The use of historical control data in clinical trials

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Symposium “Statistical Planning of Translational Studies”
Göttingen
March 20, 2024

Incorporating historical controls in preclinical trials using meta-analytic models

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Introduction

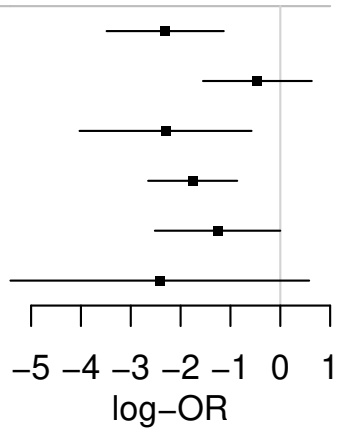
- clinical-trials background
  - meta-analysis, normal-normal model
  - mean effect, shrinkage estimation and prediction
- pre-clinical application
  - cross-checking / matching historical and concurrent data
  - augmenting a control group with historical data
- summary / outlook

The NNHM

The meta-analysis problem: pediatric transplantation example

- meta-analysis problem: want to model/combine measurements (usually: *effects*) that are associated with standard errors
- example: Effect of IL-2RA on *acute rejection* events in pediatric liver transplantation [1]

study	treatment	control	log–OR	95% CI
Heffron (2003)	14 / 61	15 / 20	–2.31	[–3.48, –1.13]
Gibelli (2004)	16 / 28	19 / 28	–0.46	[–1.55, 0.63]
Schuller (2005)	3 / 18	8 / 12	–2.30	[–4.03, –0.58]
Ganschow (2005)	9 / 54	29 / 54	–1.76	[–2.65, –0.86]
Spada (2006)	4 / 36	11 / 36	–1.26	[–2.52, –0.00]
Gras (2008)	0 / 50	3 / 34	–2.42	[–5.41, 0.58]

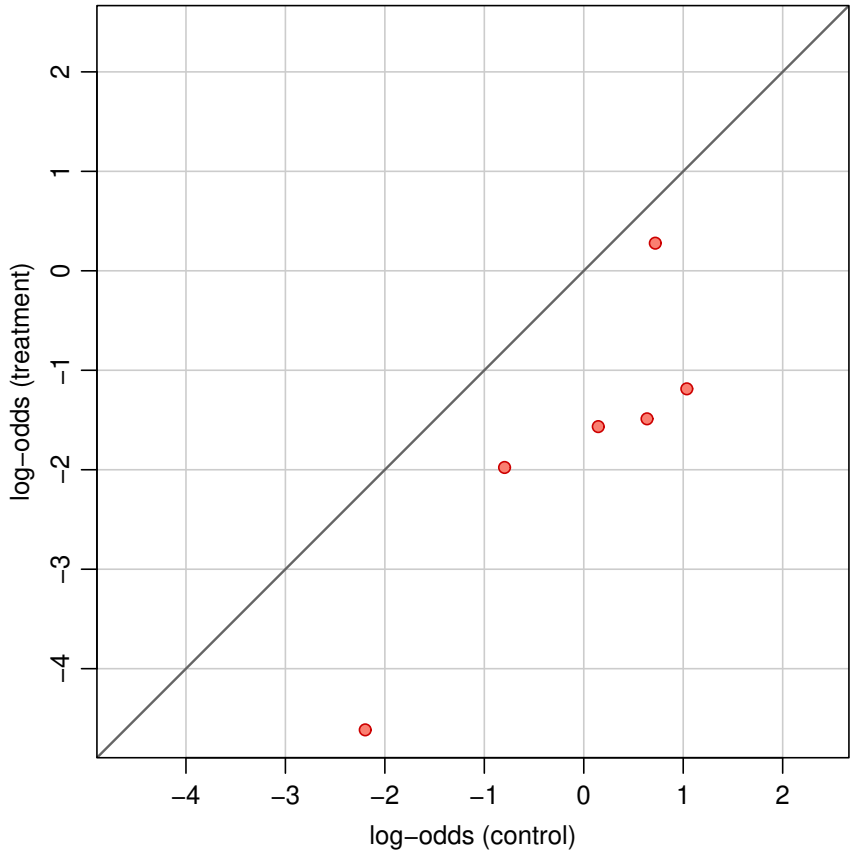


- idea: characterize/model “population” of (log-) ORs

[1] N.D. Crins, C. Röver, A.D. Goralczyk, T. Friede. Interleukin-2 receptor antagonists for pediatric liver transplant recipients: A systematic review and meta-analysis of controlled studies. *Pediatric Transplantation*, **18**(8):839–850, 2014.

The NNHM

Reminder: stratification



- important principle: **stratified analysis** of ("relative") effects (here: consideration of **log-ORs**)
- pooling of "baselines" (here: odds) may "break randomization" [2]

[2] S. Dias, A.E. Ades. Absolute or relative effects? Arm-based synthesis of trial data. *Research Synthesis Methods*, **7**(1):23–28, 2016.

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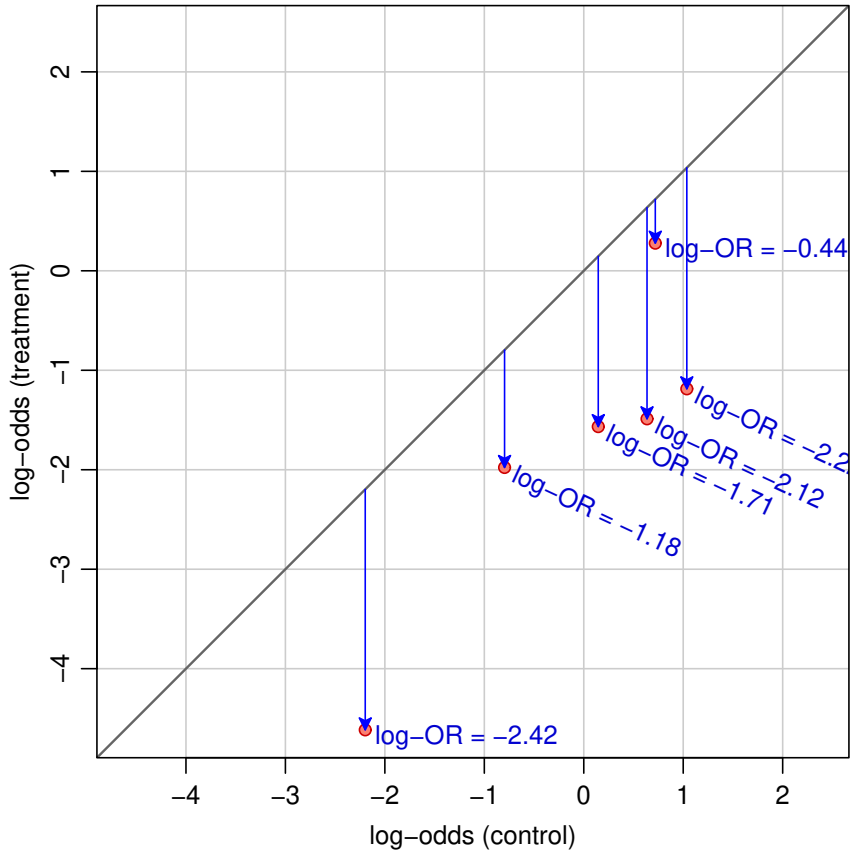

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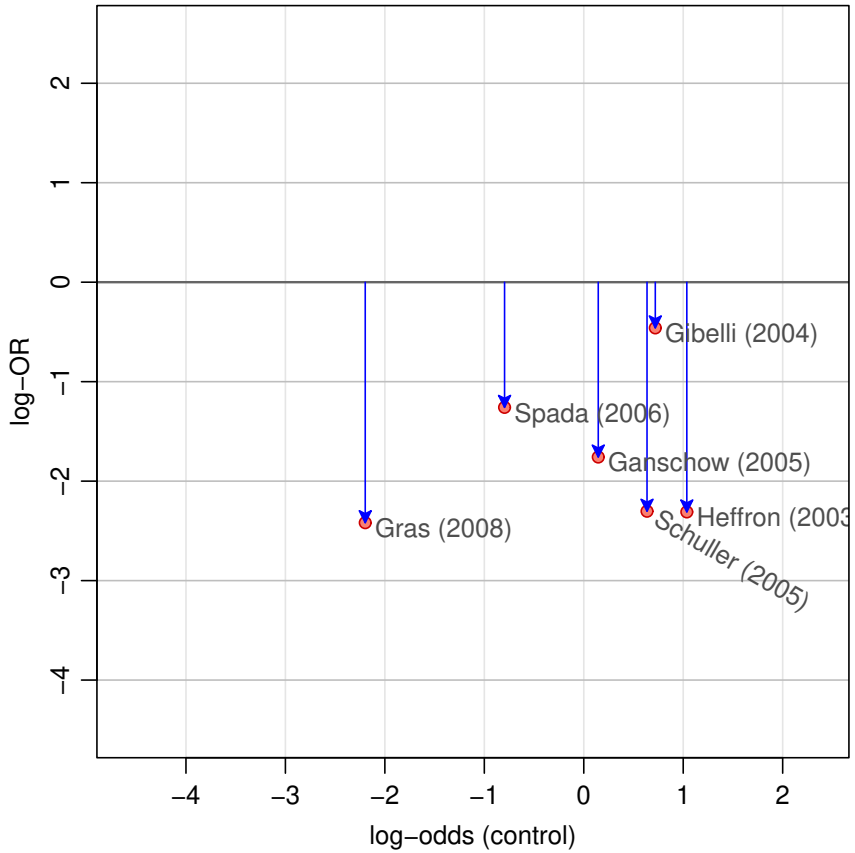

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- possible aims:
  - to characterize log-ORs,
    infer **location** (mean) and **scale** (variability)
  - mutual support of estimates — e.g., does consideration of previous studies constrain the uncertain estimate from the most recent study?
    → "**shrinkage estimation**"
  - **prediction** of a "future" study
    e.g., to aid in study design[3]

[3] H. Schmidli, B. Neuenschwander, T. Friede. Meta-analytic-predictive use of historical variance data for the design and analysis of clinical trials. *Computational Statistics and Data Analysis*, **113**:100–110, 2017.

The NNHM

The normal-normal hierarchical model (NNHM)

- have:
  - estimates y_i
  - standard errors σ_i

  $(i = 1, \ldots, k)$
- assume:

$$\begin{aligned} y_i|\theta_i &\sim \text{Normal}(\theta_i, \sigma_i^2) \\ \theta_i|\mu, \tau &\sim \text{Normal}(\mu, \tau^2) \end{aligned}$$

  or (marginally):

$$y_i|\mu, \tau \sim \text{Normal}(\mu, \tau^2 + \sigma_i^2)$$

- random-effects (RE) model,
  normal-normal hierarchical model (NNHM)
- "**overall mean**" μ
- "**study-specific effects**" θ_i
- **heterogeneity** parameter $\tau \geq 0$

The NNHM

The technical bits

- frequentist and Bayesian approaches common;
  (focus on Bayesian here)
- implementation straightforward using MCMC (e.g., JAGS, Stan)
- semi-analytically implemented in `bayesmeta` R package [4, 5]
- prior for overall mean μ:
  uniform often sensible; for informative priors: normal [5]
- prior for heterogeneity τ:
  uninformative priors possible (sensible) for large k
  otherwise (small k): (weakly) informative priors necessary. [6]

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[4] `http://cran.r-project.org/package=bayesmeta`

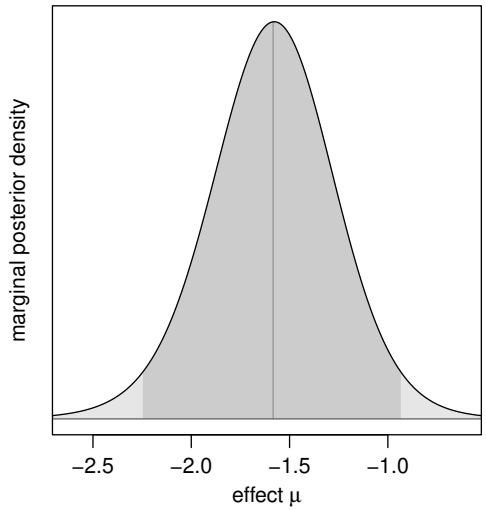
[5] C. Röver. Bayesian random-effects meta-analysis using the bayesmeta R package. *Journal of Statistical Software*, **93**(6):1–51, 2020.

[6] C. Röver, R. Bender, S. Dias, C.H. Schmid, H. Schmidli, S. Sturtz, S. Weber, T. Friede. On weakly informative prior distributions for the heterogeneity parameter in Bayesian random-effects meta-analysis. *Research Synthesis Methods*, **12**(4):448–474, 2021.

The NNHM

Pediatric transplantation example

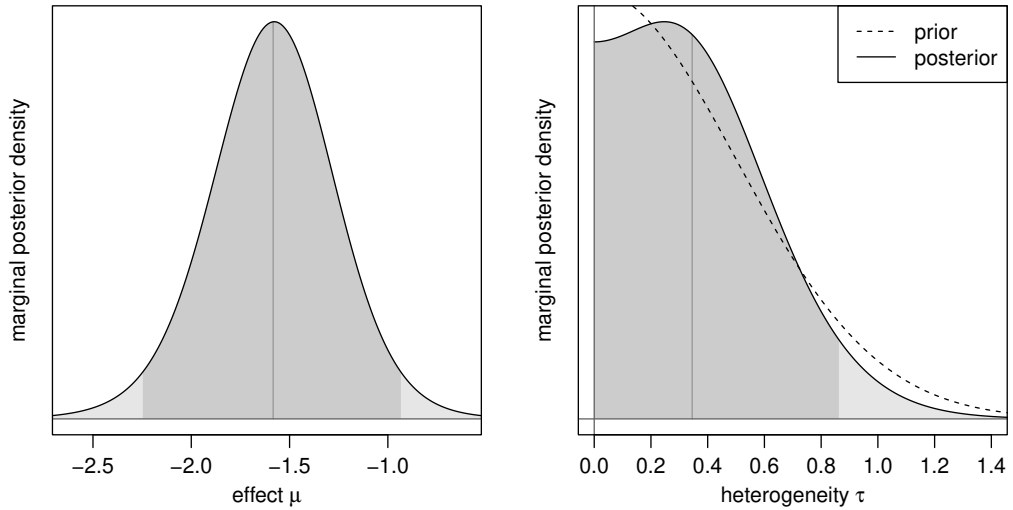
- may infer mean effect (μ)



The NNHM

Pediatric transplantation example

- may infer mean effect (μ), heterogeneity (τ)



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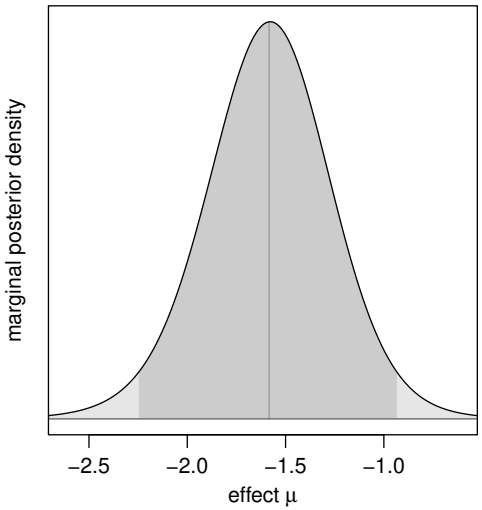
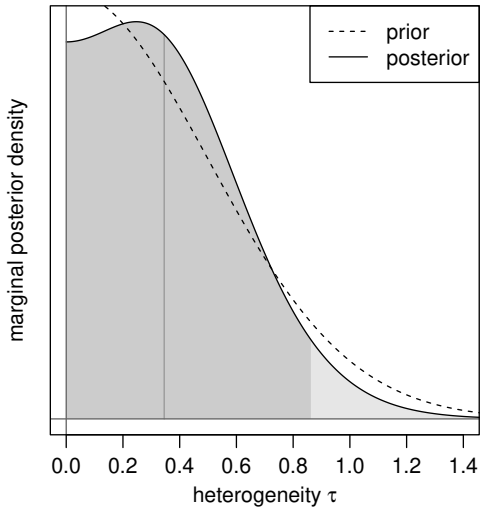
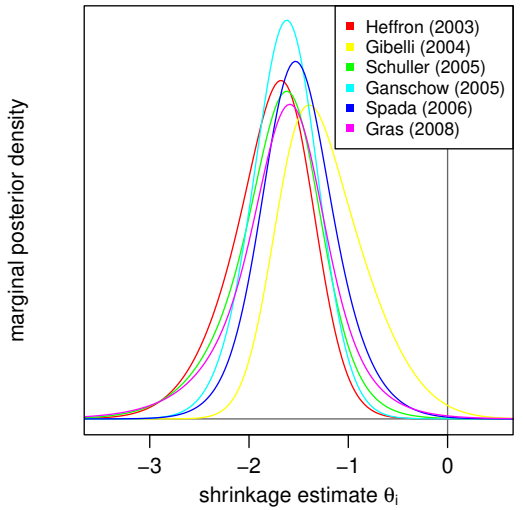
Pediatric transplantation example

- may infer mean effect (μ), heterogeneity (τ), shrinkage estimates (θ_i)







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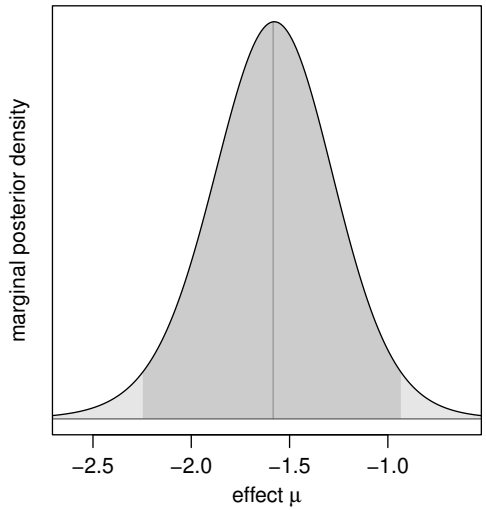
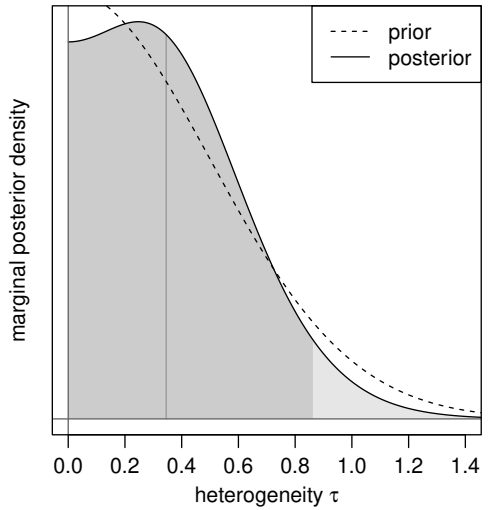
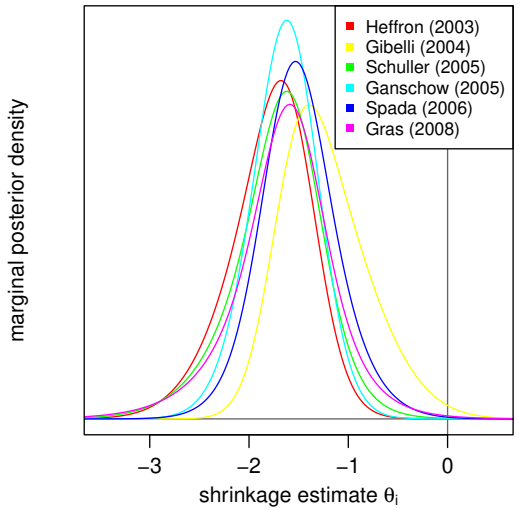
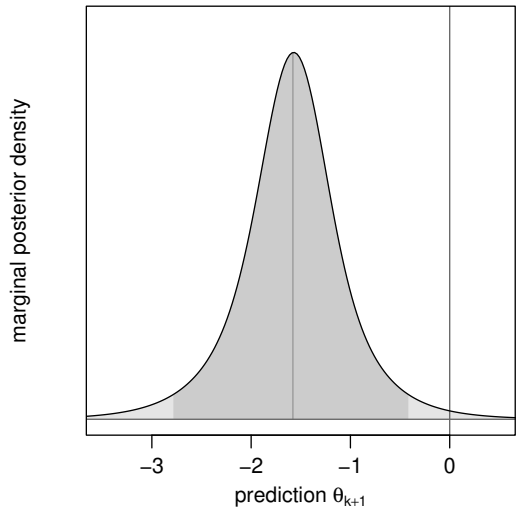






- and prediction ($\theta_{k+1}|\mu, \tau \sim \text{Normal}(\mu, \tau^2)$)



The NNHM

Example

- results commonly illustrated in a “forest plot”

study	estimate	95% CI
Heffron (2003)	–2.31	[–3.48, –1.13]
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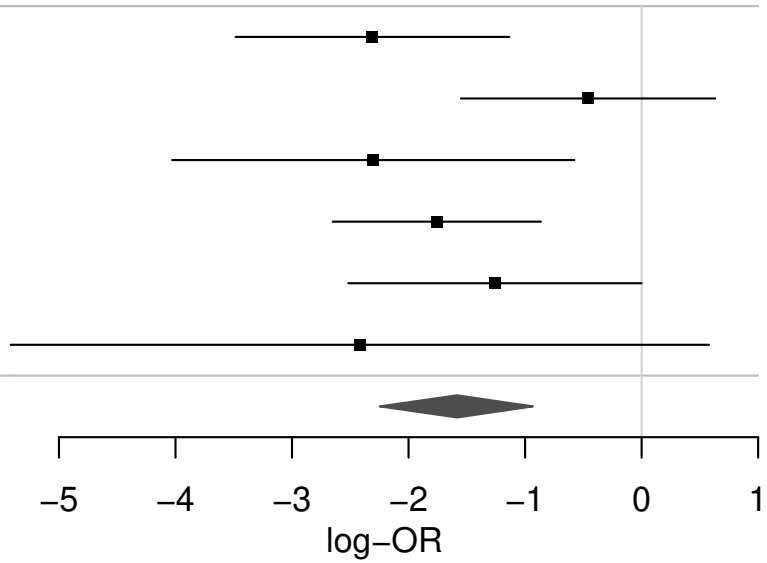

Heterogeneity (tau): 0.35 [0.00, 0.86]

- overall mean (μ) estimate shown as a diamond

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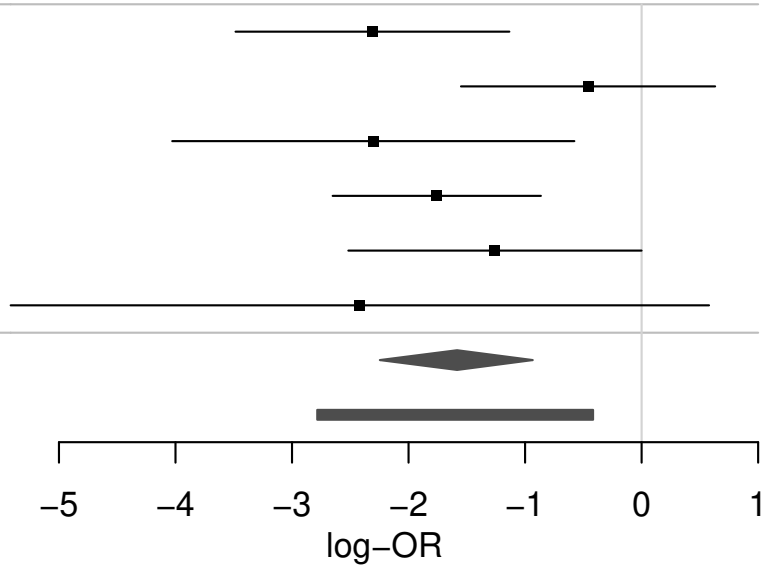
Gras (2008)	–2.42	[–5.41, 0.58]
mean	**–1.58**	**[–2.25, –0.93]**
prediction	**–1.58**	**[–2.78, –0.42]**



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- overall mean (μ) estimate shown as a diamond
- prediction interval

The NNHM

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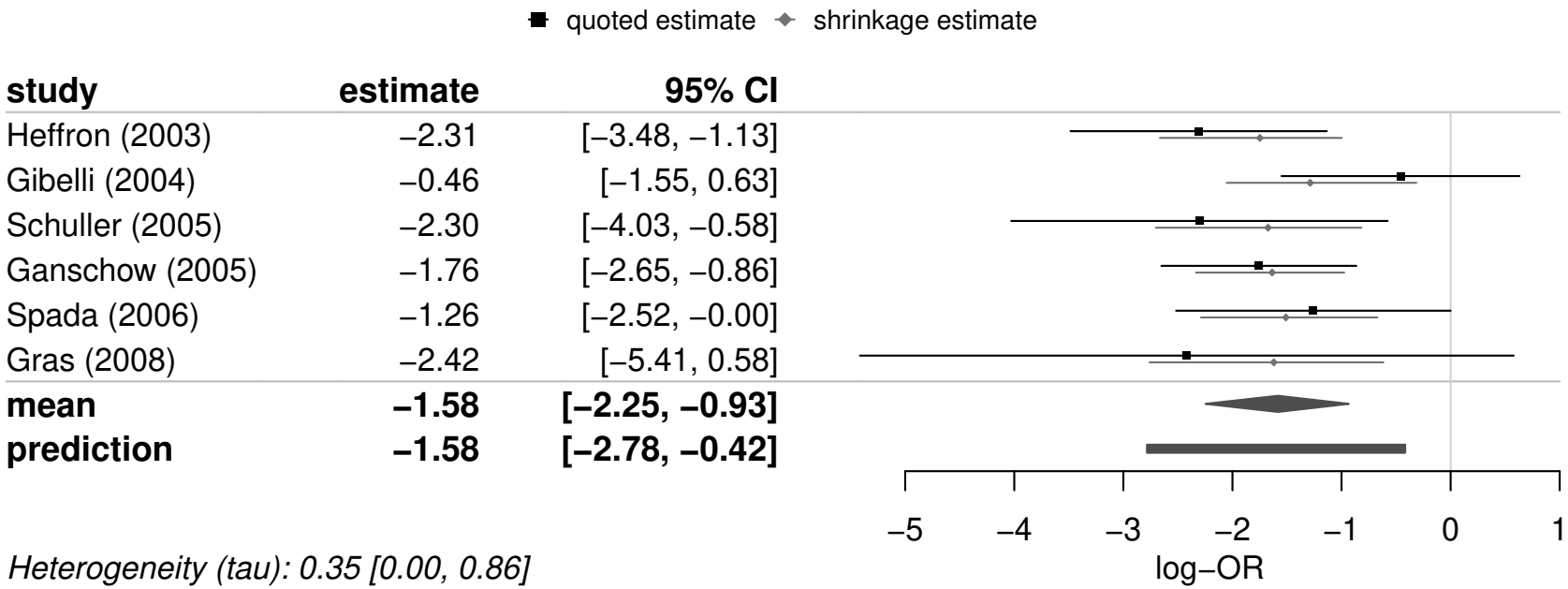


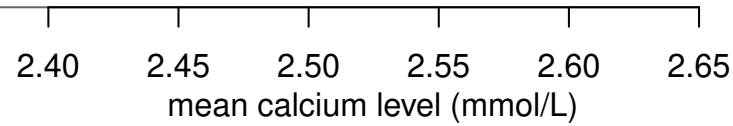
- overall mean (μ) estimate shown as a diamond
- prediction interval
- shrinkage estimates

Historical control data

Serum calcium example data set [7]

- 17 historical, 1 concurrent control group

study	N	mean	se
Study−15	10	2.501	0.018
Study−16	10	2.564	0.020
Study−17	10	2.550	0.019
Study−18	10	2.528	0.029
Study−19	10	2.488	0.012
Study−20	5	2.508	0.022
Study−21	5	2.524	0.031
Study−22	10	2.612	0.016
Study−23	10	2.480	0.013
Study−24	10	2.572	0.019
Study−25	10	2.609	0.008
Study−26	10	2.508	0.015
Study−27	10	2.561	0.025
Study−28	6	2.570	0.018
Study−29	10	2.437	0.019
Study−30	10	2.511	0.012
Study−32	10	2.533	0.031
concurrent	10	2.570	0.019



[7] A. Gurjanov, A. Kreuchwig, T. Steger-Hartmann, L.A.I. Vaas. Hurdles and signposts on the road to virtual control groups — A case study illustrating the influence of anesthesia protocols on electrolyte levels in rats. *Frontiers in Pharmacology* **14**:1142534, 2023.

Historical control data

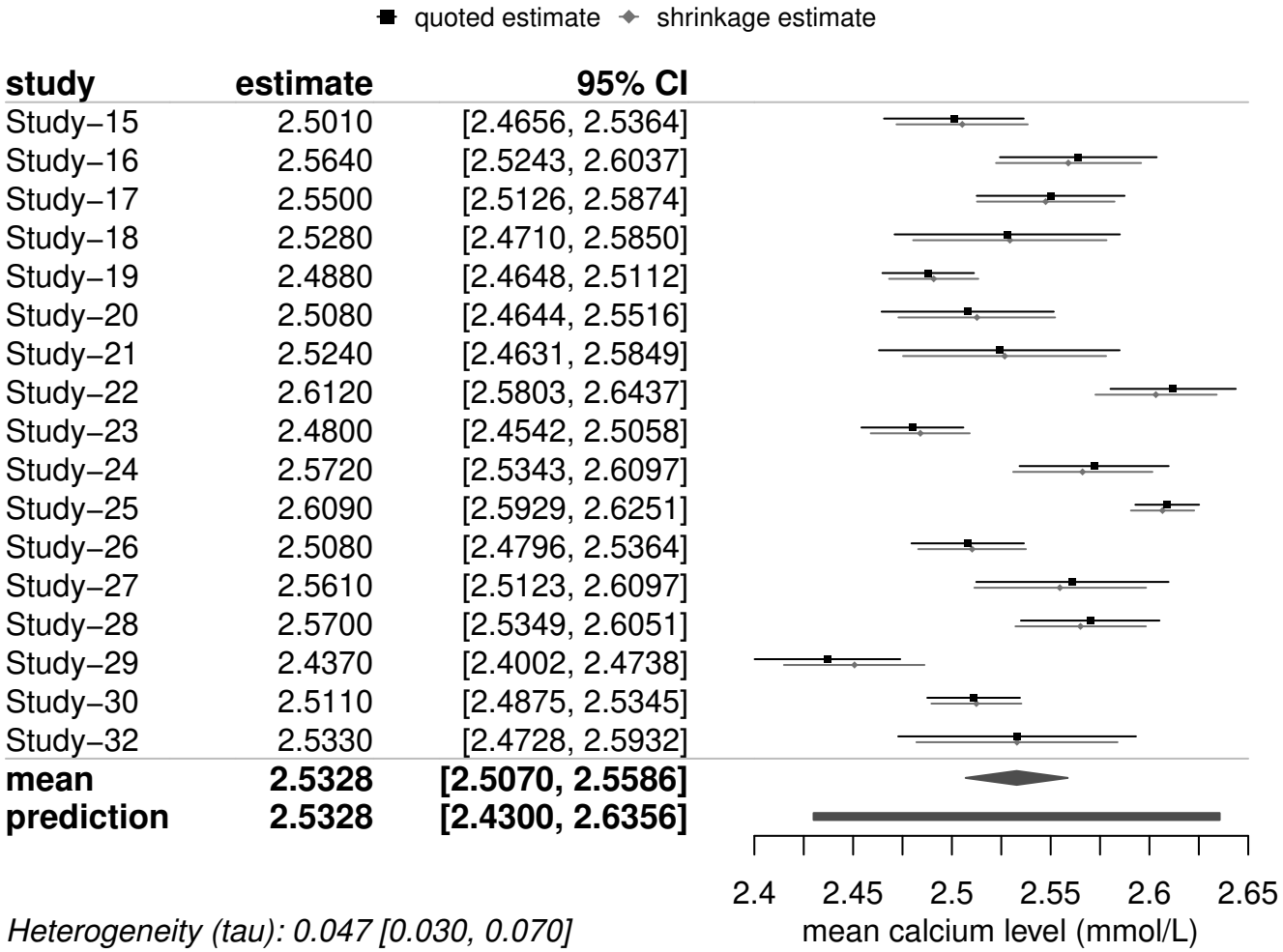
Matching historical and concurrent data

- are new data "**consistent**" with historical data?
- link between historical and new data: **predictive distribution**;
  in particular:
  - (posterior) predictive distribution $p(\theta_{18}|y_1, \ldots, y_{17})$
  - new observation y_{18} (with s.e. σ_{18})
  - link: $y_{18}|\theta_{18}, \sigma_{18} \sim \text{Normal}(\theta_{18}, \sigma_{18}^2)$
- predictive distribution of y_{18} (rather than θ_{18})
  (i.e.: $p(y_{18}|y_1, \ldots, y_{17})$)
  results as a sum of predictive distribution and an additional normal term.

Historical control data

Matching historical and concurrent data

- perform meta analysis of 17 historical estimates. . .



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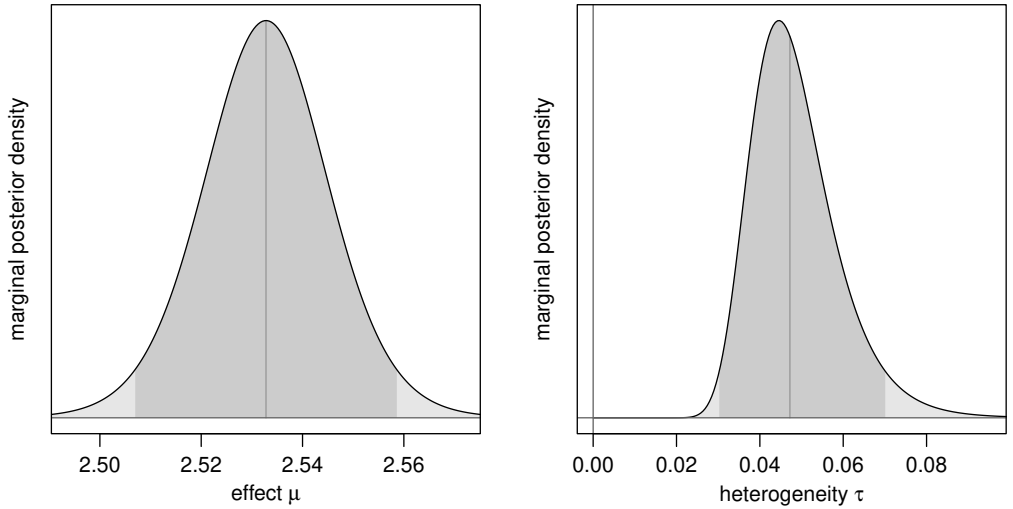
- infer mean effect (μ) and heterogeneity (τ)



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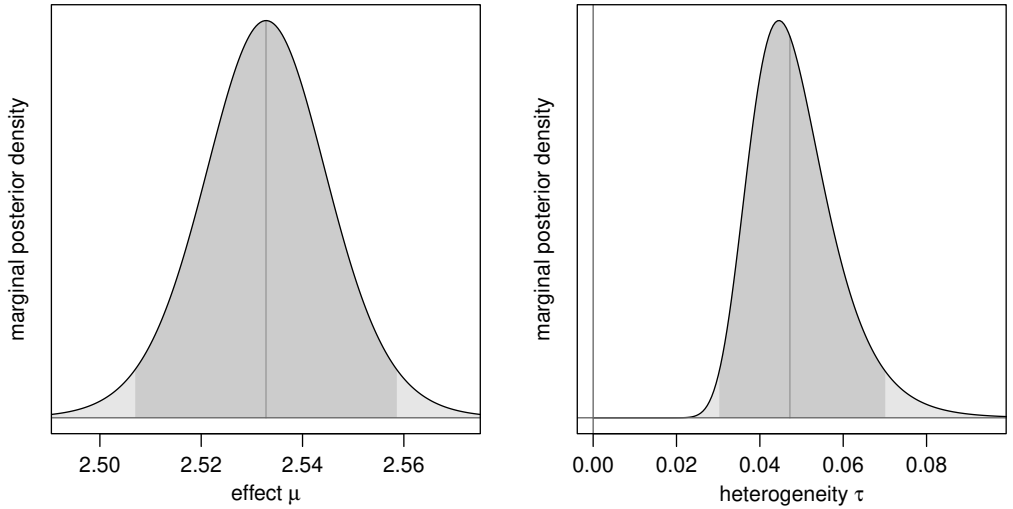
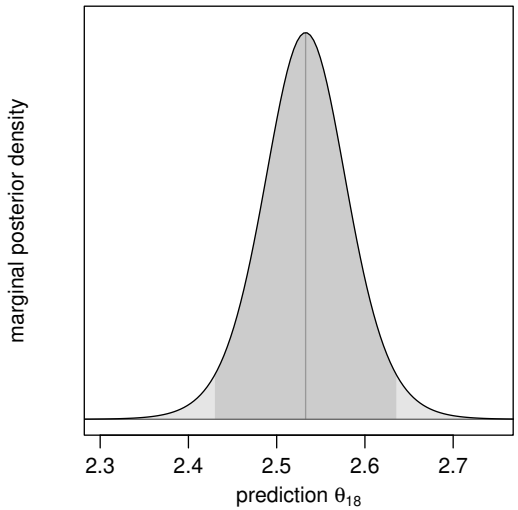


- derive prediction (parameter θ_{18})



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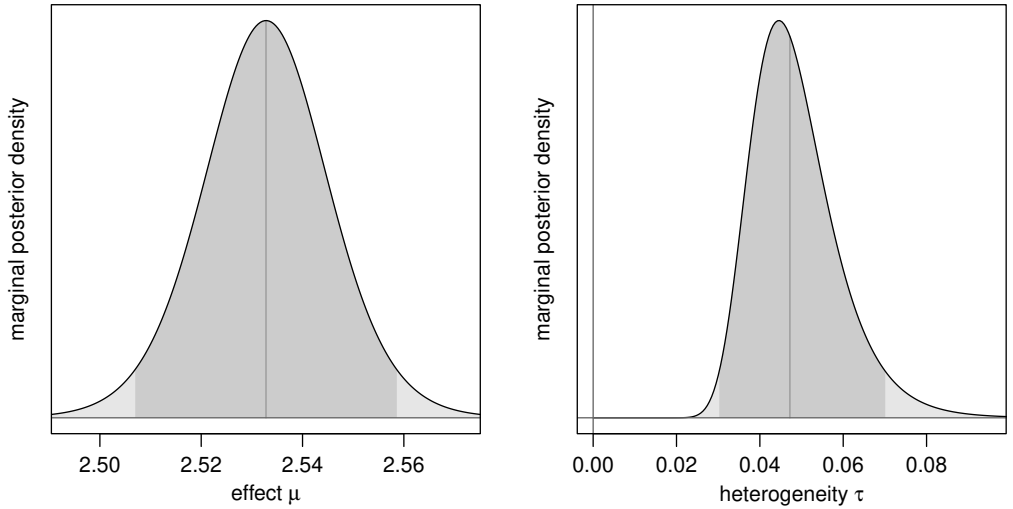
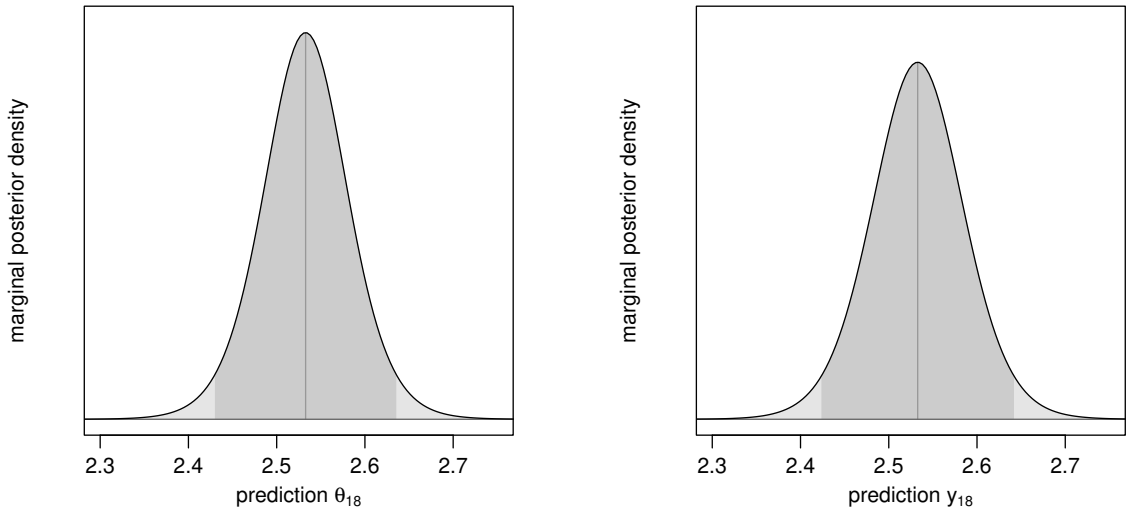


- derive prediction (parameter θ_{18}) **and data (average y_{18})**



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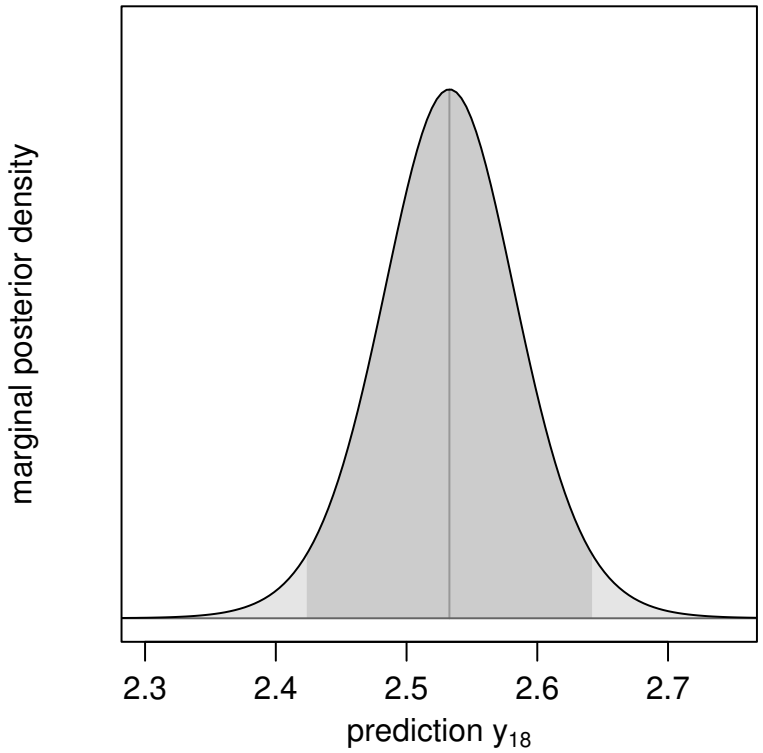

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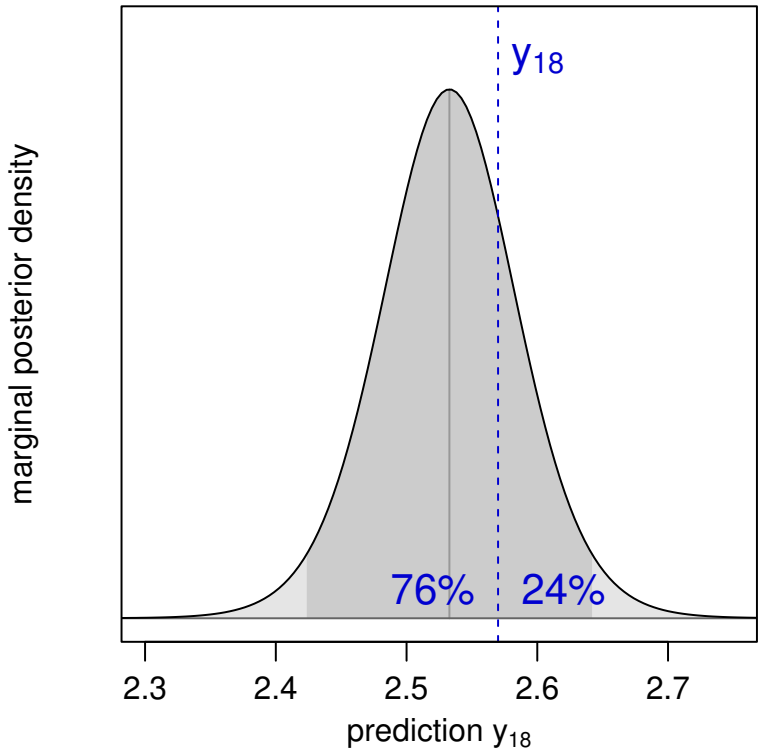

- actual measurement (average $y_{18} = 2.57$) is at 76% quantile,
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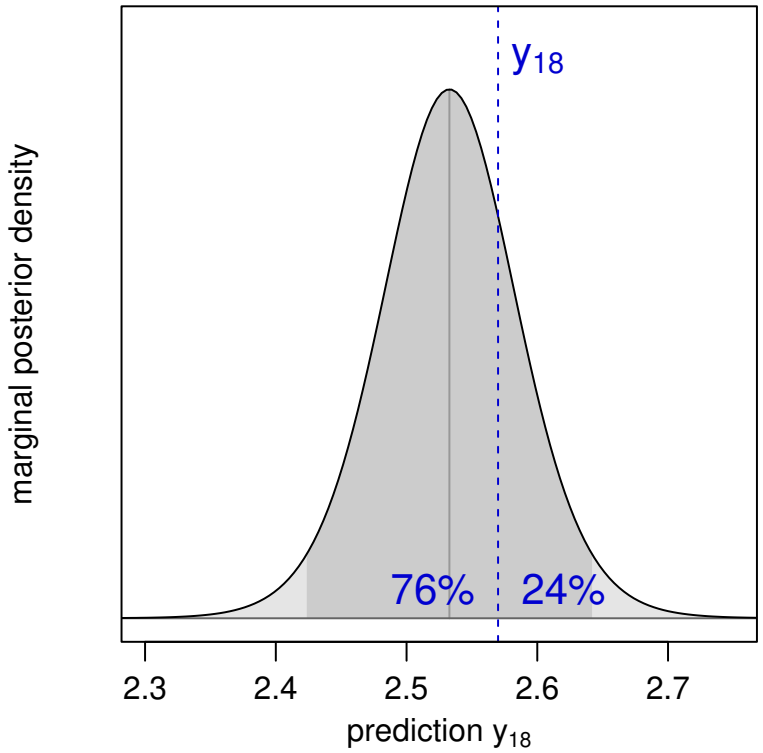

- actual measurement (average $y_{18} = 2.57$) is at 76% quantile,
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- if all assumptions are met, percentage should follow a uniform distribution [8]

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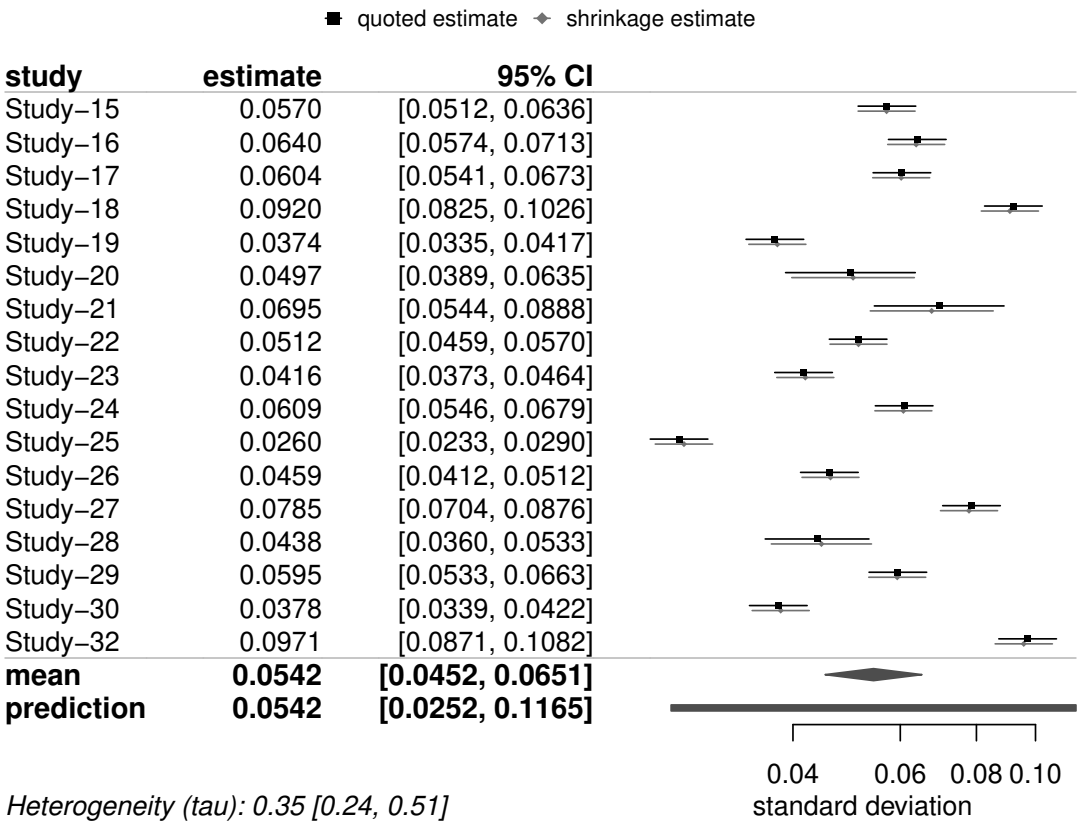
Matching historical and concurrent data

- may perform analogous analysis based on historical + concurrent (logarithmic) standard deviations



- (observed standard deviation ($s_{18} = 0.06$) ends up at 61% quantile)

Historical control data

Jointly incorporating historical and concurrent data: MAC vs. MAP

- How can historical data augment the current study's control data? [9]

[9] A. Gurjanov, C. Vieira-Vieira, J. Vienenkoetter, L.A.I. Vaas, T. Steger-Hartmann. Replacing concurrent controls with virtual control groups in rat toxicity studies. *Regulatory Toxicology and Pharmacology* **148**:105592, 2024.

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- How can historical data augment the current study's control data? [9]
- based on the NNHM, two obvious options:
  - perform a joint meta analysis of all 18 studies, derive a shrinkage estimate for the 18th study (θ_{18}) ("**meta-analytic-combined (MAC) approach**")

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    ("**meta-analytic-combined (MAC) approach**")
  - perform a meta analysis of 17 historical studies,
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    use the predictive distribution as a prior for the 18th study (θ_{18})
    ("**meta-analytic-predictive (MAP) approach**")
- it turns out, both approaches are **equivalent** [10]
- analogous approach may be used in the context of clinical trials
  (using historical data from control groups in similar experiments)

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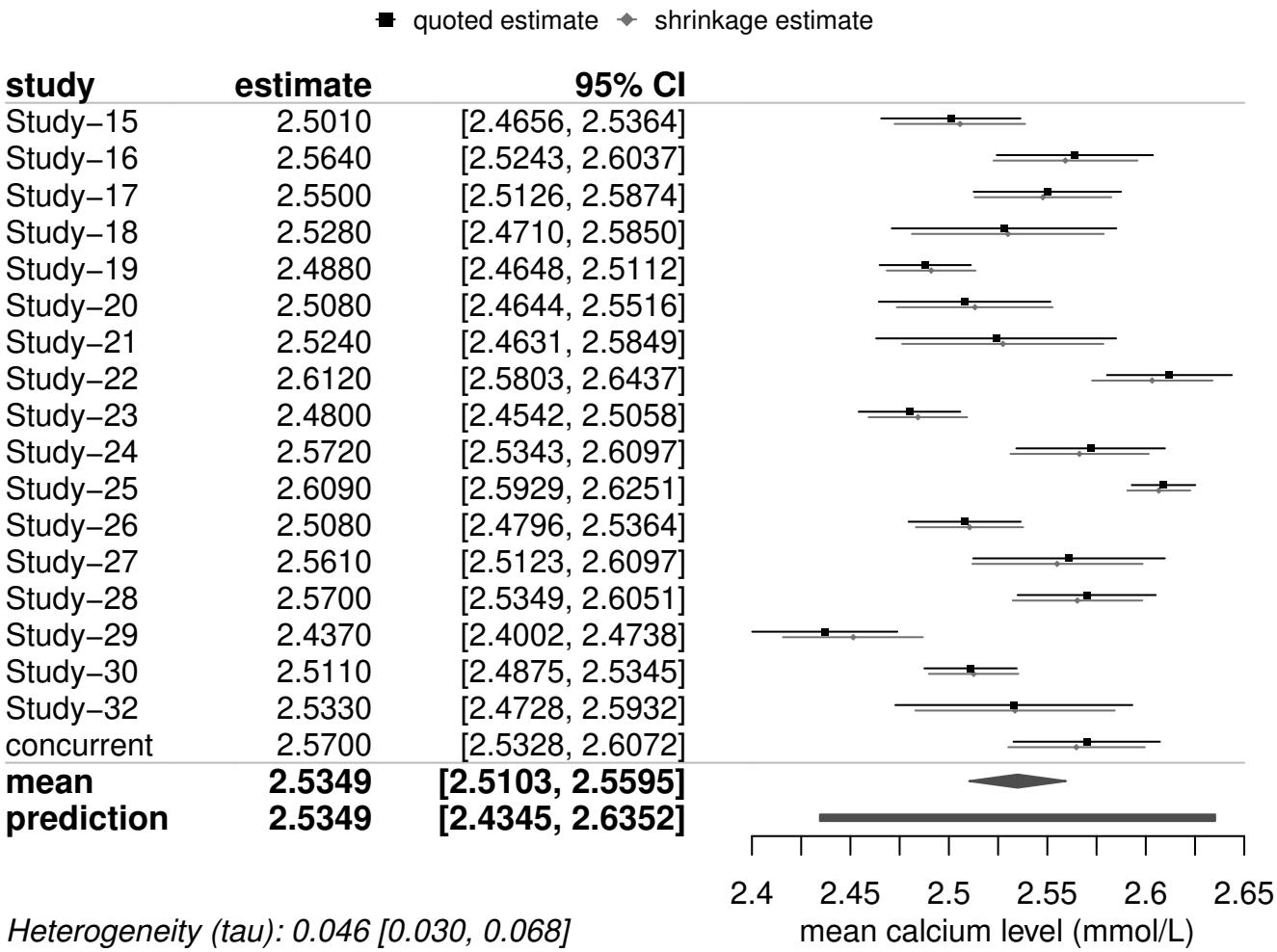
[9] A. Gurjanov, C. Vieira-Vieira, J. Vienenkoetter, L.A.I. Vaas, T. Steger-Hartmann. Replacing concurrent controls with virtual control groups in rat toxicity studies. *Regulatory Toxicology and Pharmacology* **148**:105592, 2024.

[10] H. Schmidli, S. Gsteiger, S. Roychoudhury, A. O'Hagan, D. Spiegelhalter, B. Neuenschwander. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, **70**(4):1023–1032, 2014

Historical control data

Jointly incorporating historical and concurrent data: MAC approach

- MAC: perform meta analysis of 17 historical + 1 concurrent estimate, check “concurrent” shrinkage estimate



Heterogeneity (tau): 0.046 [0.030, 0.068]

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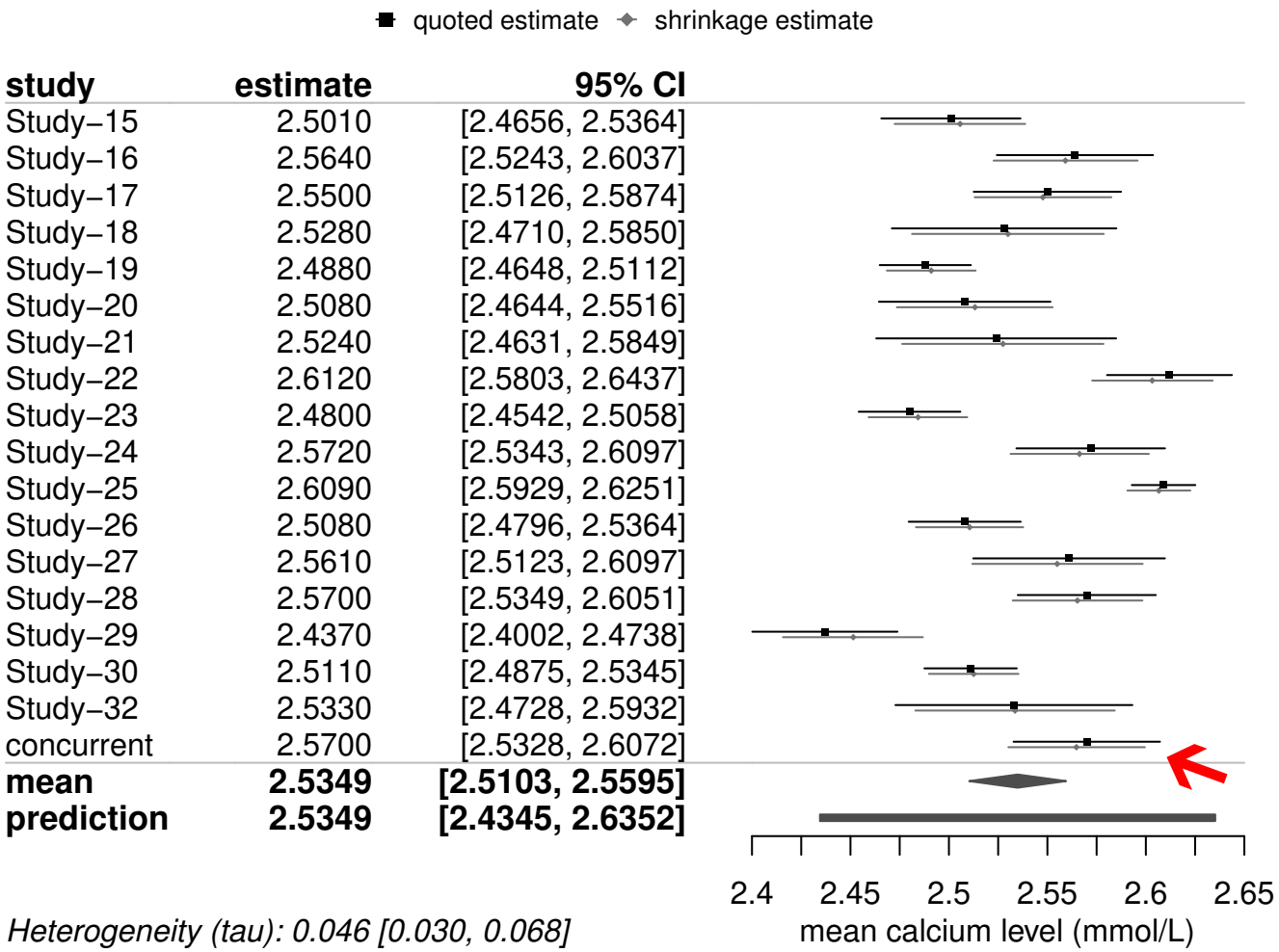

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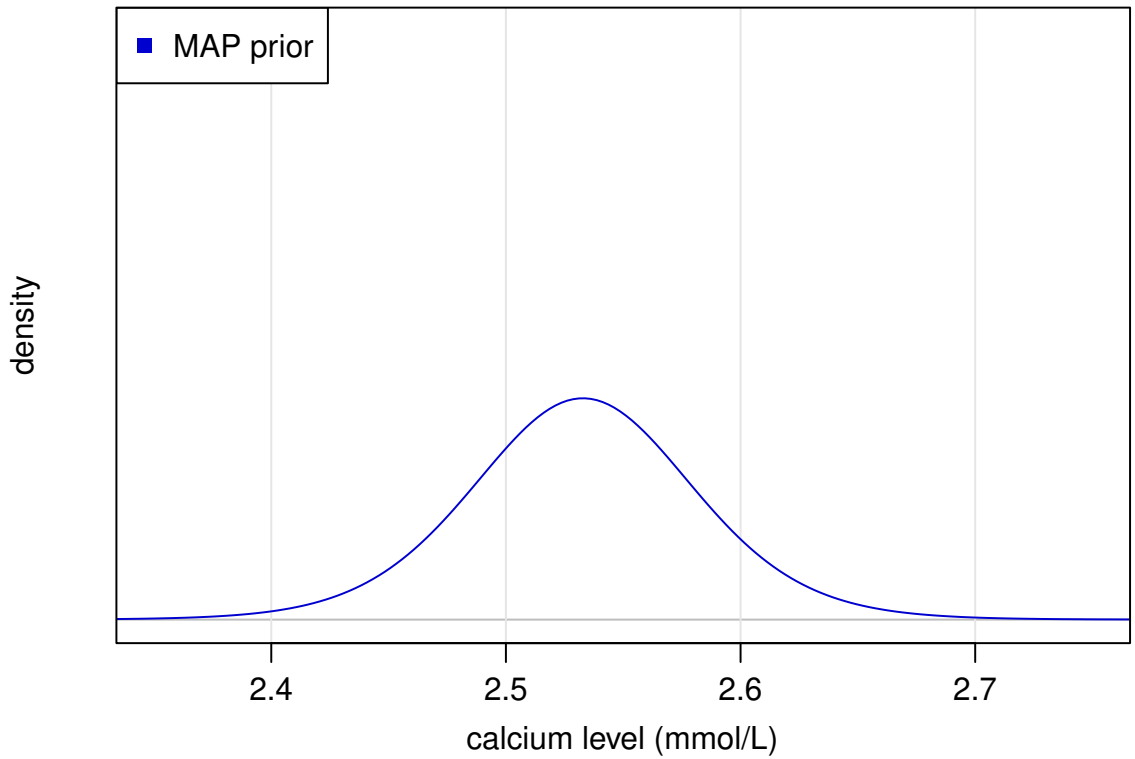
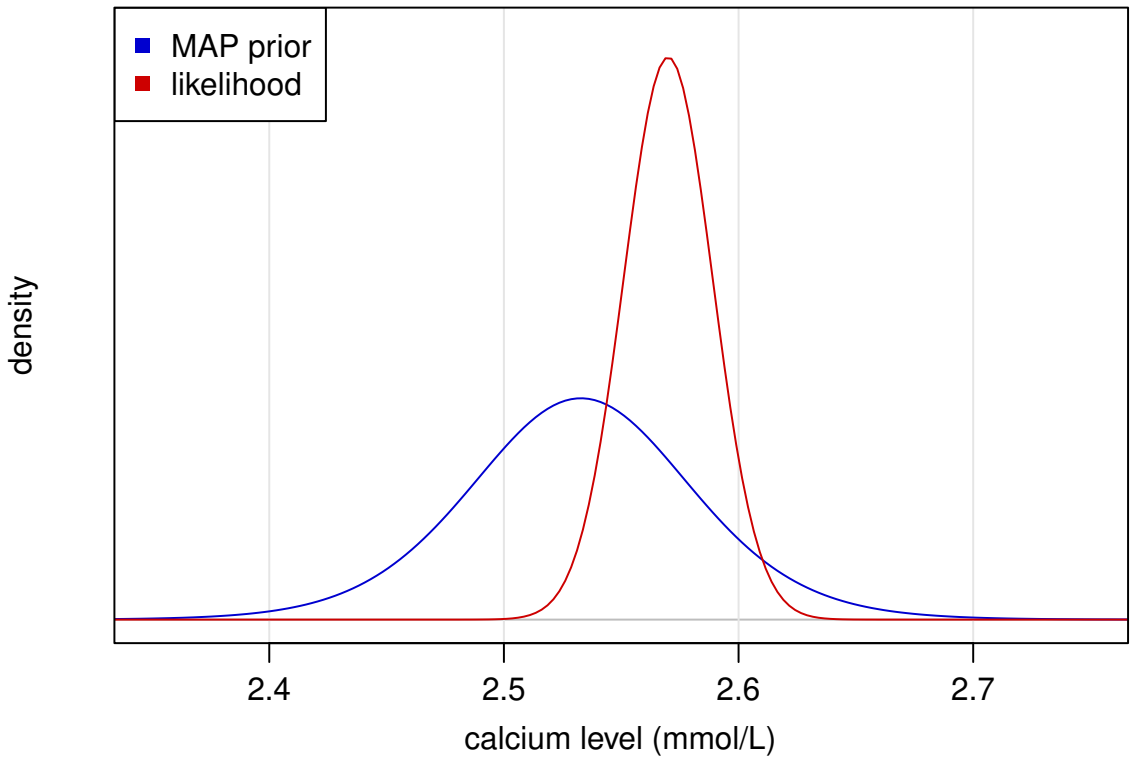


- MAP prior from meta-analysis of 17 historical control groups

Historical control data

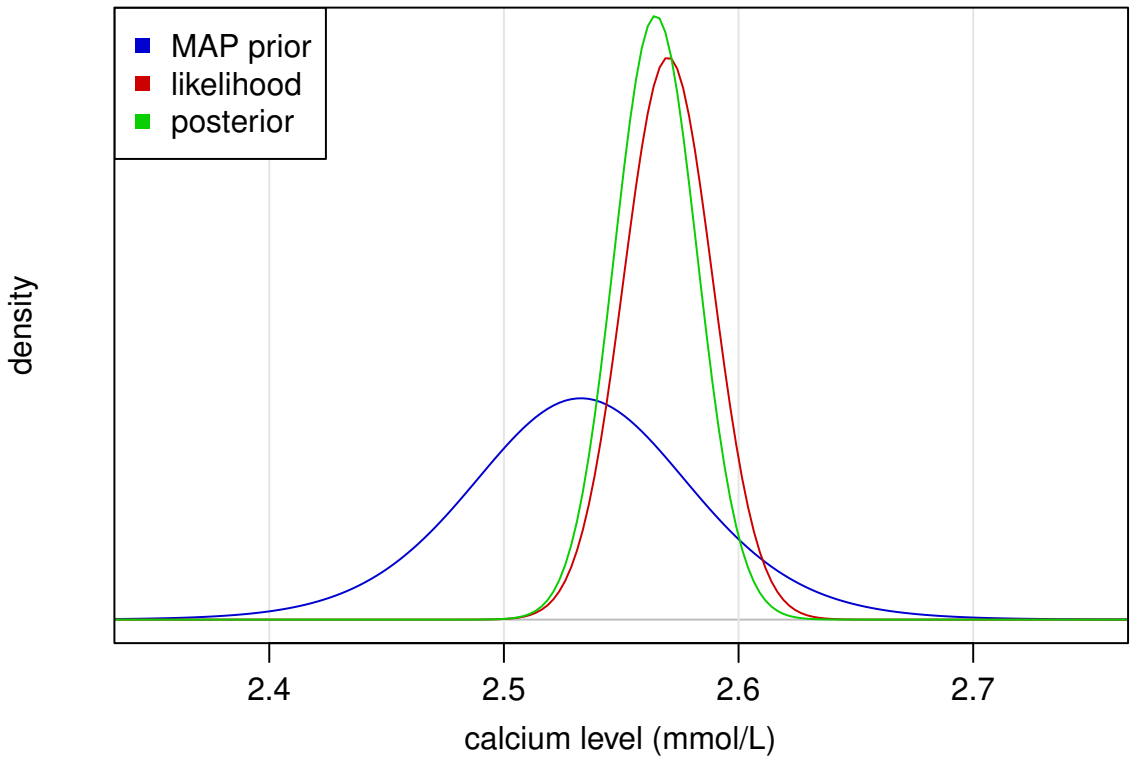
Jointly incorporating historical and concurrent data: MAP approach



- MAP prior from meta-analysis of 17 historical control groups
- “plain” likelihood from current (18th) control group (2.570 ± 0.0190)

Historical control data

Jointly incorporating historical and concurrent data: MAP approach



- MAP prior from meta-analysis of 17 historical control groups
- “plain” likelihood from current (18th) control group (2.570 ± 0.0190)
- shrinkage estimate for current (18th) control group (2.565 ± 0.0177)

Historical control data

Jointly incorporating historical and concurrent data: the shrinkage estimate

- moderate information gain here, since heterogeneity is relatively large ($\tau \approx \sqrt{n_i}\sigma_i \approx 0.05$: similar to within-study variability).
  $\rightarrow$ this leads to little borrowing / pooling.
- precision gain (interval width / standard errors): $\frac{0.0177}{0.0190} = 0.93$ corresponds to a $\approx 15\%$ increase in sample size [11]
- MAP prior's *effective sample size (ESS)* may formally be determined; [12] here also: ESS ≈ 1.4 (animals)

[11] C. Röver, T. Friede. Dynamically borrowing strength from another study through shrinkage estimation. *Statistical Methods in Medical Research*, **29**(1):293–308, 2020.

[12] B. Neuenschwander, S. Weber, H. Schmidli, A. O'Hagan. Predictively consistent prior effective sample sizes. *Biometrics*, **76**(2):578–587, 2020

Historical control data

Jointly incorporating historical and concurrent data: the effect estimates

- from here: may infer differences from *dose 0* to treatment group(s)

	"plain" control			MAP/MAC control		
comparison	Δ	s.e.	CI	Δ	s.e.	CI
dose 1	0.000	0.025	$[-0.048, 0.048]$	0.005	0.024	$[-0.041, 0.052]$
dose 2	0.070	0.023	[0.025, 0.115]	0.075	0.022	[0.033, 0.118]
dose 3	0.120	0.023	[0.075, 0.165]	0.125	0.022	[0.083, 0.168]

- as expected: slightly smaller standard errors also for contrasts

Historical control data

Jointly incorporating historical and concurrent data: the effect estimates

- *WAIT* — didn't we just **break randomization** ?

[13] H. Schmidli, S. Gsteiger, S. Roychoudhury, A. O'Hagan, D. Spiegelhalter, B. Neuenschwander. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, **70**(4):1023–1032, 2014

Historical control data

Jointly incorporating historical and concurrent data: the effect estimates

- *WAIT* — didn't we just **break randomization** ?
- yes

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- yes, . . . but in a transparent / controlled way

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Historical control data

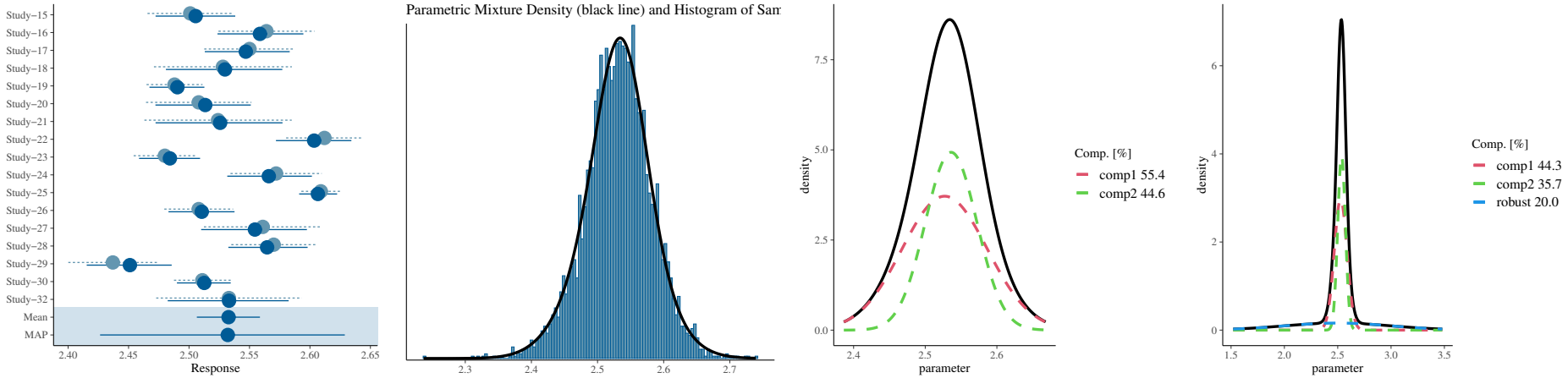
Jointly incorporating historical and concurrent data: the effect estimates

- *WAIT* — didn't we just **break randomization** ?
- yes, . . . but in a transparent / controlled way
- historical information expressed in (MAP) prior
- "robustification" possible [13]
  - deliberate specification of a "more conservative" prior
  - explicit anticipation of possible prior/data conflict
- resulting operating characteristics may be evaluated

[13] H. Schmidli, S. Gsteiger, S. Roychoudhury, A. O'Hagan, D. Spiegelhalter, B. Neuenschwander. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, **70**(4):1023–1032, 2014

Historical control data

Practical implementation: the `RBesT` package



- MAP priors from historical control data implemented in the **RBesT** R package [14, 15]
- includes flexible modeling via MCMC implementation (normal, binomial, Poisson, . . .)
- includes ESS computations, trial design evaluation,. . .

[14] `http://cran.r-project.org/package=RBesT`

[15] S. Weber, Y. Yi, J.W. Seaman, T. Kakizume, H. Schmidli. Applying meta-analytic-predictive priors with the R Bayesian evidence synthesis tools. *Journal of Statistical Software*, **100**(19):1–32, 2021

Discussion

- consistency checking
  - check of mean or standard deviation may be accommodated in meta-analysis
  - may want to extend to several parameters
    (e.g., mean and s.d. simultaneously — multivariate meta-analysis? cluster analysis?)
- recycling historical information
  - small gain in present example
    (due to large heterogeneity, $\tau \approx \sqrt{n_i}\sigma_i \approx 0.05$)
  - general tradeoff: number of studies vs. heterogeneity
    (might be better to consider fewer, more homogeneous studies;
    or: may need to look out for / focus on endpoints with small heterogeneity relative to between-individual variance)
  - "robustification" option: may anticipate possibility of (MAP-) prior/data conflict by specifying a heavier-tailed prior
  - for now, variances (standard errors) were assumed "fixed" / "known". Consideration of estimation uncertainty (and pooling?) also possible (may be sensible for relatively small sample sizes!)