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

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Basis: the univariate random-effects meta-analysis model

- data:
  - effect estimates  $y_i$  (i = 1, ..., k)
  - standard errors *s*<sub>*i*1</sub> (known, fixed)
- normal-normal hierarchical model (NNHM):

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

• marginally:

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

- parameters:
  - $\bullet~$  overall mean effect  $\mu$
  - heterogeneity  $\tau$
  - (study-specific means  $\theta_i$ )

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 <sup>1</sup>
- usually: (within-study) correlations between endpoints required

<sup>&</sup>lt;sup>1</sup>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 generalization A: known correlations (1)

- data:
  - *bivariate* effect estimates  $Y_i = (y_{i1}, y_{i2})'$  (i = 1, ..., k)
  - pairs of standard errors  $s_{i1}$ ,  $s_{i2}$  (known, fixed)
  - (within-study-) correlations r<sub>i</sub> (known, fixed)
- bivariate generalization:

$$\begin{aligned} Y_i |\Theta_i, \Sigma_i &\sim \operatorname{Normal} \left( \Theta_i = \left( \begin{array}{c} \theta_{i1} \\ \theta_{i2} \end{array} \right), \, \Sigma_i = \left( \begin{array}{c} s_{i1}^2 & r_i s_{i1} s_{i2} \\ r_i s_{i1} s_{i2} & s_{i2}^2 \end{array} \right) \right), \\ \Theta_i |\mu, T &\sim \operatorname{Normal} \left( \mu = \left( \begin{array}{c} \mu_1 \\ \mu_2 \end{array} \right), \, T = \left( \begin{array}{c} \tau_1^2 & \varrho_B \tau_1 \tau_2 \\ \varrho_B \tau_1 \tau_2 & \tau_2^2 \end{array} \right) \right) \end{aligned}$$

• marginally:

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

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

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

Bivariate generalization A: known correlations (2)

• marginally:

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

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

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

- parameters:
  - (effects  $\mu_1, \mu_2$ , heterogeneities  $\tau_2, \tau_2$ , as in univariate case)
  - *between-study* correlation  $\rho_{\rm B}$
- required: within-study correlations r<sub>i</sub>
- (what if the *r<sub>i</sub>* are not provided?)

Bivariate generalization B: common-correlation model

• marginal model:

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

• treat (within-study) correlation as **single**, **common** parameter  $\rho_W$ :

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

#### • parameters:

- (effects  $\mu_1, \mu_2$ , heterogeneities  $\tau_2, \tau_2$ , as in univariate case)
- between-study correlation *ρ*<sub>B</sub>
- within-study correlation  $\rho_W$

Bivariate generalization C: random-correlation model

• marginal model:

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

treat correlation as random effect *ρ*<sub>Wi</sub>:

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

where

$$\operatorname{atanh}(\varrho_{W_i}) \sim \operatorname{Normal}(\mu_W, \sigma_W^2)$$

- parameters:
  - (effects  $\mu_1$ ,  $\mu_2$ , heterogeneities  $\tau_2$ ,  $\tau_2$ , as in univariate case)
  - between-study correlation *ρ*<sub>B</sub>
  - (mean) within-study correlation  $tanh(\mu_W)$
  - within-study correlation heterogeneity  $\sigma_{\rm W}$

Bivariate generalization C: random-correlation model

• marginal model:

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

treat correlation as random effect *ρ*<sub>Wi</sub>:

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

where

$$\operatorname{atanh}(\varrho_{W_i}) \sim \operatorname{Normal}(\mu_W, \sigma_W^2)^*$$

- parameters:
  - (effects  $\mu_1, \mu_2$ , heterogeneities  $\tau_2, \tau_2$ , as in univariate case)
  - *between-study* correlation  $\rho_{\rm B}$
  - (mean) within-study correlation  $tanh(\mu_W)$
  - within-study correlation heterogeneity  $\sigma_{\rm W}$

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

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

• marginal model:

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

• treat correlations via a single, common parameter  $\rho\!\!:^2$ 

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

- o parameters:
  - (effects  $\mu_1, \mu_2$ , heterogeneities  $\tau_2, \tau_2$ , as in univariate case)
  - overall correlation  $\rho$
- Notes:
  - originally proposed in frequentist context
  - $\rho$  mimics  $\rho_W$  for "small"  $\tau_1, \tau_2$ ;  $\rho$  mimics  $\rho_B$  for "large"  $\tau_1, \tau_2$
  - shrinkage estimation (of  $\Theta_i$ ) or prediction (of  $\Theta_{k+1}$ ) 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 meta-analysis ...

Bivariate generalization: Four models

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

(A) known correlations model:

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

(B) common effect model:

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

(C) random effects model:

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

(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 generalization: prior specification

- to consistently generalize from univariate case, use **separation approach**<sup>3</sup>:
  - specify priors for  $\mu_1, \mu_2, \tau_1, \tau_2$  "as usual"
  - specify priors for additional correlation parameters
- "vague" priors for effects ( $\mu_1, \mu_2$ )
- weakly informative priors for heterogeneities  $(\tau_1, \tau_2)^4$
- priors for correlation parameters: Uniform[-1, 1] or arcsine prior <sup>5</sup>

<sup>&</sup>lt;sup>3</sup>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.

<sup>&</sup>lt;sup>4</sup>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.

<sup>&</sup>lt;sup>5</sup>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.

- 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*<sub>B</sub>, *ρ*<sub>W</sub>, *μ*<sub>W</sub>, *σ*<sub>W</sub>, *ρ*, ...), study-specific effects (*θ<sub>i</sub>*, *shrinkage estimates*)
- demonstrate / compare performance in example

Blood pressure data

- blood pressure data set <sup>6</sup>
- 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  $r_i = 0.71$ .

<sup>&</sup>lt;sup>6</sup>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.

### Effect estimates



• overall effect estimates very similar

### Effect estimates



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

model	$\mu_{\mathrm{SBP}}$	$\mu_{\rm DBP}$
known	95.0%	97.0%
fixed	95.8%	98.0%
random	95.5%	98.4%
RTA	95.7%	95.2%

### **Correlation estimates**



- different correlation parameters shown in common plots
- broad agreement between models
- RE variance (C): σ<sub>W</sub> posterior close to prior

Shrinkage estimation

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

prediction	-2.88 [-10.78, 5.18]	
A) known	-0.45 [-4.89, 4.34]	
B) common	-0.51 [-5.47, 4.91]	
C) random	-0.52 [-5.58, 4.60]	
data	1.84 [-0.15, 3.83]	
		-10 -8 -6 -4 -2 0 2 4 MD DBP (mmHg)

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

C. Röver

Bivariate meta-analysis ...

### 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 +++

#### systolic (SBP)

plain + shrinkage

study	estimate (x)	shrinkage (x)	
Barer 1988a	-2.470 [-20.855, 15.915]	-2.870 [-10.644, 4.610]	
Barer 1988b	1.610 [-20.608, 23.828]	-2.125 [-10.199, 5.979]	<b>_</b>
Barer 1988c	-8.160 [-16.359, 0.039]	-5.257 [-11.202, 0.021]	
Barer 1988d	-3.170 [-11.129, 4.789]	-3.089 [-8.552, 2.152]	
ASCLEPIOS 1990	-0.150 [-6.709, 6.409]	-2.195 [-6.571, 2.658]	<b></b>
Limburg 1990	-9.830 [-35.514, 15.854]	-2.128 [-10.777, 6.465]	<b>_</b>
Norris 1994	-16.250 [-22.925, -9.575]	-10.550 [-16.975, -4.265]	
Bogousslavsky 1990	-7.000 [-18.283, 4.283]	-1.091 [-8.015, 5.369]	
Kaste 1994	-1.900 [-7.530, 3.730]	-3.810 [-8.197, 0.717]	<b>_</b>
Lowe 1993	4.170 [-4.713, 13.053]	1.541 [-4.007, 7.681]	
Paci 1989	-9.000 [-20.358, 2.358]	-2.832 [-9.807, 3.122]	
Squire 1996	-2.130 [-10.019, 5.759]	-1.803 [-7.003, 3.204]	
VENUS 1995	0.530 [-4.382, 5.442]	-1.401 [-5.062, 2.655]	<b></b>
Lees 1995	7.960 [-6.214, 22.134]	-0.458 [-7.296, 7.502]	
IMAGES Pilot	-8.590 [-21.242, 4.062]	-6.805 [-14.012, -0.598]	
Muir 1995	-8.320 [-32.226, 15.586]	-3.368 [-12.280, 4.777]	
Strand 1984	18.040 [-3.997, 40.077]	-0.989 [-8.101, 7.783]	•
PRISTINE	1.370 [-2.530, 5.270]	1.155 [-2.186, 4.672]	-
Steiner 1986	-7.410 [-17.720, 2.900]	-3.762 [-10.333, 1.943]	
Herrschaft 1988	2.400 [-10.105, 14.905]	-1.657 [-8.009, 5.248]	<b>_</b>
Huczynski 1988	-5.930 [-25.536, 13.676]	-1.799 [-9.714, 5.888]	
mean		-2.636 [-5.605, 0.268]	*
prediction		–2.607 [–12.006, 6.991]	
			-30 -10 0 10 20
			MD (mmHg)

#### diastolic (DBP)

plain + shrinkage

study	estimate (y)	shrinkage (y)	
Barer 1988a	-3.440 [-13.783, 6.903]	-2.806 [-8.909, 3.155]	
Barer 1988b	-0.340 [-13.114, 12.434]	-2.031 [-8.306, 4.684]	<b>_</b>
Barer 1988c	-6.440 [-11.585, -1.295]	-4.852 [-9.200, -0.725]	
Barer 1988d	-3.410 [-8.532, 1.712]	-3.062 [-7.125, 1.124]	
ASCLEPIOS 1990	-2.390 [-5.889, 1.109]	-2.623 [-5.729, 0.452]	
Limburg 1990	1.930 [–13.875, 17.735]	-1.582 [-8.423, 5.521]	
Norris 1994	-11.880 [-15.462, -8.298]	-9.367 [-13.028, -5.753]	
Bogousslavsky 1990	1.000 [-4.996, 6.996]	0.059 [-4.521, 4.955]	<b></b>
Kaste 1994	-4.900 [-8.085, -1.715]	-4.660 [-7.577, -1.763]	-
Lowe 1993	3.810 [-0.849, 8.469]	1.740 [-2.181, 5.863]	
Paci 1989	-2.400 [-8.482, 3.682]	-1.932 [-6.604, 2.755]	
Squire 1996	-1.180 [-5.411, 3.051]	-1.480 [-5.026, 2.151]	
VENUS 1995	-1.650 [-4.145, 0.845]	-1.996 [-4.335, 0.328]	
Lees 1995	2.710 [-6.267, 11.687]	-0.719 [-6.452, 5.266]	
IMAGES Pilot	-9.810 [-15.588, -4.032]	-6.970 [-11.816, -2.501]	
Muir 1995	-7.550 [-24.304, 9.204]	-3.224 [-10.223, 3.813]	
Strand 1984	3.790 [-6.587, 14.167]	-1.297 [-7.100, 5.133]	
PRISTINE	1.840 [-0.149, 3.829]	1.473 [-0.465, 3.402]	-
Steiner 1986	-4.160 [-10.037, 1.717]	-3.238 [-7.760, 1.338]	
Herrschaft 1988	-0.700 [-7.715, 6.315]	-1.807 [-6.683, 3.445]	
Huczynski 1988	0.530 [-9.900, 10.960]	-1.272 [-7.274, 4.974]	<b>-</b>
mean		-2.460 [-4.579, -0.305]	*
prediction		-2.459 [-10.399, 5.369]	
			-20 -10 0 10
			MD (mmHg)

### Blood pressure data



• posteriors for effects ( $\mu_{\text{SBP}}, \mu_{\text{DBP}}$ ) and heterogeneities ( $\tau_{\text{SBP}}, \tau_{\text{DBP}}$ )

	effect and heterogeneity parameters			
model	$\mu_{ ext{SBP}}$	$ au_{ m SBP}$	$\mu_{ m DBP}$	$ au_{ m 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)

	correlation parameters			
model	Qw	$\sigma_{ m W}$	Qв	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				