Meta-analysis using the `bayesmeta` package

Christian Röver

Department of Medical Statistics,
University Medical Center Göttingen,
Göttingen, Germany

DFG-project Symposium, August 24, 2023

Overview

- “Bayesian” probabilities
- the normal-normal hierarchical model
- priors

- overall effect
- prediction and shrinkage estimation
- meta-regression

- approach to view / solve statistical problems [1]
- goes back to Thomas Bayes (1701–1761)
- central: "**Bayes' theorem**"

$$\mathrm{P}(A|B) \;=\; \frac{\mathrm{P}(B|A)\,\mathrm{P}(A)}{\mathrm{P}(B)}$$

- of interest:
  P(parameters|data) (the *a-posteriori probability*)
- required:
  P(data|parameters) (the *likelihood (function)*)
  P(parameters) (the *a-priori probability distribution*)
- besides specification of likelihood:
  formalizing a-priori-*information*

[1] A. Gelman, J. B. Carlin, H. Stern, D. B. Dunson, A. Vehtari, D. B. Rubin. *Bayesian data analysis*. Chapman & Hall / CRC, 2014.

- approach to view / solve statistical problems [1]
- goes back to Thomas Bayes (1701–1761)
- central: "**Bayes' theorem**"

$$\text{P}(\text{parameters}|\text{data}) = \frac{\text{P}(\text{data}|\text{parameters})\,\text{P}(\text{parameters})}{\text{P}(\text{data})}$$

- of interest:
  P(parameters|data) (the *a-posteriori probability*)
- required:
  P(data|parameters) (the *likelihood (function)*)
  P(parameters) (the *a-priori probability distribution*)
- besides specification of likelihood:
  formalizing a-priori-*information*

[1] A. Gelman, J. B. Carlin, H. Stern, D. B. Dunson, A. Vehtari, D. B. Rubin. *Bayesian data analysis*. Chapman & Hall / CRC, 2014.

Introduction

"Bayesian" probabilities

- intuitive interpretation:[2]
  - **probability** distribution as **information**
  - likelihood P(data|parameters):
    "what data do we expect given certain parameter values"
  - prior P(parameters):
    "how probable are certain parameter values"
  - posterior P(parameters|data):
    "how probable are certain parameter values in view of the data"
- ("logical") consistency
  (e.g.: posterior from one analysis may serve as a prior for a subsequent analysis. . .)

[2] E. T. Jaynes. *Probability Theory: The Logic of Science*. Cambridge University Press, 2003.

Introduction

"Bayesian" probabilities

- technically: integration (instead of optimization)
- often: fewer asymptotic arguments necessary
  (few studies! few events!) [3]
- often useful for complex models
  (e.g.: nuisance parameters, hierarchical models) [4]
- besides specification of *data model* (likelihood):
  a-priori - distribution necessary
- relevant / accepted in regulatory contexts (e.g. [5, 6])

[3] D. Jackson, I. R. White. When should meta-analysis avoid making hidden normality assumptions? *Biometrical Journal*, **60**(6):1040–1058, 2018.

[4] A. Gelman, J. Hill. *Data analysis using regression and multilevel/hierarchical models*. Cambridge University Press, 2007.

[5] European Medicines Agency (EMEA). Guideline on clinical trials in small populations. CHMP/EWP/83561/2005, 2006.

[6] U.S. Department of Health and Human Services (HHS), Food and Drug Administration (FDA). Leveraging existing clinical data for extrapolation to pediatric uses of medical devices. FDA-2015-D-1376, 2016

Meta-analysis

Normal *effect measures* within `bayesmeta`

- `bayesmeta` package is based on **normal effect measures**
- single study's outcome, often: **estimate** $\pm$ **standard error**
- **normal approximation** ("Wald" CI) often appropriate ("large" sample size within study)
- (standard errors are assumed **known**, fixed!)
- sometimes **transformations** are used; examples:
  - means, mean differences, standardized mean differences
  - risk differences
  - (log-) risk ratios, (log-) odds ratios
  - (log-) rate ratios
  - (log-) hazard ratios
  - correlation coefficients (Fisher-*z* transformed)
  - ...

- COPD **example**:[7]
  patients are treated with *tiotropium*;
  interest was in quality-of-life and disease progression, measured in terms of the **exacerbation rate**
- one study (Bateman *et al.*, 2010a) quotes:

  "During the treatment period, 685 (35.3%) patients in the tiotropium group and 842 (43.1%) in the placebo group had at least one exacerbation."

	exacerbation		
	yes	no	total
tiotropium patients	685	1304	1989
placebo patients	842	1160	2002

[7] C. Karner, J. Chong, P. Poole. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, **7**:CD009285, 2014.

- general setup (2×2 contingency table): [8]

	event		
	yes	no	total
treatment	a	b	$n_1 = a+b$
control	c	d	$n_2 = c+d$

- log-OR estimate: $y = \log\left(\frac{a/b}{c/d}\right)$
- standard error: $\sigma = \sqrt{\frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}}$

[8] e.g.: J.L. Fleiss. The statistical basis of meta-analysis. *Statistical Methods in Medical Research*, **2**(2):121–145, 1993.

- data:

	exacerbation		
	yes	no	total
tiotropium patients	685	1304	1989
placebo patients	842	1160	2002

- compute log-OR and standard error:

```
R> (685/1304) / (842/1160)
[1] 0.7237005
R> log((685/1304) / (842/1160))
[1] -0.3233776
R> sqrt(sum(1 / c(685, 1304, 842, 1160)))
[1] 0.06539452
```

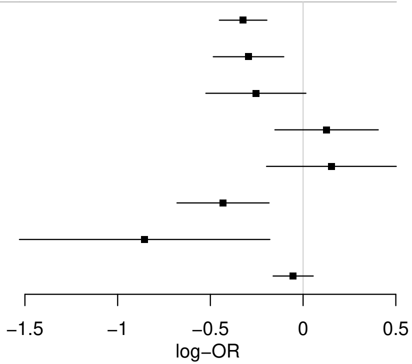
- using `metafor` package's `escalc()` function:

```
R> library("metafor")
R> escalc(measure="OR", ai=685, bi=1304, ci=842, di=1160)
       yi     vi
1 -0.3234 0.0043
```

(note: returns *squared* standard error)

- 8 "long" studies ($\geq$ 1 year follow-up)
  (Analysis 1.10.2, p. 73)

study	**estimate**	**95% CI**
Bateman2010a	–0.323	[–0.452, –0.195]
Bateman2010b	–0.294	[–0.485, –0.104]
Casaburi2002	–0.255	[–0.524, 0.015]
Chan2007	0.127	[–0.152, 0.405]
Cooper2010	0.153	[–0.197, 0.502]
Dusser2006	–0.432	[–0.680, –0.183]
Powrie2007	–0.854	[–1.530, –0.179]
Tashkin2008	–0.054	[–0.162, 0.055]



- model (likelihood):

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

  or (marginally):

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

- random-effects (RE) model,
  normal-normal hierarchical model (NNHM)
- "**study-specific effects**" θ_i
- **overall mean** parameter $\mu \in \mathbb{R}$
- (nuisance) **heterogeneity** parameter $\tau \geq 0$
- for $\tau = 0$, reduces to common-effect (fixed-effect, FE) model
  ($\tau = 0 \quad \Rightarrow \quad \theta_1 = \cdots = \theta_k = \mu$)

Meta-analysis

Combining estimates: the random-effects model (prior, generally)

- **effect** prior (μ):[9]
  - location parameter
  - (informative or vague) $\mu \sim \text{Normal}(\mu_\text{p}, \sigma_\text{p}^2)$ often appropriate
  - (improper, non-informative) uniform prior often sensible
- **heterogeneity** prior (τ):[17,10]
  - scale parameter
  - (improper, non-informative) uniform prior works for many studies (at least $k \geq 3$)
  - constraints on τ via weakly informative priors may be motivated (e.g., $\tau \sim \text{half-Normal}(\cdots)$)
- commonly: $p(\mu, \tau) = p(\mu) \times p(\tau)$ (prior independence)

[9] C. Röver. Bayesian random-effects meta-analysis using the `bayesmeta` R package. *Journal of Statistical Software*, **93**(6), 2020.

[10] 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.

Meta-analysis

Combining estimates: the random-effects model (priors COPD example)

- how to specify priors?
- in general, prior specification requires consideration of **context** (e.g., log-ORs, COPD application)
- effect (μ):
  - obvious: (improper) uniform
  - weakly informative prior, e.g. $\mu \sim \text{Normal}(0, 2.82^2)$:
    centered at "neutral" value of 0
    prior plausible (95%) OR range roughly $\frac{1}{250}$ to 250,
    also empirically motivated [11]
  - "unit information prior" $\mu \sim \text{Normal}(0, 4^2)$:
    log-OR standard errors (roughly) scale as $\sigma = \frac{4}{\sqrt{n}}$
    standard deviation of 4: *"information conveyed by a single patient"*

[11] B. K. Günhan, C. Röver, T. Friede. Random-effects meta-analysis of few studies involving rare events. *Research Synthesis Methods*, **11**(1):74–91, 2020.

Meta-analysis

Combining estimates: the random-effects model (priors for log-OR)

- how to specify priors, e.g. for log-ORs? (cont.)
- heterogeneity (τ):
  - uniform / uninformative specifications available (usually requiring “large” k) [12]
  - τ quantifies variation of θ_i relative to μ
    $\rightarrow$ how much variation in study-specific θ_i is expected?
  - consider implications, e.g.:

	heterogeneity τ		95% predictive interval	
$p(\tau)$	median	95%	$\theta_i - \mu$	$\exp(\theta_i - \mu)$
half-Normal(0.1)	0.07	0.20	[-0.22, 0.22]	[0.80, 1.24]
half-Normal(0.2)	0.13	0.39	[-0.44, 0.44]	[0.65, 1.55]
half-Normal(0.5)	0.34	0.98	[-1.09, 1.09]	[0.34, 2.98]
half-Normal(1.0)	0.67	1.96	[-2.18, 2.18]	[0.11, 8.89]
half-Normal(2.0)	1.35	3.92	[-4.37, 4.37]	[0.013, 79.0]

  - more arguments available (e.g., considering empirical information)[13]

[12] C. Röver. Bayesian random-effects meta-analysis using the `bayesmeta` R package. *Journal of Statistical Software*, **93**(6), 2020.

[13] 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.

Meta-analysis

Combining estimates: the random-effects model (posterior(s), the technical bits)

- posterior (density) results as product of likelihood and prior:

$$p(\mu, \tau | y_1, \ldots, y_k) \;\propto\; p(y_1, \ldots, y_k | \mu, \tau) \times p(\mu, \tau)$$

- bivariate probability distribution
- relevant (marginal, univariate) posteriors result via **integration**, e.g.:

$$p(\mu | y_1, \ldots, y_k) \;=\; \int p(\mu, \tau | y_1, \ldots, y_k) \, \mathrm{d}\tau$$

- posterior inferences (e.g., mean, median, quantiles, intervals) require further integration
- often approached via MCMC (approximating integrals/expectations by sample averages)
- in `bayesmeta`: semi-analytically

Meta-analysis

Combining estimates: the random-effects model (application)

- NNHM implemented in `bayesmeta` package
- required input: estimates (y_i), standard errors (σ_i), effect prior ($p(\mu)$), heterogeneity prior ($p(\tau)$)
- check `bayesmeta()` function:

```
R> ?bayesmeta
```

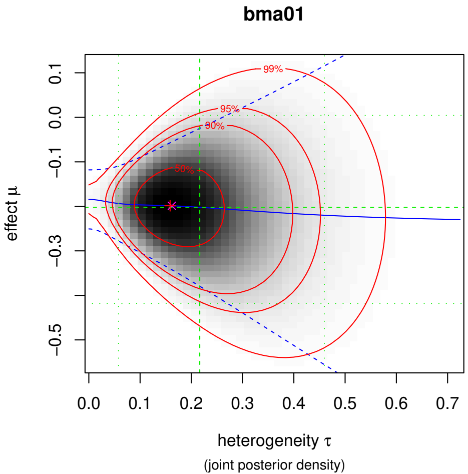
- perform analysis:

```
R> exa.long <- escalc(measure="OR", [...],
+                      subset = (duration=="1 year or longer"),
+                      slab=study, data=KarnerEtAl2014)
R> bma01 <- bayesmeta(y=exa.long$yi, sigma=sqrt(exa.long$vi),
+                      labels=exa.long$study,
+                      mu.prior=c(0,4),
+                      tau.prior=function(t){dhalfnormal(t,scale=0.5)})
```

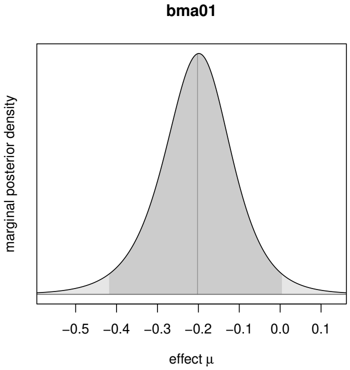
or simply

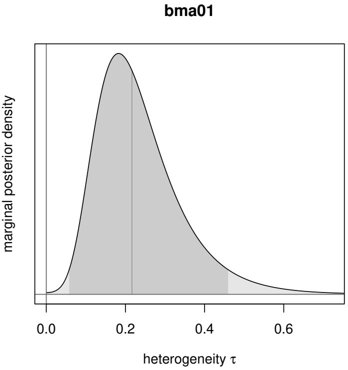
```
R> bma01 <- bayesmeta(exa.long,
+                      mu.prior=c(0,4),
+                      tau.prior=function(t){dhalfnormal(t,scale=0.5)})
```

```
R> plot(bma01)
```



- (joint) posterior density



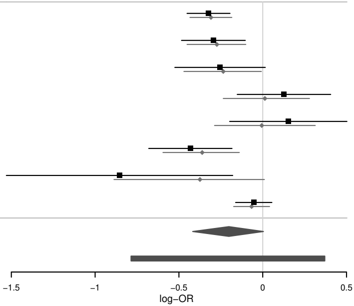


- (marginal) posterior densities

```
R> forestplot(bma01, xlab="log-OR")
```

■ quoted estimate ◆ shrinkage estimate

study	estimate	95% CI
Bateman2010a	–0.323	[–0.452, –0.195]
Bateman2010b	–0.294	[–0.485, –0.104]
Casaburi2002	–0.255	[–0.524, 0.015]
Chan2007	0.127	[–0.152, 0.405]
Cooper2010	0.153	[–0.197, 0.502]
Dusser2006	–0.432	[–0.680, –0.183]
Powrie2007	–0.854	[–1.530, –0.179]
Tashkin2008	–0.054	[–0.162, 0.055]
mean	**–0.202**	**[–0.418, 0.004]**
prediction	**–0.201**	**[–0.786, 0.370]**



Heterogeneity (tau): 0.216 [0.058, 0.459]

- forest plot: shrinkage estimates, overall mean, prediction, heterogeneity

Meta-analysis

Combining estimates: the random-effects model (application)

```
R> bma01
 'bayesmeta' object.

8 estimates:
Bateman2010a, Bateman2010b, Casaburi2002, Chan2007,
Cooper2010, Dusser2006, Powrie2007, Tashkin2008

tau prior (proper):
function(t){dhalfnormal(t,scale=0.5)}
<bytecode: 0x560ae715e468>

mu prior (proper):
normal(mean=0, sd=4)

ML and MAP estimates:
                   tau         mu
ML joint     0.1620103 -0.1988699
ML marginal  0.1879257 -0.1988890
MAP joint    0.1585792 -0.1986505
MAP marginal 0.1827378 -0.1988048

marginal posterior summary:
                 tau           mu
mode      0.18273777 -0.198804845
median    0.21640336 -0.202032865
mean      0.23622412 -0.204219500
sd        0.11053165  0.104357370
95% lower 0.05787102 -0.418091441
95% upper 0.45946622  0.004282775

(quoted intervals are shortest credible intervals.)
```

- default printout: parameter estimates, intervals, . . .

- returned object is a `list` object
- access to summary figures via `...$summary` element
- access to (marginal) posterior distribution (densities etc.) via `...$dposterior()`, `...$pposterior()`, `...$qposterior()` functions:

```
R> # posterior CDF:
R> bma01$pposterior(mu=0)
[1] 0.9746926

R> # posterior quantile:
R> bma01$qposterior(mu.p=0.90)
[1] -0.08287674

R> # posterior density plot:
R> x <- seq(from=-1.0, to=0.5, length=200)
R> plot(x, bma01$dposterior(mu=x), type="l")
R> abline(h=0, v=0, col="grey")
```

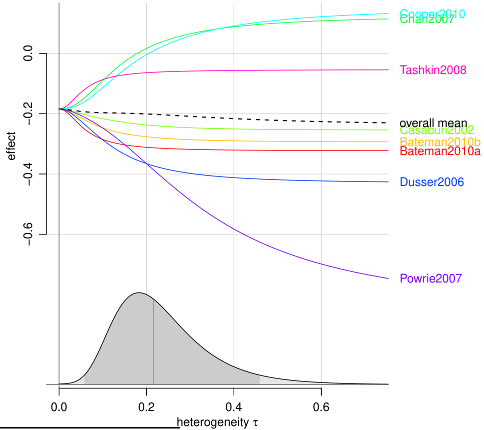
- recall: model involves μ, τ **and θ_i parameters**

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

- θ_i are the **study-specific means**
- information on θ_i originates from study-specific **data** (y_i, σ_i) as well as overall model **parameters** (μ, τ)
- a "compromise";
  original estimates (y_i) are **shrunk** towards overall mean (μ)

- trace plot, showing *conditional* estimates: [14]

```
R> traceplot(bma01)
```



[14] C. Röver, D. Rindskopf, T. Friede. How trace plots help interpret meta-analysis results. arXiv: 2306.17043, 2023.

Meta-analysis

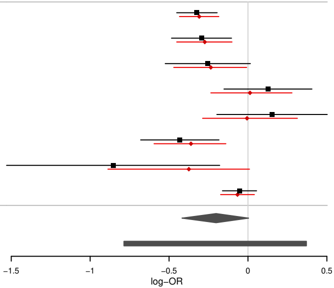
Shrinkage estimation

- **shrinkage estimates** also shown in forest plot

■ quoted estimate ◆ shrinkage estimate

study	estimate	95% CI
Bateman2010a	–0.323	[–0.452, –0.195]
Bateman2010b	–0.294	[–0.485, –0.104]
Casaburi2002	–0.255	[–0.524, 0.015]
Chan2007	0.127	[–0.152, 0.405]
Cooper2010	0.153	[–0.197, 0.502]
Dusser2006	–0.432	[–0.680, –0.183]
Powrie2007	–0.854	[–1.530, –0.179]
Tashkin2008	–0.054	[–0.162, 0.055]
mean	**–0.202**	**[–0.418, 0.004]**
prediction	**–0.201**	**[–0.786, 0.370]**

Heterogeneity (tau): 0.216 [0.058, 0.459]



- quantification of θ_i “in the light of remaining estimates”
- precision gain especially for small studies or small heterogeneity

- **summary** statistics quoted in "`...$theta`" element

```
R> bma01$theta
          Bateman2010a Bateman2010b Casaburi2002    Chan2007   Cooper2010
y          -0.32337763  -0.29428538 -0.254582124  0.12668448  0.152559590
sigma       0.06539452   0.09705565  0.137669290  0.14222544  0.178489990
mode       -0.30840910  -0.27089496 -0.230346479 -0.08294548 -0.082945479
median     -0.30888137  -0.27366544 -0.235537664  0.01299017 -0.005908566
mean       -0.30913967  -0.27484627 -0.237257561  0.01738271  0.002560609
sd          0.06375413   0.08937384  0.117014284  0.13276673  0.155096413
95% lower  -0.43420554  -0.45146744 -0.470289654 -0.23541576 -0.287440349
95% upper  -0.18442168  -0.10112218 -0.008360574  0.27892657  0.313289531
          Dusser2006   Powrie2007 Tashkin2008
y         -0.4317214 -0.854415328 -0.05355778
sigma      0.1267174  0.344546794  0.05519895
mode      -0.3282845 -0.309703501 -0.08294548
median    -0.3612026 -0.374533284 -0.06636582
mean      -0.3643220 -0.402724962 -0.06630907
sd         0.1169852  0.230981508  0.05463051
95% lower -0.5952293 -0.887465067 -0.17337550
95% upper -0.1399293  0.009802466  0.04079575
```

- access e.g. to **density** via "`...$dposterior()`" function by setting `individual=...` argument
- similarly for quantiles, intervals, etc.

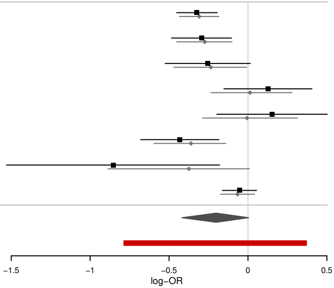
- besides the (k) included studies, often of interest: implications for “new” or “future” study (denoted as θ_{k+1} or θ^*)
- conditionally:

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

(for inference, need to marginalize over uncertain (posterior) μ, τ)
- **prediction** also shown in forest plot

■ quoted estimate ✦ shrinkage estimate

study	estimate	95% CI
Bateman2010a	–0.323	[–0.452, –0.195]
Bateman2010b	–0.294	[–0.485, –0.104]
Casaburi2002	–0.255	[–0.524, 0.015]
Chan2007	0.127	[–0.152, 0.405]
Cooper2010	0.153	[–0.197, 0.502]
Dusser2006	–0.432	[–0.680, –0.183]
Powrie2007	–0.854	[–1.530, –0.179]
Tashkin2008	–0.054	[–0.162, 0.055]
mean	**–0.202**	**[–0.418, 0.004]**
prediction	**–0.201**	**[–0.786, 0.370]**



Heterogeneity (tau): 0.216 [0.058, 0.459]

Meta-analysis

Prediction

- **summary** statistics quoted in "`...$summary`" table
- access e.g. to **density** via "`...$dposterior()`" function
  by setting `predict=TRUE` argument
- similarly for quantiles, intervals, etc.

[15] H. Schmidli *et al.* Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, **70**(4):1023–1032, 2014.

- **summary** statistics quoted in "`...$summary`" table
- access e.g. to **density** via "`...$dposterior()`" function by setting `predict=TRUE` argument
- similarly for quantiles, intervals, etc.

- **predictive distribution** plays a central role when using MA of historical data to inform a future study (via a meta-analytic-predictive (MAP) prior)
- equivalently: joint MA of all studies, consideration of **shrinkage estimate** (meta-analytic-combined (MAC) approach)[15]

- (more in following presentation!)

[15] H. Schmidli *et al.* Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, **70**(4):1023–1032, 2014.

- meta-*regression*:
  generalization of NNHM to include (study-level) **covariables** $x_{i,1}, \ldots, x_{i,d}$
- model (likelihood):

$$\begin{aligned} y_i|\theta_i &\sim \text{Normal}(\theta_i, \sigma_i^2) \\ \theta_i|\beta_1, \ldots, \beta_d, \tau &\sim \text{Normal}(\beta_1 x_{i,1} + \ldots + \beta_d x_{i,d}, \tau^2) \end{aligned}$$

Meta-analysis

Meta-regression: example (binary covariables)

- consider COPD data set;
  two study types: *short* (<1 year) and *long* (≥ 1 year) follow-up

study			log-OR	
i	name	follow-up	y_i	σ_i
1	Bateman (2010a)	long	-0.32	0.07
2	Bateman (2010b)	long	-0.29	0.10
3	Beeh (2006)	short	-0.37	0.15
4	Brusasco (2003)	short	-0.30	0.15
5	Casaburi (2003)	long	-0.25	0.14
⋮	⋮	⋮	⋮	⋮

- besides estimates (y) and standard errors (σ), specify regressor matrix:

$$X = \begin{pmatrix} 0 & 1 \\ 0 & 1 \\ 1 & 0 \\ 1 & 0 \\ 0 & 1 \\ \vdots & \vdots \end{pmatrix}$$

Meta-analysis

Meta-regression: R code

- need to specify regressor matrix

```
R> # assemble regressor matrix:
R> X <- cbind("short"=as.numeric(exa.all$duration=="up to 1 year"),
+             "long" =as.numeric(exa.all$duration=="1 year or longer"))
R> head(X)
     short long
[1,]     0    1
[2,]     0    1
[3,]     1    0
[4,]     1    0
[5,]     0    1
[6,]     0    1
```

- `bmr()` function for meta-regression
  (behaviour mostly analogous to `bayesmeta()`)

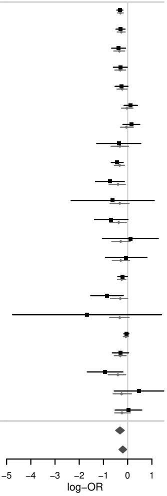
```
R> # perform analysis:
R> bmr01 <- bmr(exa.all, X=X,
                tau.prior=function(tau){dhalfnormal(tau, scale=0.5)})
```

Meta-analysis

Meta-regression: forest plot

■ quoted estimate ◆ shrinkage estimate

study	short	long	estimate	95% CI
Bateman2010a	0	1	−0.323	[−0.452, −0.195]
Bateman2010b	0	1	−0.294	[−0.485, −0.104]
Beeh2006	1	0	−0.374	[−0.665, −0.082]
Brusasco2003	1	0	−0.302	[−0.593, −0.012]
Casaburi2002	0	1	−0.255	[−0.524, 0.015]
Chan2007	0	1	0.127	[−0.152, 0.405]
Cooper2010	0	1	0.153	[−0.197, 0.502]
Covelli2005	1	0	−0.368	[−1.281, 0.546]
Dusser2006	0	1	−0.432	[−0.680, −0.183]
Freeman2007	1	0	−0.734	[−1.332, −0.137]
Johansson2008	1	0	−0.620	[−2.338, 1.098]
Magnussen2008	1	0	−0.679	[−1.371, 0.013]
Moita2008	1	0	0.114	[−1.040, 1.268]
NCT00144326	1	0	−0.061	[−0.919, 0.798]
Niewoehner2005	1	0	−0.212	[−0.412, −0.012]
Powrie2007	0	1	−0.854	[−1.530, −0.179]
Sun2007	1	0	−1.677	[−4.756, 1.402]
Tashkin2008	0	1	−0.054	[−0.162, 0.055]
Tonnel2008	1	0	−0.296	[−0.635, 0.044]
Trooster2011	1	0	−0.932	[−1.671, −0.193]
Verkindre2006	1	0	0.468	[−0.559, 1.495]
Voshaar2008	1	0	0.033	[−0.522, 0.588]
short	**1**	**0**	**−0.315**	**[−0.496, −0.140]**
long	**0**	**1**	**−0.199**	**[−0.358, −0.044]**



Heterogeneity (tau): 0.158 [0.047, 0.305]

- besides “main” coefficients, other linear combinations of interest
- e.g.: treatment effect for “short” and “long” follow-up, and their **difference**

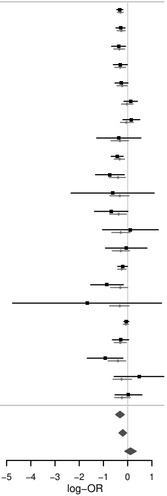
```
R> # default forest plot:
R> forestplot(bmr01,
+             xlab="log-OR")

R> # forest plot with additional estimates:
R> forestplot(bmr01,
+             X.mean=rbind("short"     =c(1,0),
+                          "long"      =c(0,1),
+                          "difference"=c(-1,1)),
+             xlab="log-OR")

R> # show estimates only:
R> summary(bmr01,
+         X.mean=rbind("short"     =c(1,0),
+                      "long"      =c(0,1),
+                      "difference"=c(-1,1)))
```

Meta-analysis

Meta-regression: forest plot, additional estimates

■ quoted estimate ◆ shrinkage estimate

study	short	long	estimate	95% CI
Bateman2010a	0	1	−0.323	[−0.452, −0.195]
Bateman2010b	0	1	−0.294	[−0.485, −0.104]
Beeh2006	1	0	−0.374	[−0.665, −0.082]
Brusasco2003	1	0	−0.302	[−0.593, −0.012]
Casaburi2002	0	1	−0.255	[−0.524, 0.015]
Chan2007	0	1	0.127	[−0.152, 0.405]
Cooper2010	0	1	0.153	[−0.197, 0.502]
Covelli2005	1	0	−0.368	[−1.281, 0.546]
Dusser2006	0	1	−0.432	[−0.680, −0.183]
Freeman2007	1	0	−0.734	[−1.332, −0.137]
Johansson2008	1	0	−0.620	[−2.338, 1.098]
Magnussen2008	1	0	−0.679	[−1.371, 0.013]
Moita2008	1	0	0.114	[−1.040, 1.268]
NCT00144326	1	0	−0.061	[−0.919, 0.798]
Niewoehner2005	1	0	−0.212	[−0.412, −0.012]
Powrie2007	0	1	−0.854	[−1.530, −0.179]
Sun2007	1	0	−1.677	[−4.756, 1.402]
Tashkin2008	0	1	−0.054	[−0.162, 0.055]
Tonnel2008	1	0	−0.296	[−0.635, 0.044]
Trooster2011	1	0	−0.932	[−1.671, −0.193]
Verkindre2006	1	0	0.468	[−0.559, 1.495]
Voshaar2008	1	0	0.033	[−0.522, 0.588]
short	**1**	**0**	**−0.315**	**[−0.496, −0.140]**
long	**0**	**1**	**−0.199**	**[−0.358, −0.044]**
difference	**−1**	**1**	**0.116**	**[−0.119, 0.355]**



Heterogeneity (tau): 0.158 [0.047, 0.305]

Meta-analysis

Meta-regression: example (continuous covariables)

- consider COPD data set;
  differing disease severity (as measured through FEV_1)

study			log-OR	
i	name	FEV_1 (%)	y_i	σ_i
1	Bateman (2010a)	40	-2.31	0.60
2	Bateman (2010b)	38	-0.46	0.56
3	Beeh (2006)	45	-2.30	0.88
4	Brusasco (2003)	39	-1.76	0.46
5	Casaburi (2003)	39	-1.26	0.64
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$

- regressor matrix (intercept / slope):

$$X = \begin{pmatrix} 1 & 40 \\ 1 & 38 \\ 1 & 45 \\ 1 & 39 \\ 1 & 39 \\ \vdots & \vdots \end{pmatrix}$$

Meta-analysis

Meta-regression: R code

- need to specify regressor matrix

```
R> # assemble regressor matrix:
R> X <- cbind("intercept" = 1,
+             "FEV1"      = exa.all$baseline.fev1pp)
R> head(X)
     intercept FEV1
[1,]         1   40
[2,]         1   38
[3,]         1   45
[4,]         1   39
[5,]         1   39
[6,]         1   39
```

(may also use "`model.matrix()`" function and formula interface)

- again, `bmr()` function

```
R> # perform analysis:
R> bmr02 <- bmr(exa.all[-13,], X=X[-13,],
+               tau.prior=function(t){dhalfnormal(t, scale=0.5)})
R> # (note: missing data for 13th study)
```

Meta-analysis

Meta-regression: forest plot

■ quoted estimate ◆ shrinkage estimate

study	intercept	FEV1	estimate	95% CI
Bateman2010a	1	40	−0.3234	[−0.4515, −0.1952]
Bateman2010b	1	38	−0.2943	[−0.4845, −0.1041]
Beeh2006	1	45	−0.3737	[−0.6650, −0.0823]
Brusasco2003	1	39	−0.3023	[−0.5926, −0.0121]
Casaburi2002	1	39	−0.2546	[−0.5244, 0.0152]
Chan2007	1	39	0.1267	[−0.1521, 0.4054]
Cooper2010	1	38	0.1526	[−0.1973, 0.5024]
Covelli2005	1	39	−0.3677	[−1.2815, 0.5460]
Dusser2006	1	48	−0.4317	[−0.6801, −0.1834]
Freeman2007	1	49	−0.7342	[−1.3319, −0.1366]
Johansson2008	1	73	−0.6197	[−2.3378, 1.0983]
Magnussen2008	1	53	−0.6793	[−1.3712, 0.0126]
NCT00144326	1	46	−0.0606	[−0.9191, 0.7979]
Niewoehner2005	1	36	−0.2117	[−0.4119, −0.0115]
Powrie2007	1	50	−0.8544	[−1.5297, −0.1791]
Sun2007	1	47	−1.6773	[−4.7563, 1.4017]
Tashkin2008	1	39	−0.0536	[−0.1617, 0.0546]
Tonnel2008	1	44	−0.2958	[−0.6351, 0.0436]
Trooster2011	1	66	−0.9321	[−1.6710, −0.1933]
Verkindre2006	1	35	0.4683	[−0.5586, 1.4952]
Voshaar2008	1	52	0.0329	[−0.5224, 0.5883]
intercept	**1**	**0**	**0.8184**	**[0.0913, 1.5513]**
slope	**0**	**1**	**−0.0256**	**[−0.0430, −0.0083]**
FEV1=40%	**1**	**40**	**−0.2049**	**[−0.3084, −0.0983]**
FEV1=50%	**1**	**50**	**−0.4603**	**[−0.6356, −0.2847]**
FEV1=60%	**1**	**60**	**−0.7161**	**[−1.0493, −0.3835]**
FEV1=70%	**1**	**70**	**−0.9719**	**[−1.4736, −0.4717]**

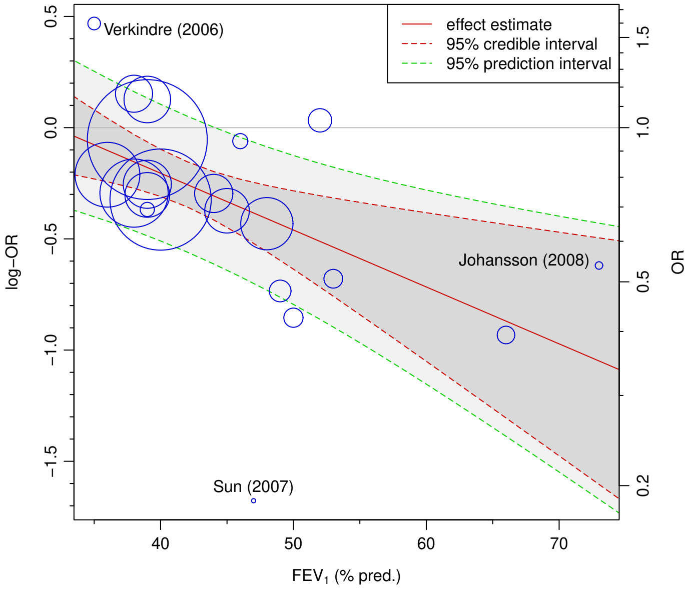
Heterogeneity (tau): 0.117 [0.018, 0.239]

- again, may derive “plain” estimates, or sensible linear combinations

```
R> forestplot(bmr02, xlab="log-OR",
+             X.mean=rbind("intercept"=c(1,0),
+                          "slope"    =c(0,1),
+                          "FEV1=40%" =c(1,40),
+                          "FEV1=50%" =c(1,50),
+                          "FEV1=60%" =c(1,60),
+                          "FEV1=70%" =c(1,70)))

R> summary(bmr02,
+         X.mean=rbind("intercept" = c(1,0),
+                      "slope"     = c(0,1),
+                      "FEV1=40%"  = c(1,40),
+                      "FEV1=50%"  = c(1,50),
+                      "FEV1=60%"  = c(1,60),
+                      "FEV1=70%"  = c(1,70)))
```

Meta-analysis

Meta-regression: bubble plot



- meta-regression allows to approach range of interesting models, e.g.
  - several intercepts (study subgroups)
  - intercept / slope (effect moderators / interactions)
  - network meta-analysis (simple cases)
  - Bayes factors (variable selection / model averaging)
  - ...

Outlook

Issues not covered here

- discussion of prior distributions
  (uninformative, weakly informative, empirical, . . .)
- alternative setups for regressor matrices (`X`)
- (multivariate) priors for regression parameters
- indirect comparisons, network meta-analysis
- Bayes factors, model selection
- computational details
- . . .

References

Bayesian meta-analysis & meta-regression using `bayesmeta`

- C. Röver. Bayesian random-effects meta-analysis using the `bayesmeta` R package. *Journal of Statistical Software*, **93**(6), 2020.
- C. Röver, T. Friede. Using the `bayesmeta` R package for Bayesian random-effects meta-regression. *Computer Methods and Programs in Biomedicine*, **229**:107303, 2023.
- 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.

- D.J. Spiegelhalter, K.R. Abrams, J.P. Myles. *Bayesian approaches to clinical trials and health-care evaluation*, John Wiley & Sons, 2004.
- S. G. Thompson, J. P. T. Higgins. How should meta-regression analyses be undertaken and interpreted? *Statistics in Medicine*, **21**(11):1559–1573, 2002.