Bivariate meta-analysis with insufficient reporting of the correlation between outcomes on the study level

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Bivariate model

Basis: the univariate random-effects meta-analysis model

- data:
  - effect estimates y_i $(i = 1, \ldots, k)$
  - standard errors s_{i1} (known, fixed)
- **normal-normal hierarchical model (NNHM)**:

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

- marginally:

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

- parameters:
  - overall mean effect μ
  - heterogeneity τ
  - (study-specific means θ_i)

Bivariate model

Bivariate model: motivation

- sometimes **two** (or more) similar/related effect estimates per study, examples:
  - overall survival / disease-free survival
  - pain relief / pain free
  - different symptom scales
  - ...
- both may be reported by all or some studies
- use of additional data may improve estimation and broaden evidence base [1]
- usually: (within-study) correlations between endpoints required

[1] e.g.: R.D. Riley, K.R. Abrams, P.C. Lambert, A.J. Sutton, J.R. Thompson. An evaluation of bivariate random-effects meta-analysis for the joint synthesis of two correlated outcomes. *Statistics in Medicine*, **26**(1):78-97, 2007.

Bivariate model

Bivariate generalization A: known correlations (1)

- data:
  - *bivariate* effect estimates $Y_i = (y_{i1}, y_{i2})' \;\; (i = 1, \ldots, k)$
  - *pairs of* standard errors $s_{i1}, \; s_{i2}$ (known, fixed)
  - *(within-study-)* correlations r_i (**known**, fixed)
- bivariate generalization:

$$Y_i|\Theta_i, \Sigma_i \;\; \sim \;\; \text{Normal}\left(\Theta_i = \begin{pmatrix} \theta_{i1} \\ \theta_{i2} \end{pmatrix}, \Sigma_i = \begin{pmatrix} s_{i1}^2 & r_i s_{i1} s_{i2} \\ r_i s_{i1} s_{i2} & s_{i2}^2 \end{pmatrix}\right),$$

$$\Theta_i|\mu, T \;\; \sim \;\; \text{Normal}\left(\mu = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, T = \begin{pmatrix} \tau_1^2 & \varrho_B \tau_1 \tau_2 \\ \varrho_B \tau_1 \tau_2 & \tau_2^2 \end{pmatrix}\right)$$

- marginally:

$$Y_i|\mu, \Sigma_i, T \ldots \;\; \sim \;\; \text{Normal}\left(\mu = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \Lambda_i = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \lambda_{i;1,2} \\ \lambda_{i;2,1} & s_{i2}^2 + \tau_2^2 \end{pmatrix}\right)$$

where $\Lambda_i = \Sigma_i + T$, and the covariance term is

$$\lambda_{i;1,2} \;\; = \;\; \lambda_{i;2,1} \;\; = \;\; r_i s_{i1} s_{i2} + \varrho_B \tau_1 \tau_2$$

Bivariate model

Bivariate generalization A: known correlations (2)

- marginally:

$$Y_i|\mu, \Sigma_i, T \ldots \sim \text{Normal}\left(\mu = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \Lambda_i = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \lambda_{i;1,2} \\ \lambda_{i;2,1} & s_{i2}^2 + \tau_2^2 \end{pmatrix}\right)$$

  where $\Lambda_i = \Sigma_i + T$, and the covariance term is

$$\lambda_{i;1,2} = \lambda_{i;2,1} = r_i s_{i1} s_{i2} + \varrho_B \tau_1 \tau_2$$

- parameters:
  - (effects μ_1, μ_2, heterogeneities τ_2, τ_2, as in univariate case)
  - *between-study* correlation ϱ_B
- required: *within-study* correlations r_i
- (what if the r_i are not provided?)

Bivariate model

Bivariate generalization B: common-correlation model

- marginal model:

$$Y_i|\mu, \Sigma_i, T \ldots \sim \text{Normal}\left(\mu = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \Lambda_i = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \lambda_{i;1,2} \\ \lambda_{i;2,1} & s_{i2}^2 + \tau_2^2 \end{pmatrix}\right)$$

- treat (within-study) correlation as **single, common** parameter ϱ_W:

$$\lambda_{i;1,2} = \lambda_{i;2,1} = \varrho_W s_{i1} s_{i2} + \varrho_B \tau_1 \tau_2$$

- parameters:
  - (effects μ_1, μ_2, heterogeneities τ_2, τ_2, as in univariate case)
  - *between-study* correlation ϱ_B
  - *within-study* correlation ϱ_W

Bivariate model

Bivariate generalization C: random-correlation model

- marginal model:

$$Y_i|\mu, \Sigma_i, T \ldots \sim \text{Normal}\left(\mu = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \Lambda_i = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \lambda_{i;1,2} \\ \lambda_{i;2,1} & s_{i2}^2 + \tau_2^2 \end{pmatrix}\right)$$

- treat correlation as **random effect** $\varrho_{\text{W}\,i}$:

$$\lambda_{i;1,2} = \lambda_{i;2,1} = \varrho_{\text{W}\,i} s_{i1} s_{i2} + \varrho_{\text{B}} \tau_1 \tau_2$$

where

$$\text{atanh}\left(\varrho_{\text{W}\,i}\right) \sim \text{Normal}(\mu_{\text{W}}, {\sigma_{\text{W}}}^2)$$

- parameters:
  - (effects μ_1, μ_2, heterogeneities τ_2, τ_2, as in univariate case)
  - *between-study* correlation ϱ_{B}
  - (mean) *within-study* correlation $\tanh(\mu_{\text{W}})$
  - *within-study* correlation heterogeneity σ_{W}

Bivariate model

Bivariate generalization C: random-correlation model

- marginal model:

$$Y_i|\mu, \Sigma_i, T \ldots \sim \text{Normal}\left(\mu = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \Lambda_i = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \lambda_{i;1,2} \\ \lambda_{i;2,1} & s_{i2}^2 + \tau_2^2 \end{pmatrix}\right)$$

- treat correlation as **random effect** $\varrho_{\text{W}\,i}$:

$$\lambda_{i;1,2} = \lambda_{i;2,1} = \varrho_{\text{W}\,i} s_{i1} s_{i2} + \varrho_{\text{B}} \tau_1 \tau_2$$

where

$$\text{atanh}\left(\varrho_{\text{W}\,i}\right) \sim \text{Normal}(\mu_{\text{W}}, \sigma_{\text{W}}{}^2)^*$$

- parameters:
  - (effects μ_1, μ_2, heterogeneities τ_2, τ_2, as in univariate case)
  - *between-study* correlation ϱ_{B}
  - (mean) *within-study* correlation $\tanh(\mu_{\text{W}})$
  - *within-study* correlation heterogeneity σ_{W}

*(NB: choice of atanh ("Fisher-z") transform is somewhat *ad hoc* here)

Bivariate model

Bivariate generalization D: alternative model due to Riley, Thompson and Abrams (2008)

- marginal model:

$$Y_i|\mu, \Sigma_i, T \ldots \sim \text{Normal}\left(\mu = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \Lambda_i = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \lambda_{i;1,2} \\ \lambda_{i;2,1} & s_{i2}^2 + \tau_2^2 \end{pmatrix}\right)$$

- treat correlations via a **single, common** parameter ρ: [2]

$$\lambda_{i;1,2} = \lambda_{i;2,1} = \rho\sqrt{(s_{i1}^2 + \tau_1^2)(s_{i2}^2 + \tau_2^2)}$$

- parameters:
  - (effects μ_1, μ_2, heterogeneities τ_2, τ_2, as in univariate case)
  - *overall correlation* ρ
- Notes:
  - originally proposed in frequentist context
  - ρ mimics ϱ_W for "small" τ_1, τ_2; ρ mimics ϱ_B for "large" τ_1, τ_2
  - shrinkage estimation (of Θ_i) or prediction (of Θ_{k+1}) not possible.

[2] R.D. Riley *et al.* An alternative model for bivariate random-effects meta-analysis when the within-study correlations are unknown. *Biostatistics*, **9**(1):172–186, 2008.

Bivariate model

Bivariate generalization: Four models

$$Y_i|\mu, \Sigma_i, T \ldots \sim \text{Normal}\left(\mu = \begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \Lambda_i = \begin{pmatrix} s_{i1}^2 + \tau_1^2 & \lambda_{i;1,2} \\ \lambda_{i;2,1} & s_{i2}^2 + \tau_2^2 \end{pmatrix}\right)$$

(A) **known correlations** model:

$$\lambda_{i;1,2} = \lambda_{i;2,1} = r_i s_{i1} s_{i2} + \varrho_B \tau_1 \tau_2$$

(B) **common effect** model:

$$\lambda_{i;1,2} = \lambda_{i;2,1} = \varrho_W s_{i1} s_{i2} + \varrho_B \tau_1 \tau_2$$

(C) **random effects** model:

$$\lambda_{i;1,2} = \lambda_{i;2,1} = \varrho_{W\,i} s_{i1} s_{i2} + \varrho_B \tau_1 \tau_2$$

(D) **RTA** model

$$\lambda_{i;1,2} = \lambda_{i;2,1} = \rho \sqrt{(s_{i1}^2 + \tau_1^2)(s_{i2}^2 + \tau_2^2)}$$

Bivariate model

Bivariate generalization: prior specification

- to consistently generalize from univariate case, use **separation approach**[3]:
  - specify priors for μ_1, μ_2, τ_1, τ_2 "as usual"
  - specify priors for additional correlation parameters
- "vague" priors for effects (μ_1, μ_2)
- weakly informative priors for heterogeneities (τ_1, τ_2) [4]
- priors for correlation parameters: Uniform$[-1, 1]$ or *arcsine prior* [5]

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[3] D.L. Burke *et al.* Bayesian bivariate meta-analysis of correlated effects: Impact of the prior distributions on the between-study correlation, borrowing of strength, and joint inferences. *Statistical Methods in Medical Research*, **27**(2):428–450, 2018.

[4] 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.

[5] B.K. Fosdick, A.E. Raftery. Estimating the correlation in bivariate normal data with known variances and small sample sizes. *The American Statistician*, **66**(1):34–41, 2012.

Implementation

in R

- four models implemented in R (using JAGS)
- corresponding univariate models ($\lambda_{i;1,2} = \lambda_{i;2,1} = 0.0$): using `bayesmeta` package
- estimation of overall means, heterogeneity, correlations (ϱ_B, ϱ_W, μ_W, σ_W, ρ, ...), study-specific effects (θ_i, *shrinkage estimates*)
- demonstrate / compare performance in example

Example application

Blood pressure data

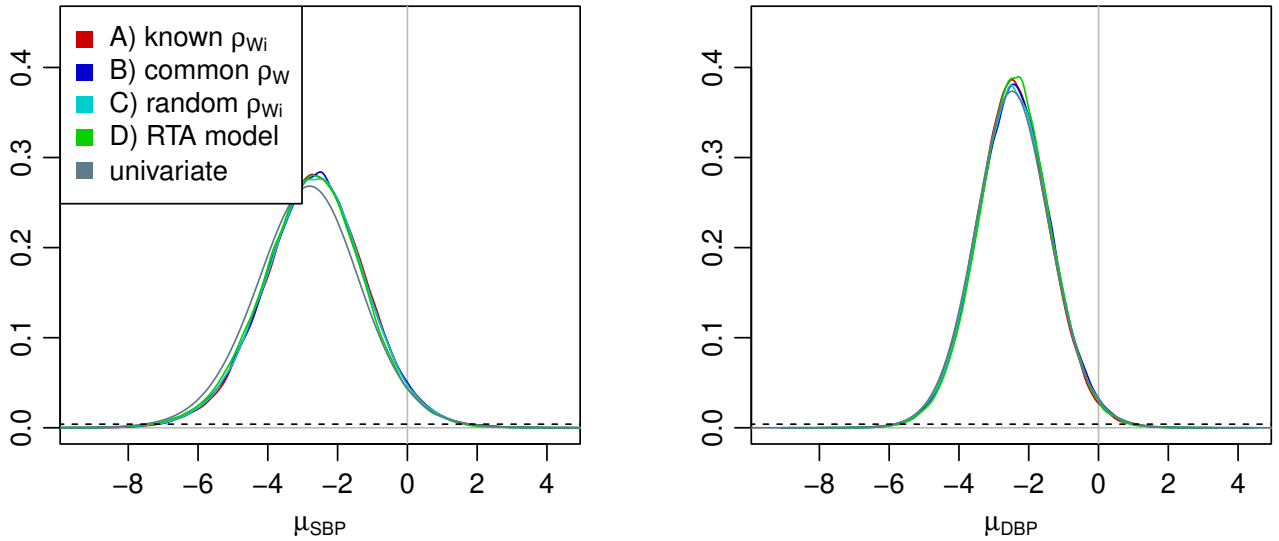
- blood pressure data set [6]
- two correlated endpoints:
  drug effects (mean difference, mmHg)
  on systolic and diastolic blood pressure (SBP, DBP)
- 21 studies
- based on external evidence, within-study correlation (r_i) had also been fixed at $r_i = 0.71$.

[6] C. Geeganage and P.M.W. Bath. Vasoactive drugs for acute stroke. *Cochrane Database of Systematic Reviews*, **7**:1465–1858, 2010.

Y. Wei and J.P.T. Higgins. Estimating within-study covariances in multivariate meta-analysis with multiple outcomes. *Statistics in Medicine*, **32**(7):1191–1205, 2013.

Example application

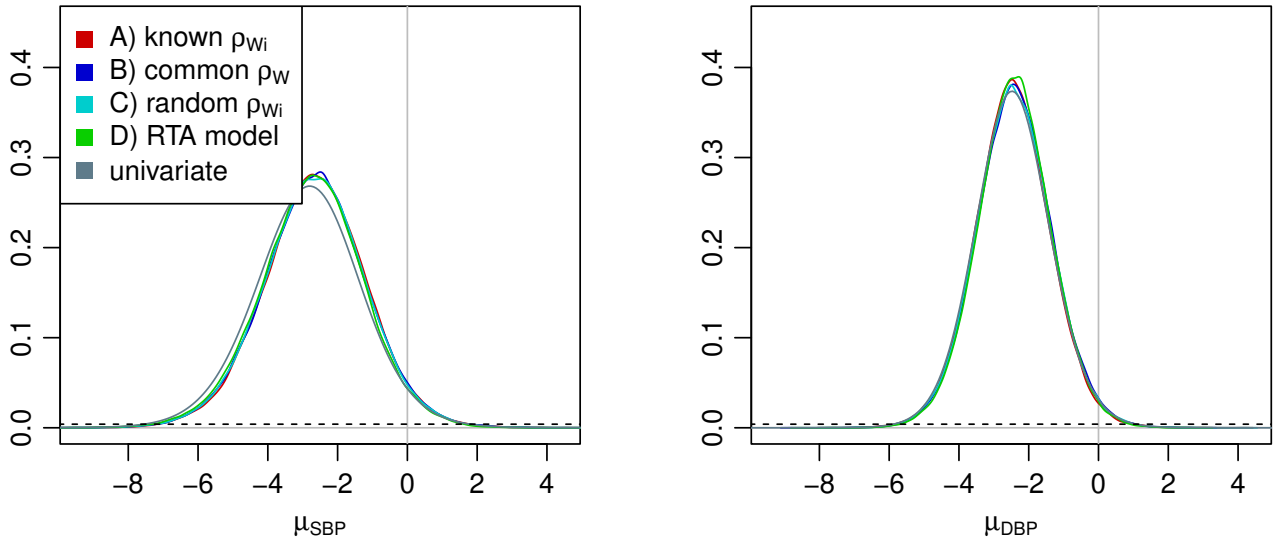
Effect estimates



- overall effect estimates very similar

Example application

Effect estimates

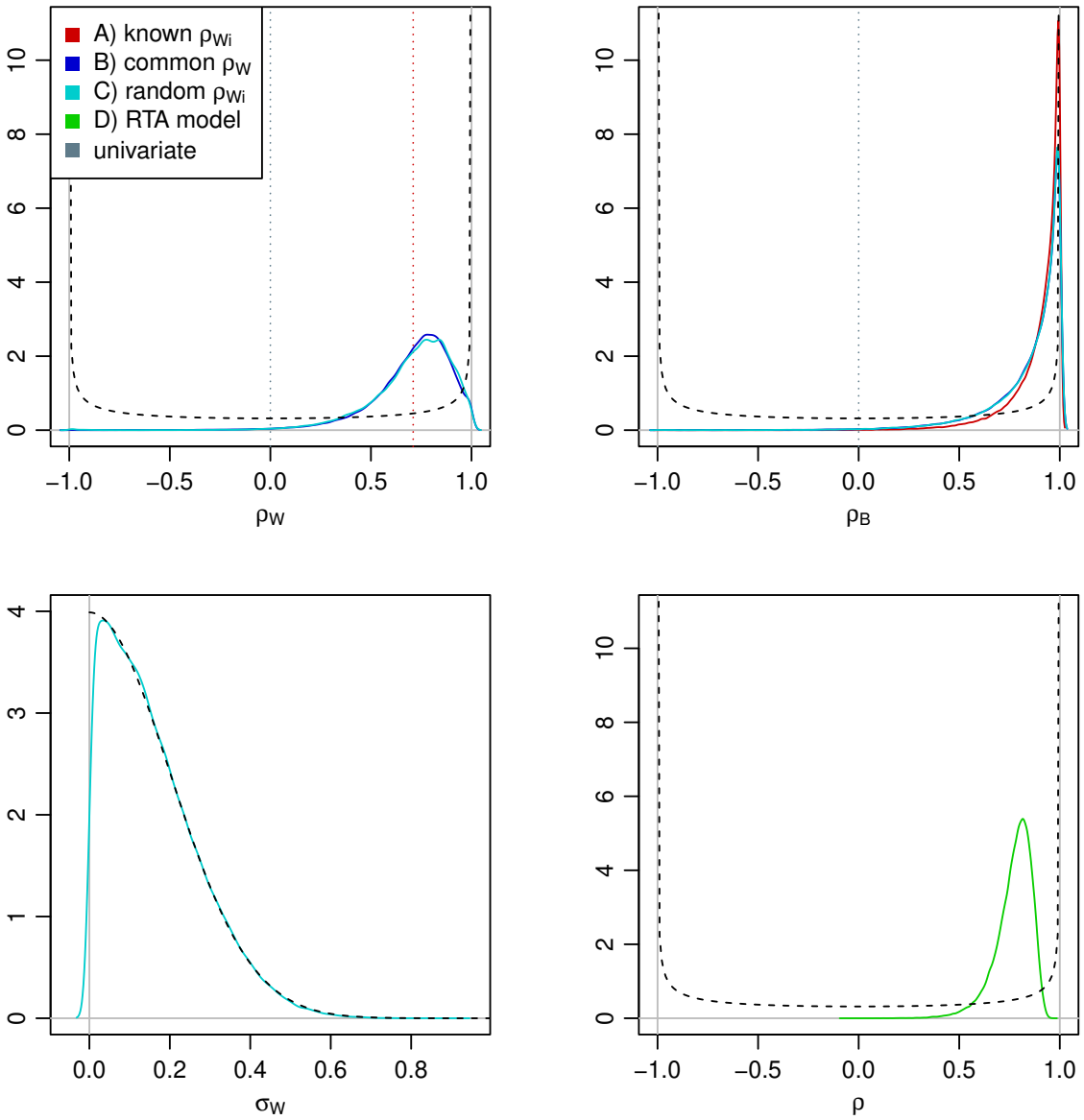


- overall effect estimates very similar
- some precision gain once correlations are considered;
  CI widths compared to univariate analyses:

model	μ_{SBP}	μ_{DBP}
known	95.0%	97.0%
fixed	95.8%	98.0%
random	95.5%	98.4%
RTA	95.7%	95.2%

Example application

Correlation estimates

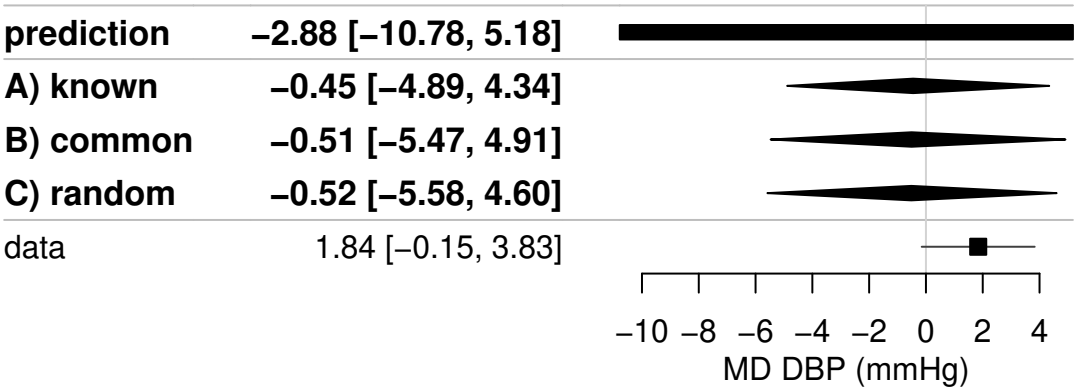


- different correlation parameters shown in common plots
- broad agreement between models
- RE variance (C): σ_W posterior close to prior

Example application

Shrinkage estimation

- consideration of correlations particularly useful if **only one of two** endpoints is given
- allows (e.g.) prediction of 2nd endpoint (θ_{i2}) given the 1st (y_{i1}, s_{i1})
- consider (constructed) case of one missing endpoint:
  no DBP data for recent "PRISTINE" study



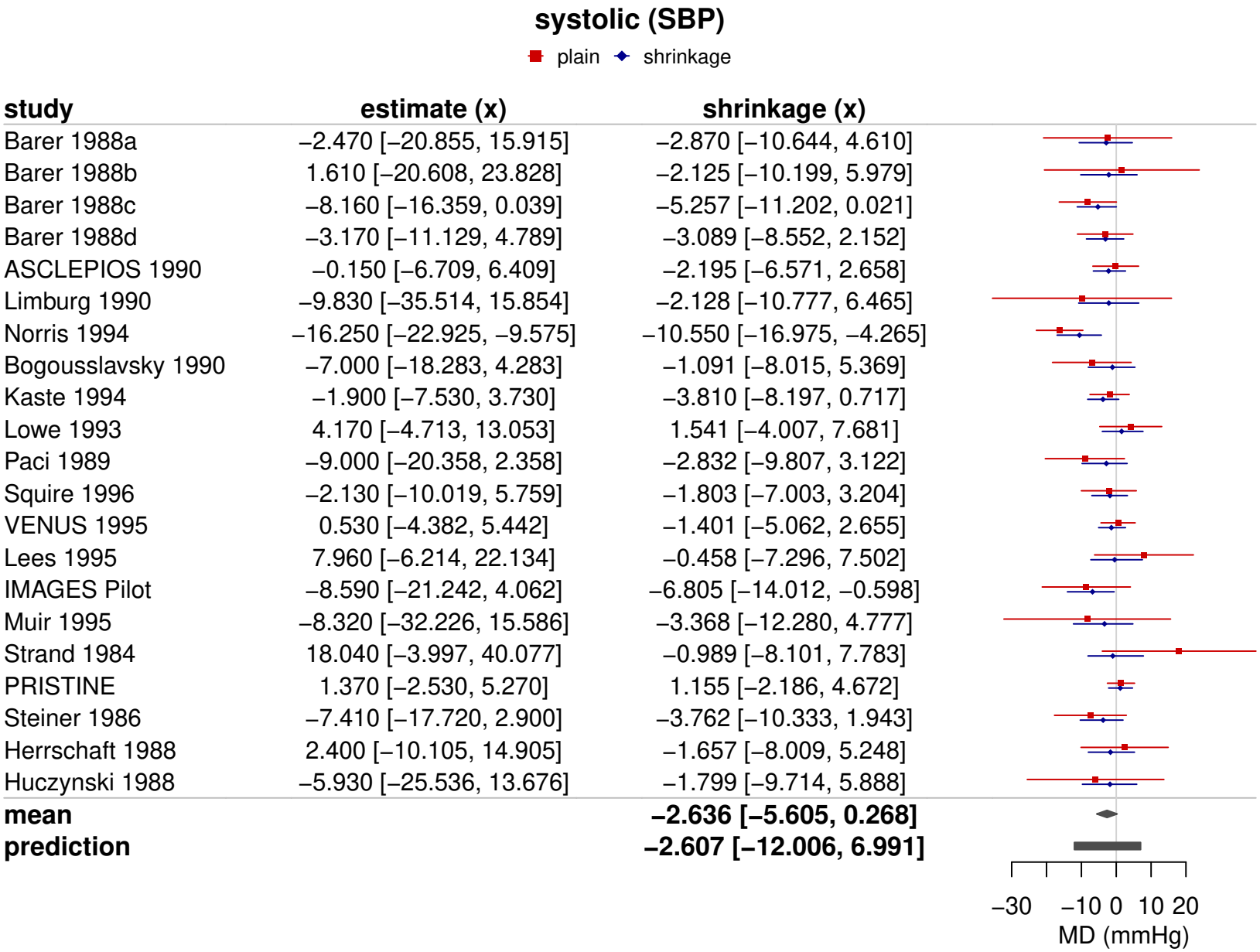
- vague prediction based on 20 remaining DBP estimates alone (univariate MA)
- more precise predictions (θ_{i2}) based on 20 DBP + 21 SBP estimates (PRISTINE's SBP estimate (y_{i1}) was also above average)

Discussion

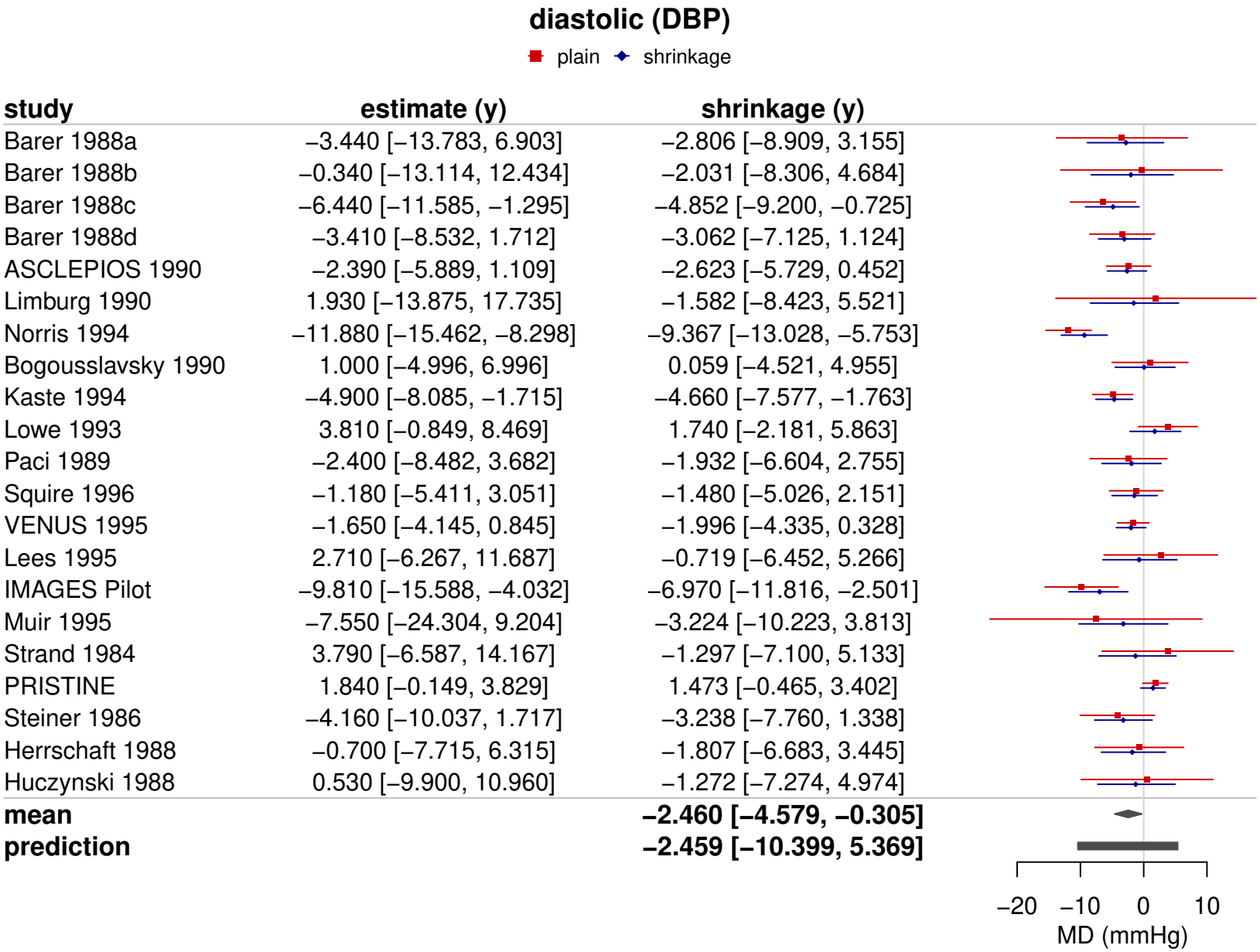
- model setup:
  - fixed-effect model sensible / pragmatic?
    (RE variance seems poorly constrained, may require lots of data)
  - atanh ("Fisher-z") transform for 2nd stage sensible?
    (Motivation? Alternatives?)
  - noticeable advantages also for "simple" RTA model
- prior choice
  - besides "usual" parameters — correlation priors required
  - "arcsine" prior mimics Jeffreys prior,
    emphasizes larger (absolute) correlations
  - uniform prior as a "conservative" alternative
  - alternatives, if, e.g., only positive correlations are expected?
- advantages: precision gain (even for overall means),
  opportunity to jointly analyze similar/different endpoints
- when can we expect advantages for overall mean or shrinkage estimates? (large number of studies, high correlation or large heterogeneity required?)

+++ additional slides +++

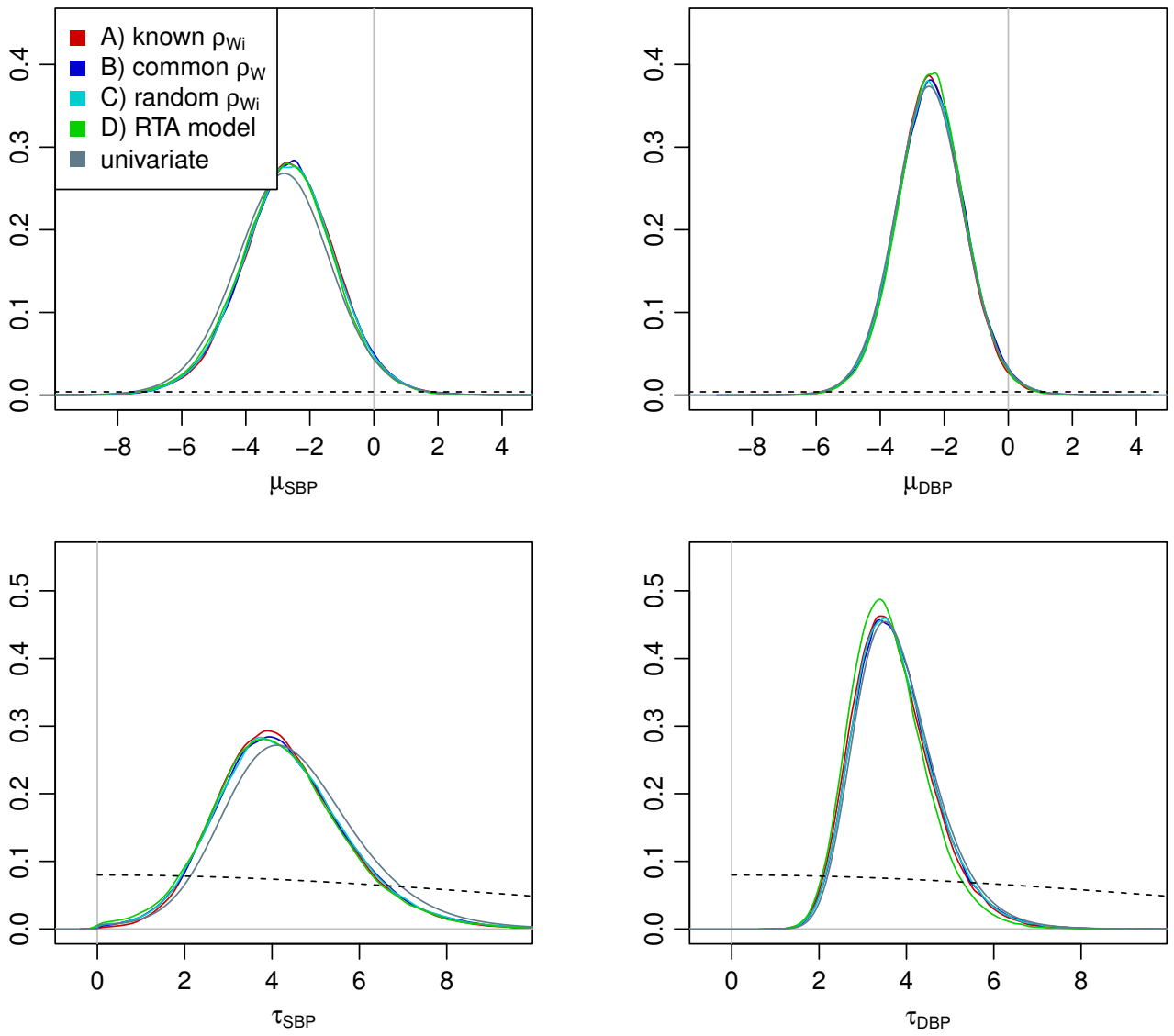
Blood pressure data set (x)



Blood pressure data set (y)



Blood pressure data



- posteriors for effects (μ_{SBP}, μ_{DBP}) and heterogeneities (τ_{SBP}, τ_{DBP})

Blood pressure data

	effect and heterogeneity parameters			
model	μ_{SBP}	τ_{SBP}	μ_{DBP}	τ_{DBP}
known	-2.62 (-5.52, 0.28)	4.07 (1.44, 7.11)	-2.45 (-4.57, -0.33)	3.59 (2.03, 5.54)
FE	-2.66 (-5.68, 0.18)	4.12 (1.38, 7.30)	-2.42 (-4.58, -0.26)	3.65 (2.09, 5.65)
RE	-2.64 (-5.62, 0.27)	4.10 (1.41, 7.31)	-2.42 (-4.55, -0.25)	3.64 (2.04, 5.60)
RTA	-2.72 (-5.74, 0.15)	3.52 (2.03, 5.37)	-2.41 (-4.52, -0.34)	3.52 (2.03, 5.37)
univariate	-2.83 (-5.96, 0.22)	4.35 (1.48, 7.75)	-2.46 (-4.65, -0.24)	3.70 (2.10, 5.73)

Blood pressure data

	correlation parameters			
model	ϱ_W	σ_W	ϱ_B	ρ
known	·	·	0.94 (0.62, 1.00)	·
FE	0.74 (0.34, 1.00)	·	0.92 (0.45, 1.00)	·
RE	0.75 (0.33, 1.00)	0.14 (0.00, 0.39)	0.92 (0.46, 1.00)	·
RTA	·	·	·	0.79 (0.59, 0.92)
univariate	·	·	·	·