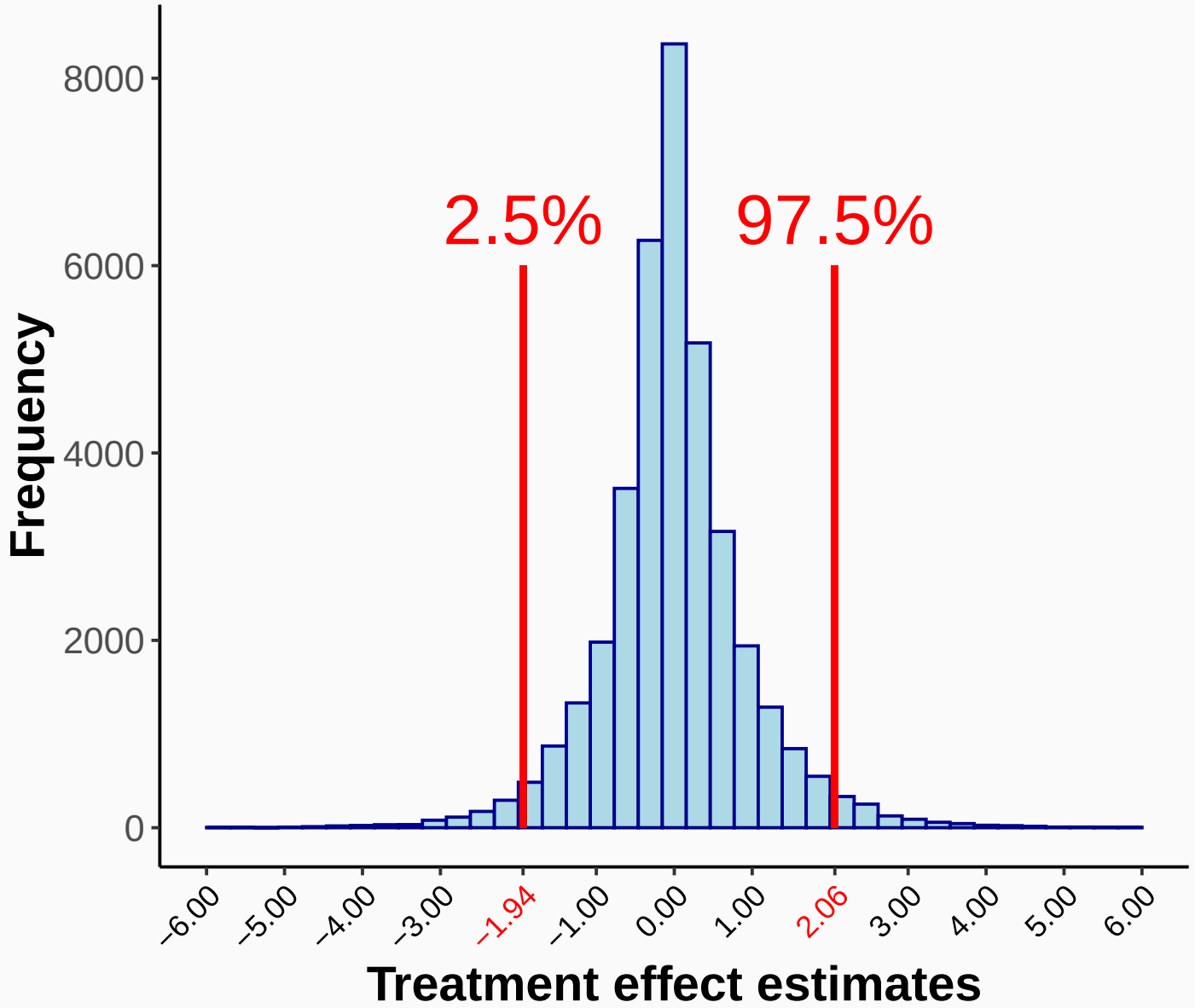


Further results

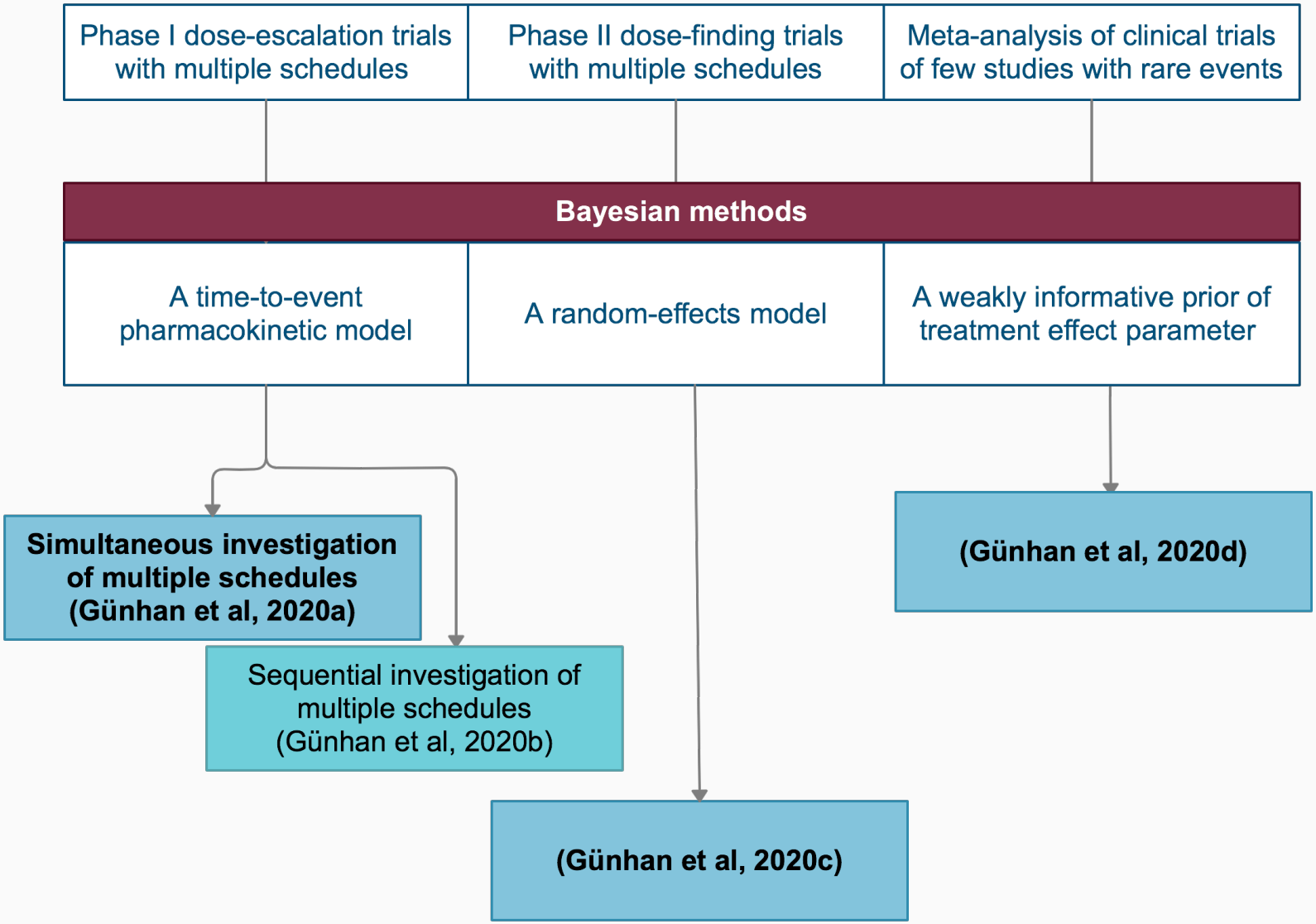
- Simulations are conducted to assess the performance of the use of WIP for θ
- Compared to alternatives, the proposed method displayed
  - lower bias for θ
  - shorter interval estimates for θ with somewhat higher coverage than nominal level
- An R package `MetaStan` is available on CRAN

Discussion and outlook

- Use of WIP for θ and τ for the meta-analysis of few studies involving rare events
  - A WIP can be derived for θ by considering a priori interval for θ on the log-odds ratio scale
  - Empirical investigation from the Cochrane Library supports the proposed WIP
- Future extensions include other type of models, e.g.
  - Poisson-Normal Hierarchical model (Böhning et al., 2015), which can take into account length of follow-up
  - Network meta-analysis (Günhan et al., 2018) models, which investigates multiple treatments and multi-arm trials

Conclusion

Conclusion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Phase II dose-finding trials with multiple schedules
Meta-analysis of clinical trials of few studies with rare events
Bayesian methods
A time-to-event pharmacokinetic model
A random-effects model
A weakly informative prior of treatment effect parameter
Simultaneous investigation of multiple schedules (Günhan et al, 2020a)
Sequential investigation of multiple schedules (Günhan et al, 2020b)
(Günhan et al, 2020c)
(Günhan et al, 2020d)

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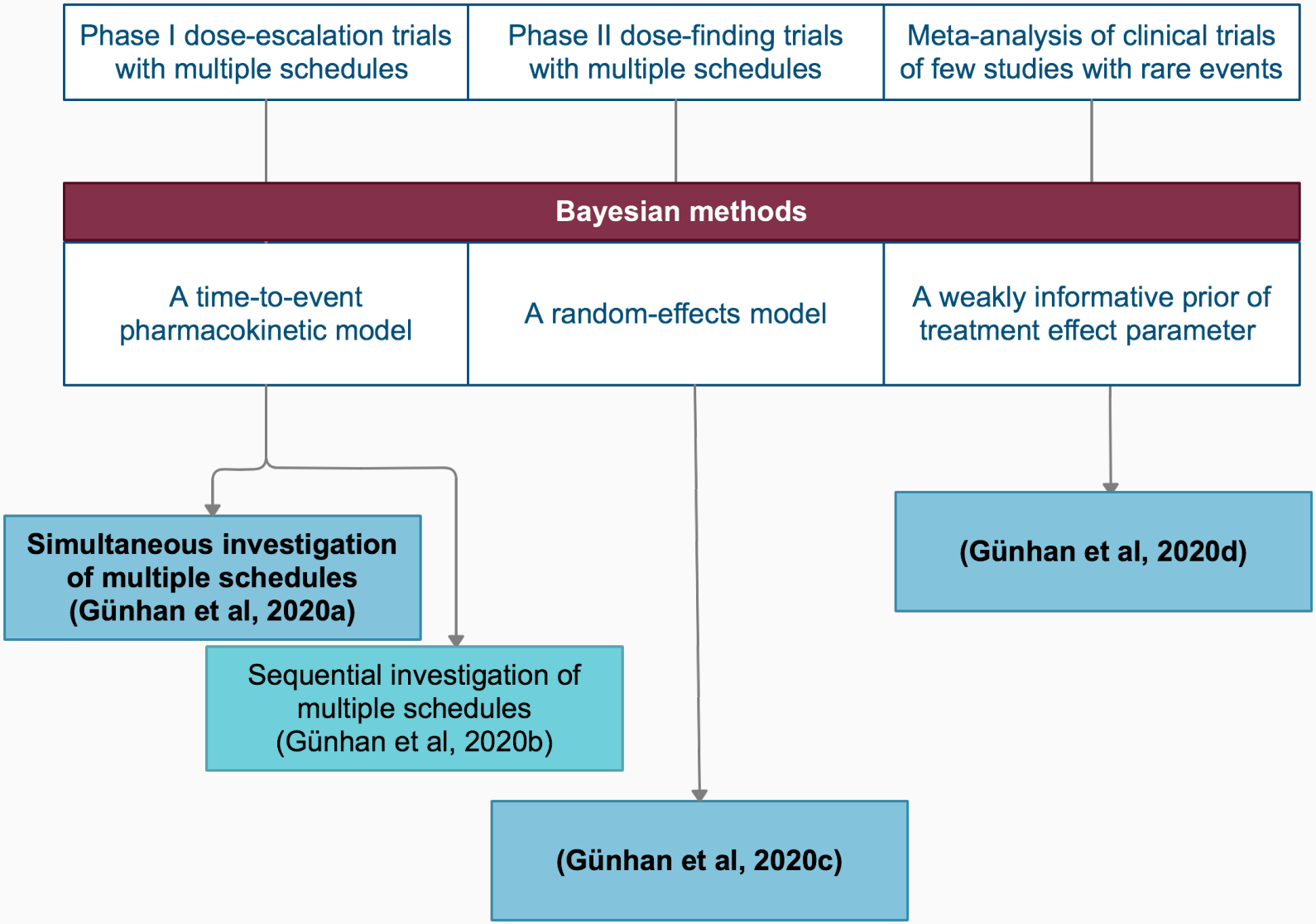
Conclusion


Phase I dose-escalation trials with multiple schedules
Phase II dose-finding trials with multiple schedules
Meta-analysis of clinical trials of few studies with rare events
Bayesian methods
A time-to-event pharmacokinetic model
A random-effects model
A weakly informative prior of treatment effect parameter
Simultaneous investigation of multiple schedules (Günhan et al, 2020a)
Sequential investigation of multiple schedules (Günhan et al, 2020b)
(Günhan et al, 2020c)
(Günhan et al, 2020d)

Stan: A programming language

- Calculating posterior distributions can be hard
  Conjugate models (analytically solvable) restrict the choice of likelihood and priors

- Markov chain Monte Carlo methods
  Generate samples from posterior distribution

- BUGS-based programs (WinBUGS, JAGS) uses Gibbs and Metropolis-Hasting samplers

- Stan uses Hamiltonian Monte Carlo sampler, uses the geometric nature of the target distribution

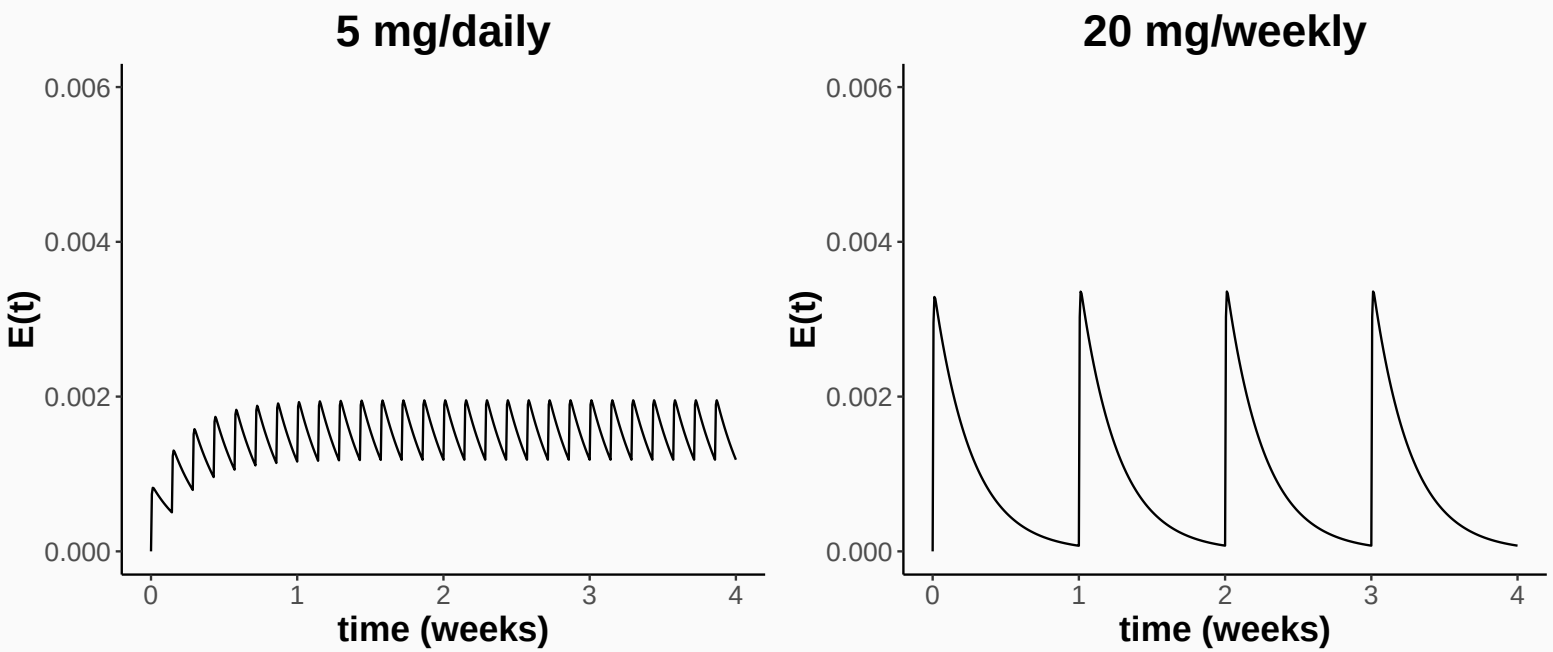
Vaccine trials

- Unlike drugs, which are given to patients, vaccines are received by whole population, thus the safety margin should be very high
- Efficacy based on the protection offered: Binomial enpoint
- Immunogenic endpoint: Antibody concentration, continous endpoint
- Phase I trials:
  - Oncology vs non-oncology
  - Oncology: The higher the dose, the greater the likelihood of efficacy and toxicity
  - DLT cause the halting of the trial
- Phase II trials:
  - Binomial endpoint: Use of a binomial likelihood
- Rare events:
  - Binomial endpoint
  - Based on the prevalence, we may encounter rare events

Likelihood estimation

- Firth penalization:
  - Penalty terms may be specified so that these nudge the MLE into a desired direction if the maximum is not or poorly defined; one such example is Firth penalization (Firth, 1993)
- Random-effects meta-analysis
  - Bayesian modal estimation to avoid zero estimates (Chung et al, 2013)

Pseudo-PK model



Pseudo-PK model

What body does to the drug

$$\frac{dC(t)}{dt} = -k_e\, C(t),$$

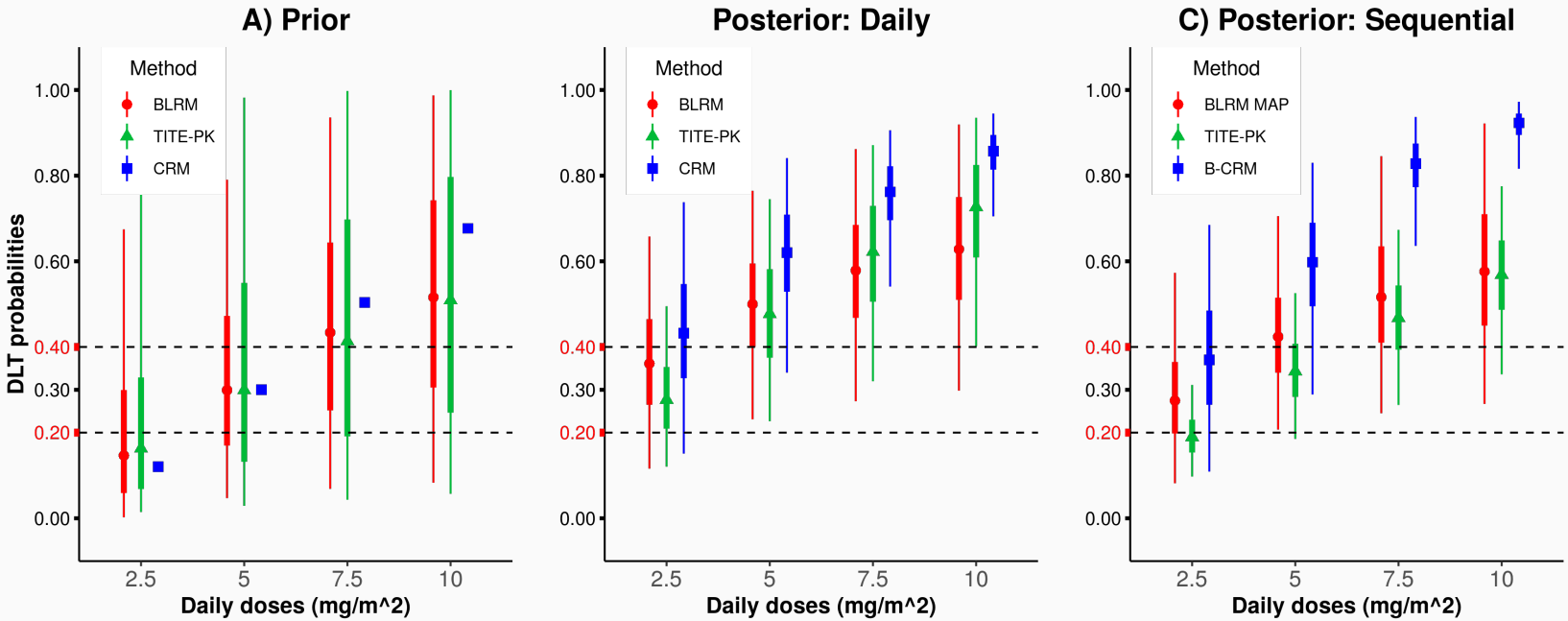
$$E(t|d,f) = \frac{C_{\text{eff}}(t|d,f)}{\int_0^{t^*} C_{\text{eff}}(t|d^*,f^*)\,dt}$$

$$\text{AUC}_E(t^*|d^*,f^*) = \int_0^{t^*} E(t|d^*,f^*)\,dt = 1.$$

Priors in TITE-PK

- TITE-PK: $\log(\beta) \sim \mathcal{N}(\text{cloglog}(P(T \leq t^* | d^*, f^*) = 0.30), 1.25^2)$
  where cloglog (x) = log(-log(1-x))

Everolimus trial



Dose-escalation decision criteria

- Cohort sizes of 3
- Next dose / Current dose ≤ 2
- Minimum number of patients at MTD: 6
- Maximum number of patients: 60
- Minimum number of patients: 21
- MTD declaration: $P(OD) \leq 0.25$

WIP for the heterogeneity parameter

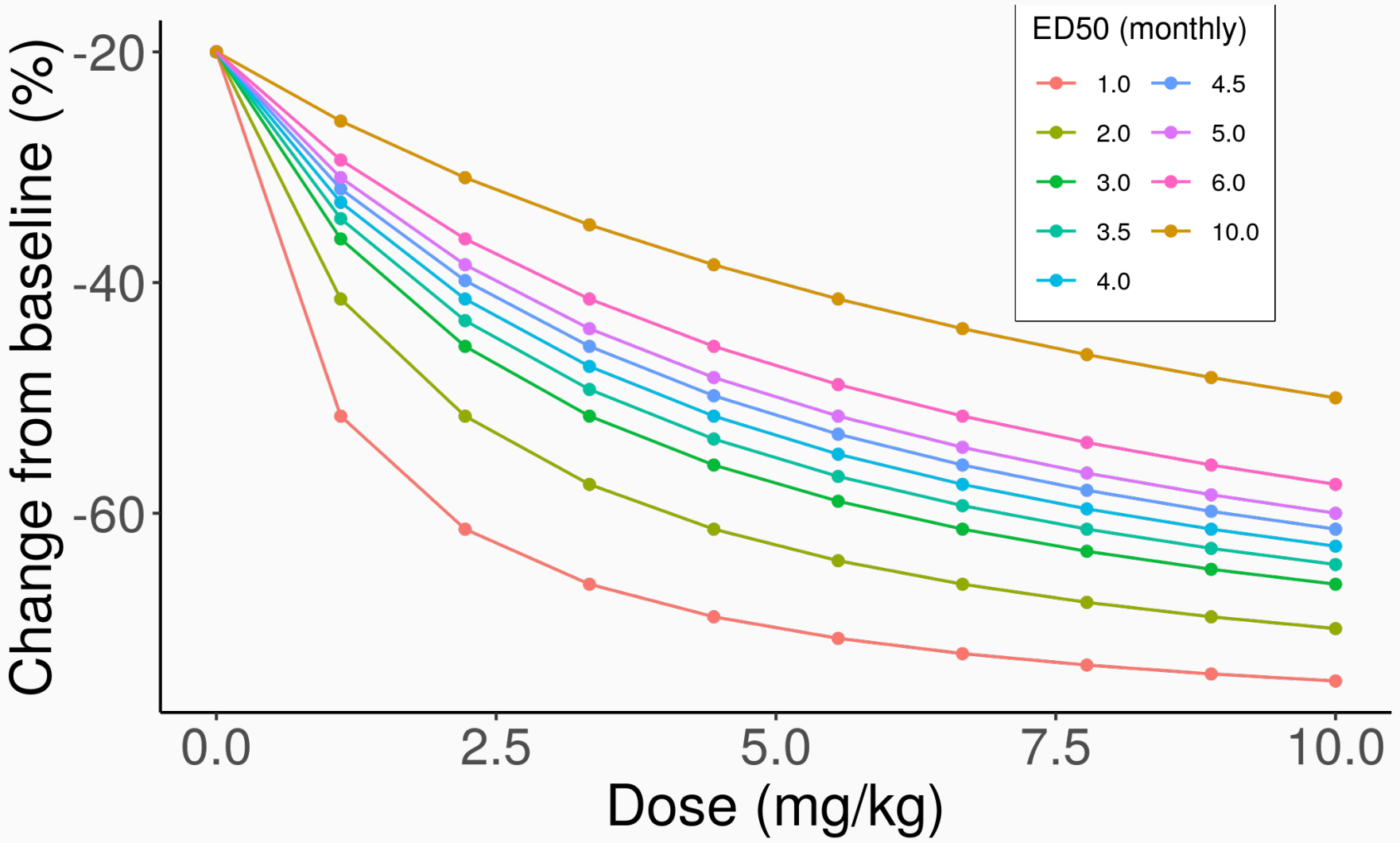
Table 2: Between-schedule heterogeneity $\tau_{\mathrm{ED}_{50}}$ in $\log(\mathrm{ED}_{50}^{*(i)})$: $\tau_{\mathrm{ED}_{50}}$ referring small to very large heterogeneity. The "range", $\exp(3.92 \cdot \tau_{\mathrm{ED}_{50}})$, refers to the ratio of the 97.5% to the 2.5% point of the distribution of $\mathrm{ED}_{50}^{*(i)}$.

$\tau_{\mathrm{ED}_{50}}$	"range" of $\mathrm{ED}_{50}^{*(i)}$
0.125 (small)	1.63
0.25 (moderate)	2.66
0.5 (substantial)	7.10
1 (large)	50.40
2 (very large)	2540.20

Simulation setup

- Motivated by the MOR106 trial
- Each generated trial includes one placebo arm and 1, 3, and 10 mg/kg for both bi-weekly and monthly schedules.
- Outcome: Percentage change from baseline in EASI score
- True values for $E_0^{(i)}$, $E_{max}^{(i)}$ and σ_i are taken as -20%, -60%, and 35% for both schedules, respectively.
- $ED_{50}^{\text{bi-weekly}}$ is 2 mg/kg.
- Sample sizes 45 for each arm.
- 9 scenarios: $ED_{50}^{\text{monthly}} \in \{1, 2, 3, 3.5, 4, 4.5, 5, 6, 10 \text{ (mg/kg)}\}$
- Data-generating process: Emax model
- 1 000 replications

Scenarios (monthly schedule)



Comparison of four methods

1. **CP (Frequentist)**: Complete pooling using a frequentist framework

2. **CP (Bayesian)**: Complete pooling using a Bayesian framework

3. **PP - FE**: Partial pooling with schedule specific fixed-effects for $\text{ED}_{50}^{(i)}$ using a Bayesian framework

4. **PP - RE**: Partial pooling with schedule specific random-effects for $\text{ED}_{50}^{(i)}$ using a Bayesian framework

Performance measures for the biweekly schedule

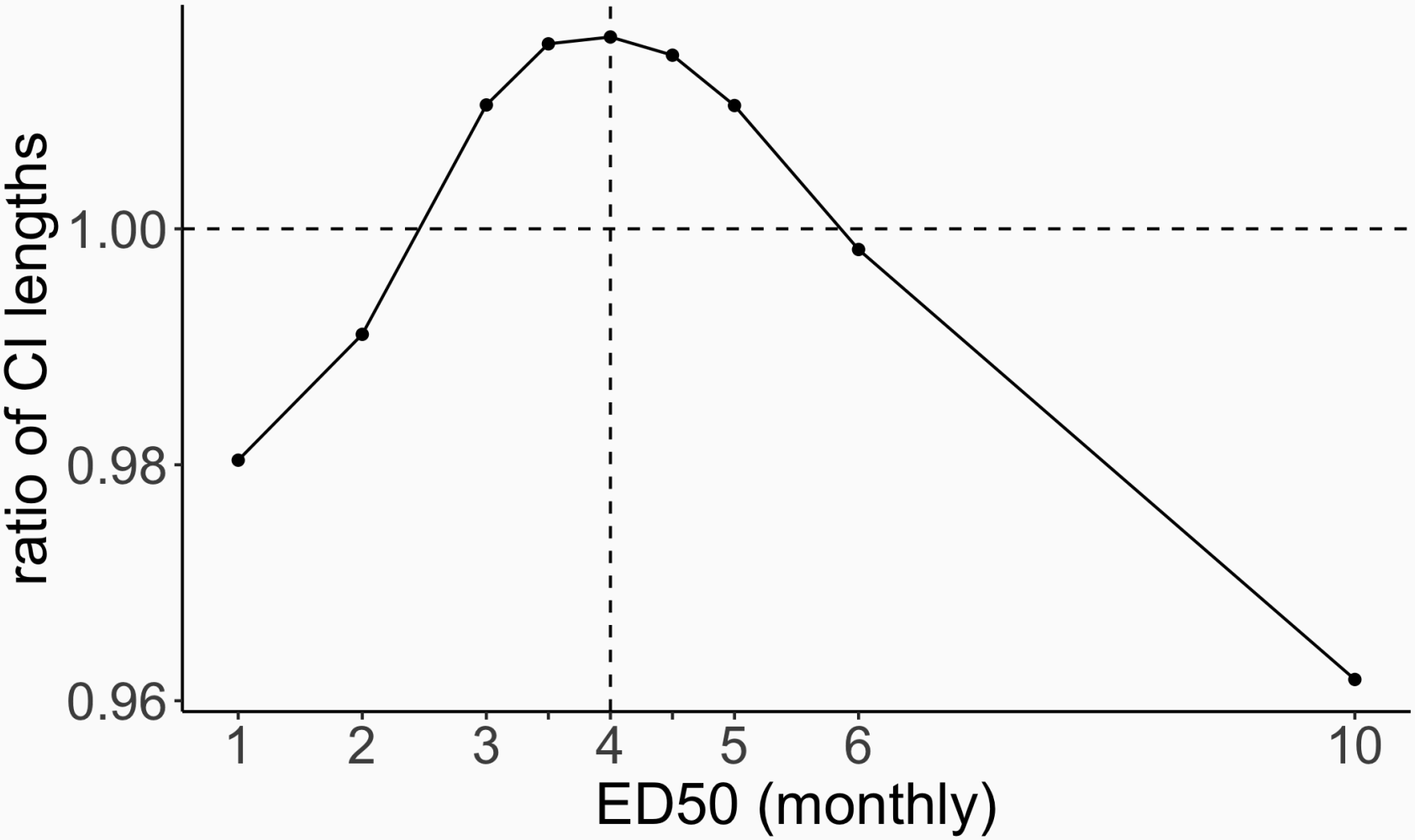
1. **Mean absolute error**
   $1/|D| \sum_{i \in D} |f(i) - \hat{f}(i)|$ at each i (prespecified dose levels), $\hat{f}(i)$ the point estimates for the dose-response function $f(i)$

2. **Mean coverage probability**
   Mean coverage probability of the interval estimates evaluated at each i

3. **Mean interval length**
   Mean length of the interval estimates at each i

Simulation results

- Ratio of the CI lengths obtained by PP - FE to PP - RE



Bococizumab trial: NCT01592240

- A phase II dose-finding trial: Bococizumab investigated for the treatment of hypercholesterolemia
- Primary outcome: The change from baseline in low-density lipoprotein cholesterol (LDL-C) at Day 85

Arm	Schedule	Dose (mg)
1	Bi-weekly	0
2	Bi-weekly	50
3	Bi-weekly	100
4	Bi-weekly	150
5	Monthly	0
6	Monthly	200
7	Monthly	300

Simulation settings

- Numbers of studies:
  $k \in \{2, 3, 5\}$

- Treatment effects:
  $\theta \in \{-5, -4, -3, -2, -1, -0.5, 0, 0.5, 1, 2, 3, 4, 5\}$

- Baseline risks μ_i on the probability scale are taken uniformly between 0.005 and 0.05.

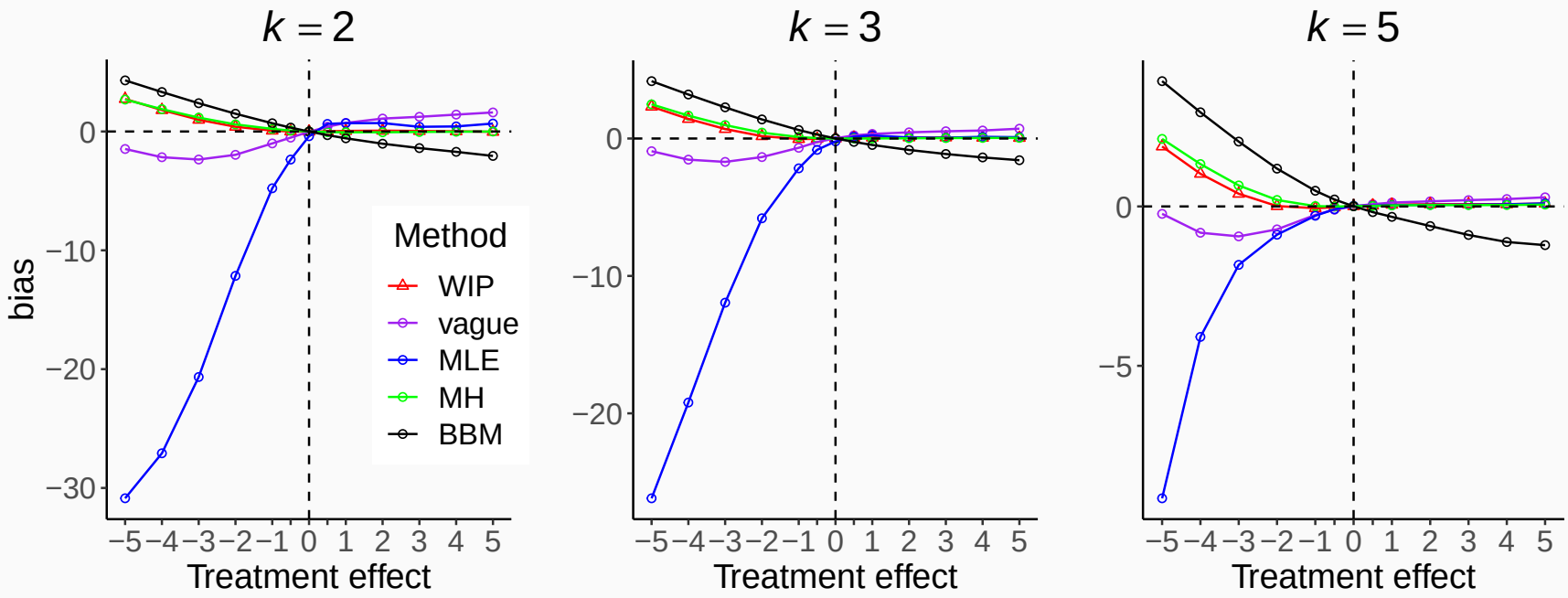
- The degree of heterogeneity ($\tau = 0.28$) and sample sizes are based on Cochrane Database.

- Data-generating process: BNHM

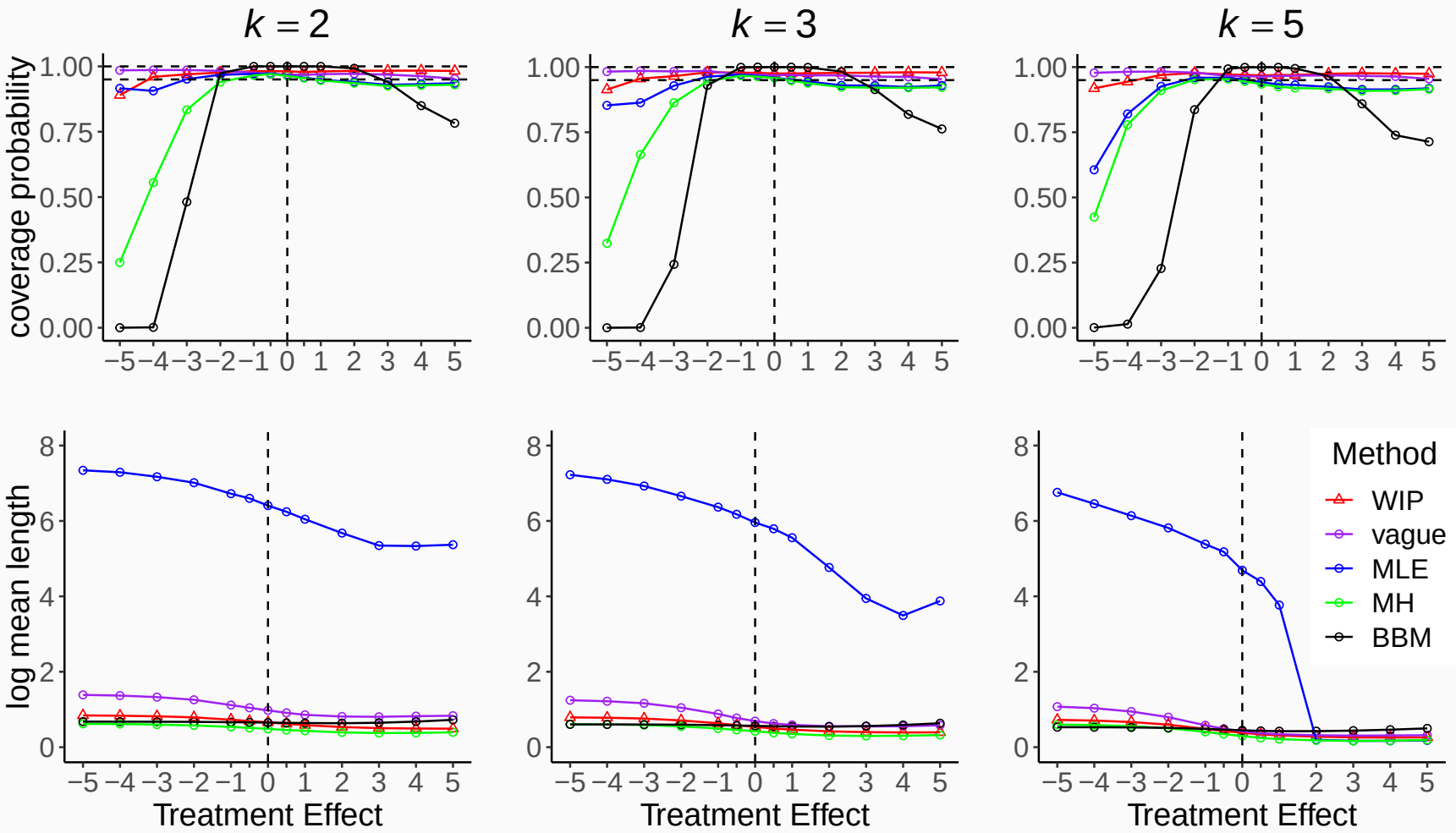
Comparison of five meta-analysis methods

1. WIP: WIP for τ and WIP for θ, BNHM
2. vague: WIP for τ and vague prior for θ ($\theta \sim \mathcal{N}(0, 100^2)$), BNHM
3. MLE: BNHM
4. MH: Mantel-Haenszel method, a fixed-effect method
5. BBM: Beta-binomial model (Bayesian)

Simulation results



Simulation results



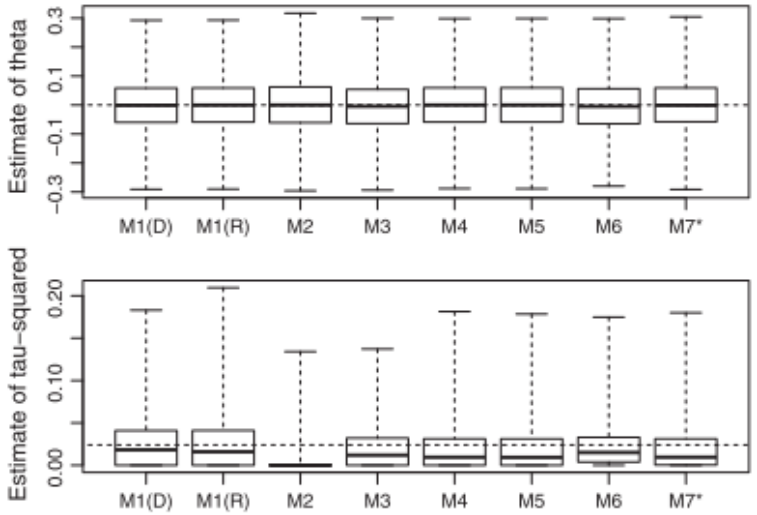
Effects of treatment coding (Jackson et al., 2018)

we have

$$\begin{pmatrix} \text{logit}(\pi_{i0}) \\ \text{logit}(\pi_{i1}) \end{pmatrix} \sim N\left(\begin{pmatrix} \gamma_i \\ \gamma_i + \theta \end{pmatrix}, \begin{pmatrix} 0 & 0 \\ 0 & \tau^2 \end{pmatrix} \right),$$

and from Equation 2, for model 4, we have

$$\begin{pmatrix} \text{logit}(\pi_{i0}) \\ \text{logit}(\pi_{i1}) \end{pmatrix} \sim N\left(\begin{pmatrix} \gamma_i \\ \gamma_i + \theta \end{pmatrix}, \begin{pmatrix} \tau^2/4 & -\tau^2/4 \\ -\tau^2/4 & \tau^2/4 \end{pmatrix} \right).$$



An R package for meta-analysis using Stan: MetaStan

Available on CRAN

```
install.packages("MetaStan")
```

Fitting a BNHM using WIP for θ and τ

```
meta_stan(data = mydata,
          nctrl = nctrl,
          rctrl = rctrl,
          ntrt = ntrt,
          rtrt = rtrt,
          tau_prior_dist = "half-normal",
          tau_prior = 0.5,
          delta = 250)
```

```
vignette("MetaStan_BNHM")
```