

Meta-Analysis Workshop

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Evidence Synthesis & Meta-Analysis in R Conference

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1

Systematic Reviews

- research synthesis as a scientific process
- based on replicable and systematic methods that are meant to “limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic” (Last, 2001)
- **methods should be made explicit**
- synthesis part can make use of qualitative or quantitative methods
- for some history, see Chalmers et al. (2002)

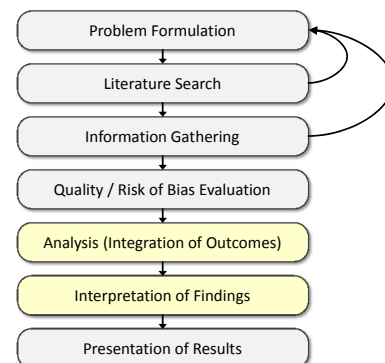
2

Meta-Analysis

- a set of statistical methods and techniques for aggregating, summarizing, and drawing inferences from collections of related studies
- **key idea:** quantify the size, direction, and/or strength of the effect or association in each study and use this as primary data in further analyses

3

Stages of a Research Synthesis



(Cooper, 2016)

4

Analysis and Interpretation

- what is the overall (average) size and direction of the effect or association?
- is the effect or association constant?
- if it varies across studies, by how much?
- does the effect or association depend on the characteristics of the studies?

5

Outcome Measures for Meta-Analysis

- a measure that quantifies the phenomenon of interest so that it is comparable across studies
- some commonly used outcome measures:
 - raw or standardized mean differences
 - risk differences, log risk ratios, log odds ratios
 - raw or r-to-z transformed correlation coefficients
 - raw means, proportions, Cronbach's alpha values
 - regression coefficients, (semi)partial correlations
 - standard deviations, coefficients of variation
 - ...

6

Terminology

- 'effect size' seems a bit strange for measures that reflect the association between variables or some property of individual groups
- effect size \neq standardized mean difference (or any kind of standardized measure in general) (e.g., raw mean differences and raw regression coefficients are effect sizes as well)
- hence prefer 'outcome measure' (but not to be confused with the DV in a primary study!)

7

Observed vs. True Outcomes

- y_i = observed outcome in the i th study
- θ_i = true outcome in the i th study
- assumption: $E[y_i] = \theta_i$ (i.e., unbiasedness)
- bias adjustments may be necessary:
 - standardized mean difference (Hedges, 1981)
 - log risk/odds ratio (Haldane, Anscombe, Gart, ...)
 - correlation coefficient (Olkin & Pratt, 1958)
 - ...

8

Sampling Distribution / Variance

- theoretical distribution of the outcome measure that would arise if one were to repeat a study (repeatedly sample) under identical circumstances (with constant θ_i)
- **sampling variance:** the variance of the values in a sampling distribution
- **standard error:** the square root of the sampling variance (i.e., the standard deviation of the values in a sampling distribution)

9

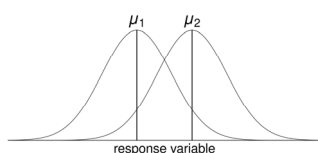
Assumptions

- normal sampling distribution
 - often only true asymptotically
- known sampling variance
 - often based on an asymptotic approximation
 - often we need to substitute observed values into the equation, so we really only get an estimate

10

Two Groups + Quantitative Variable

- subjects in two groups are measured on some quantitative response variable within a study
- assume that the response variable is normally distributed with variance σ^2 and that:
 - the true mean in group 1 is μ_1
 - the true mean in group 2 is μ_2



11

Standardized Mean Difference

- standardized mean difference (Cohen's d):

$$d = \frac{\bar{x}_1 - \bar{x}_2}{SD_p} \text{ is an estimate of } \theta = \frac{\mu_1 - \mu_2}{\sigma}$$

- bias correction:

$$y \approx \left[1 - \frac{3}{4(n_1 + n_2) - 9} \right] d \quad \text{(also known as Hedges' g)}$$

- asymptotic sampling variance:

$$v = \frac{1}{n_1} + \frac{1}{n_2} + \frac{\theta^2}{2(n_1 + n_2)}$$

12

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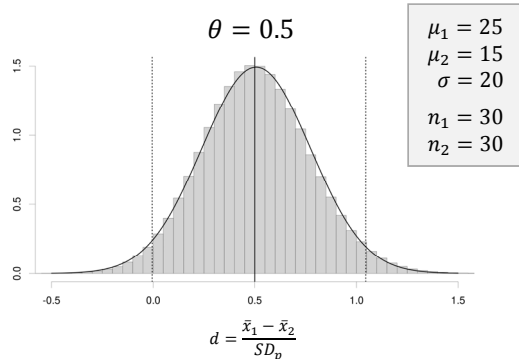
13

Example

		Sample Size	Mean (SD) Depression Score	Std. Mean Difference	Sampling Variance
Study 1	Treatment	70	34.5 (14.62)	-0.56	0.030
	Control	70	42.8 (15.04)		
Study 2	Treatment	43	4.4 (1.77)	-0.47	0.048
	Control	42	5.3 (2.04)		
...					

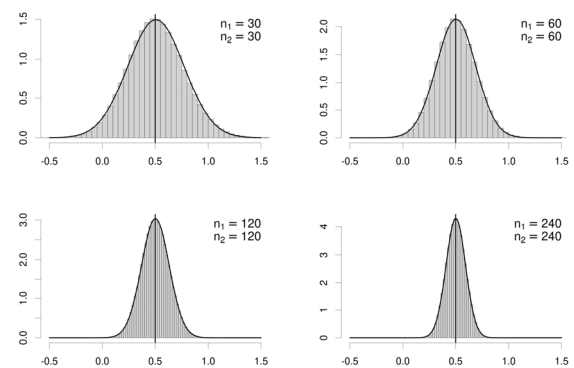
14

Standardized Mean Difference



15

Standardized Mean Difference



Interpretation of SMDs

- often cited: 0.2/0.5/0.8 = small/medium/large
- better: relate SMD value back to a familiar scale with known standard deviation
- example: cognitive functions in children have been found to be negatively affected by lead exposure ($d = -0.20$)
- SD of IQ scores ≈ 15
- hence, this implies a $-0.20 \times 15 = -3$ point difference in IQ scores (on average)

17

Two Groups + Dichotomous Variable

- subjects in two groups are measured on some dichotomous response variable (with categories out1 and out2) in a study
- let out1 be the 'outcome of interest'
- assume that:
 - the true probability of out1 in group 1 is π_1
 - the true probability of out1 in group 2 is π_2

18

2 × 2 Table Data

		out1	out2		
Table of True Probabilities	grp1	π_1	$1 - \pi_1$		
	grp2	π_2	$1 - \pi_2$		
		out1	out2	Observed Probabilities/Risks	
Table with Observed Counts	grp1	a	b	n_1	$p_1 = a/n_1$
	grp2	c	d	n_2	$p_2 = c/n_2$

19

Log Risk Ratio

- log risk ratio (also called log relative risk):

$$y = \ln \left[\frac{a/n_1}{c/n_2} \right] \text{ is an estimate of } \theta = \ln \left[\frac{\pi_1}{\pi_2} \right]$$

- bias correction:

$$y \approx \ln \left[\frac{(a + \frac{1}{2})/(n_1 + 1)}{(c + \frac{1}{2})/(n_2 + 1)} \right]$$

(often only applied when one of the 2x2 table cells is a 0; sometimes $n_1 + \frac{1}{2}$ and $n_2 + \frac{1}{2}$ are used)

- asymptotic sampling variance:

$$v = \frac{1}{\pi_1 n_1} - \frac{1}{n_1} + \frac{1}{\pi_2 n_2} - \frac{1}{n_2}$$

20

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- estimated sampling variance:

$$v = \frac{1}{a + \frac{1}{2}} - \frac{1}{n_1 + 1} + \frac{1}{c + \frac{1}{2}} - \frac{1}{n_2 + 1}$$

21

Example

		Sample Size	Patients (%) with Complications	RR	ln(RR)	Sampling Variance
Study 1	Treatment	52	12 (23.1%)	0.64	-0.44	0.100
	Control	50	18 (36.0%)			
Study 2	Treatment	123	37 (30.1%)	0.93	-0.07	0.035
	Control	130	42 (32.3%)			

...

22

Expressing RRs in Words

- first study: $RR = 0.64$ for complications in the treatment versus the control group
 - "The risk of complications in the treatment group is .64 times (or 64% of) the risk of complications in the control group"
 - "The risk of complications is 36% ($1 - .64 = .36$) lower in the treatment group compared to the control group"
 - "The risk of complications is 1.56 ($1/.64 \approx 1.56$) times higher (= 56% higher) in the control group compared to the treatment group"

23

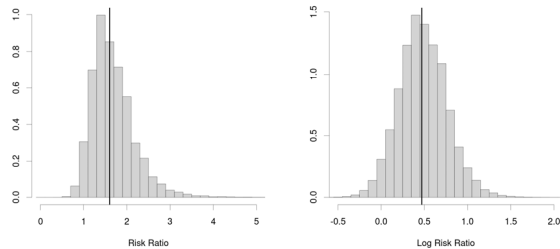
Why Use the Logarithm?

- to get a symmetrical measure:
 - study 1: $p_1 = .50$ and $p_2 = .25 \rightarrow RR = 2.0$
 - study 2: $p_1 = .25$ and $p_2 = .50 \rightarrow RR = 0.5$
 - the average of the two RR values is 1.25
 - the $\ln[RR]$ values are .6932 and -.6932
 - the average of the two $\ln[RR]$ values is 0
 - back-transformation: $e^0 = 1$
- to get approximate normality

24

Why Use the Logarithm?

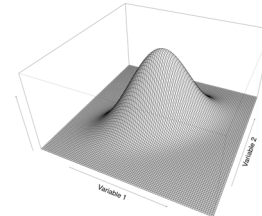
- group 1: $\pi_1 = .40, n_1 = 64$
 - group 2: $\pi_2 = .25, n_2 = 64$
- true $RR = .40 / .25 = 1.6$
true $\ln(RR) \approx 0.47$



25

Association of Quantitative Variables

- two quantitative variables are measured in a single group of subjects
- assume that the variables have a bivariate normal distribution with true correlation ρ



26

Correlation Coefficient

- Pearson product-moment correlation coefficient:
 $y = r$ is an estimate of $\theta = \rho$

- bias correction:

$$y \approx r + \frac{r(1-r^2)}{2(n-4)} \quad \text{(not very common to apply this bias correction)}$$

- asymptotic sampling variance:

$$v = \frac{(1-\rho^2)^2}{n-1}$$

27

Correlation Coefficient

- Pearson product-moment correlation coefficient:
 $y = r$ is an estimate of $\theta = \rho$

- bias correction:

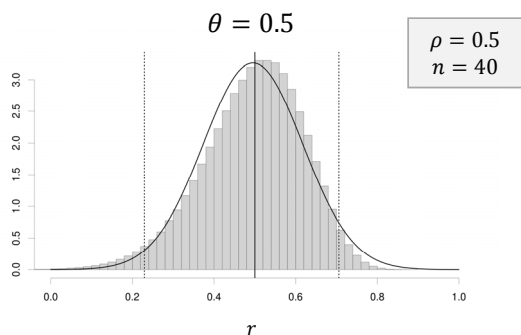
$$y \approx r + \frac{r(1-r^2)}{2(n-4)} \quad \text{(not very common to apply this bias correction)}$$

- estimated sampling variance:

$$v = \frac{(1-r^2)^2}{n-1}$$

28

Example: Correlation Coefficient



29

r-to-z Transformed Correlation

- Fisher's r-to-z transformed correlation coefficient:

$$y = z_r = \frac{1}{2} \ln \left[\frac{1+r}{1-r} \right] \text{ is an estimate of } \theta = \frac{1}{2} \ln \left[\frac{1+\rho}{1-\rho} \right]$$

- bias correction:

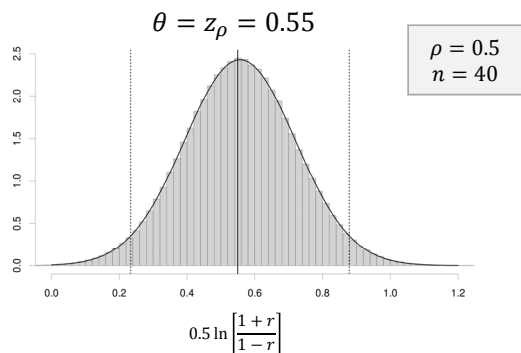
$$y \approx \frac{1}{2} \ln \left[\frac{1+r}{1-r} \right] - \frac{r}{2(n-1)} \quad \text{(not very common to apply this bias correction)}$$

- asymptotic / estimated sampling variance:

$$v = \frac{1}{n-3}$$

30

Example: Transformed Correlation



32

Literature

- Borenstein, M. (2009). Effect sizes for continuous data. In H. Cooper, L. V. Hedges, & J. C. Valentine (Eds.), *The handbook of research synthesis and meta-analysis* (2nd ed., pp. 221-235). New York: Russell Sage Foundation.
- Cooper, H. M. (2016). *Research synthesis and meta-analysis: A step-by-step approach* (5th ed.). Thousand Oaks, CA: Sage.
- Chalmers, I., Hedges, L. V., & Cooper, H. (2002). A brief history of research synthesis. *Evaluation and the Health Professions*, 25(1), 12-37.
- Fleiss, J. L., & Berlin, J. A. (2009). Effect sizes for dichotomous data. In H. Cooper, L. V. Hedges, & J. C. Valentine (Eds.), *The handbook of research synthesis and meta-analysis* (2nd ed., pp. 237-253). New York: Russell Sage Foundation.
- Siddaway, A. P., Wood, A. M., & Hedges, L. V. (2019). How to do a systematic review: A best practice guide for conducting and reporting narrative reviews, meta-analyses, and meta-syntheses. *Annual Review of Psychology*, 70, 747-770.

33

Meta-Analytic Data

- $i = 1, \dots, k$ studies
- have y_i and corresponding v_i
- we assume:

$$y_i | \theta_i \sim N(\theta_i, v_i)$$

- and independence of the estimates
- approx. 95% CI for θ_i : $y_i \pm 1.96\sqrt{v_i}$

34

Example: BCG Vaccine

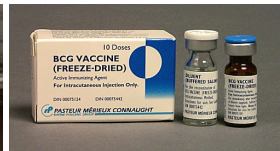
- BCG: Bacillus Calmette-Guérin (BCG)
- BCG is a vaccine against tuberculosis (TB)
- effectiveness study: compare proportion of TB positive cases in a vaccinated and a non-vaccinated group



Camille Guérin



Albert Calmette



BCG Vaccine

35

Example: BCG Vaccine

	Tuberculosis		
	Positive	Negative	
Vaccinated	4	119	123
Not Vaccinated	11	128	139

$$p_T = 4/123 = .0325$$

$$p_C = 11/139 = .0791$$

$$RR = \frac{4/123}{11/139} = .41$$

$$y = \ln[RR] = \left[\frac{4/123}{11/139} \right] = -.89$$

$$v = \frac{1}{4} - \frac{1}{123} + \frac{1}{11} - \frac{1}{139} = .326$$

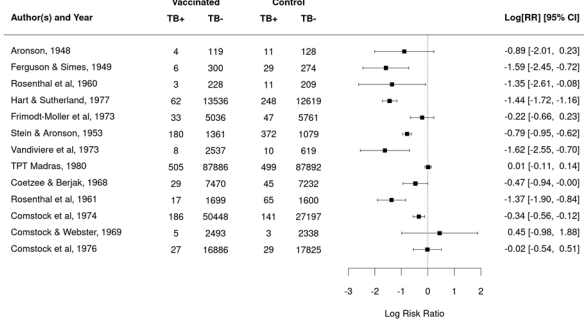
36

Example: BCG Vaccine

Study	Year	RR	$y = \ln(RR)$	v	$w = 1/v$	Latitude	Allocation
1	1948	.41	-.89	.326	3.071	44	random
2	1949	.20	-1.59	.195	5.139	55	random
3	1960	.26	-1.35	.415	2.408	42	random
4	1977	.24	-1.44	.020	49.975	52	random
5	1973	.80	-.22	.051	19.527	13	alternate
6	1953	.46	-.79	.007	144.810	44	alternate
7	1973	.20	-1.62	.223	4.484	19	random
8	1980	1.01	.01	.004	252.425	13	random
9	1968	.63	-.47	.056	17.720	27	random
10	1961	.25	-1.37	.073	13.694	42	systematic
11	1974	.71	-.34	.012	80.566	18	systematic
12	1969	1.56	.45	.533	1.878	33	systematic
13	1976	.98	-.02	.071	14.005	33	systematic

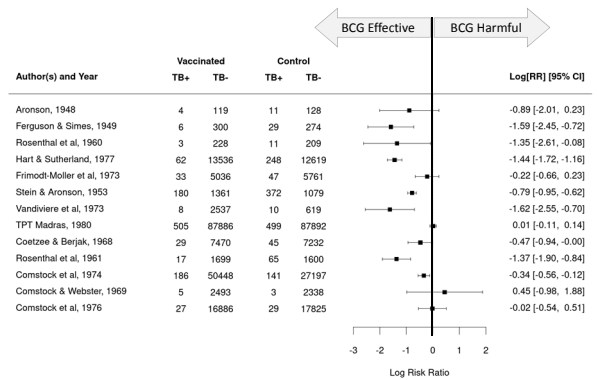
37

Example: BCG Vaccine (forest plot)



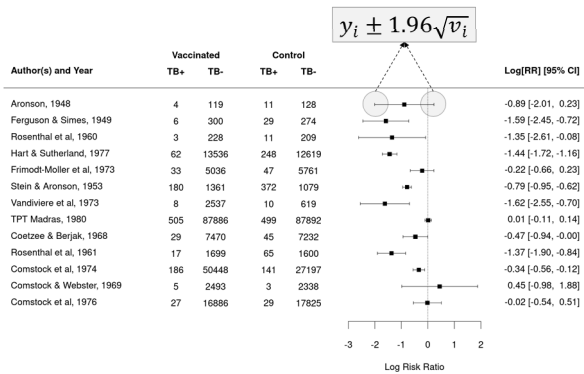
38

Example: BCG Vaccine (forest plot)



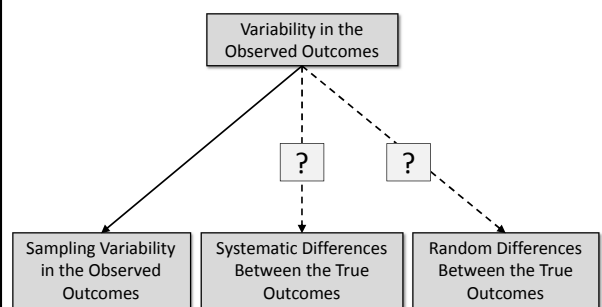
39

Example: BCG Vaccine (forest plot)



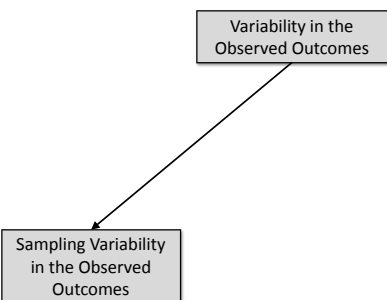
40

Sources of Variability



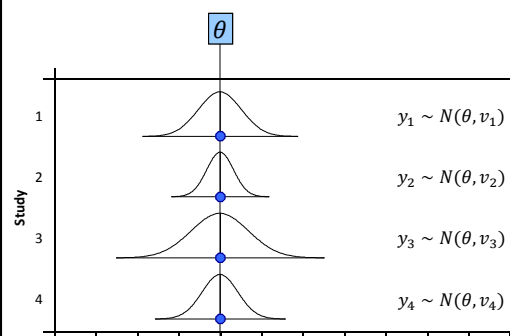
41

Sources of Variability

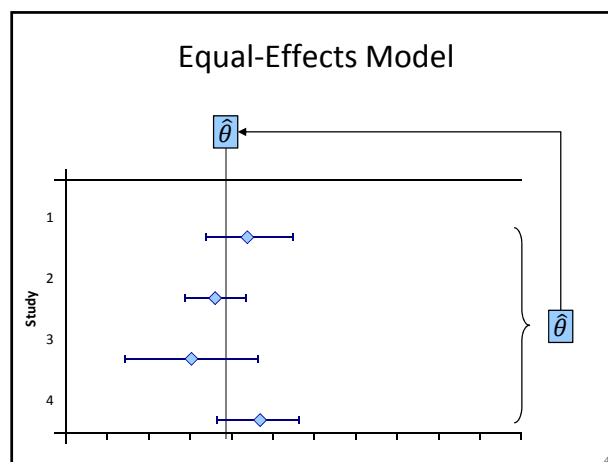
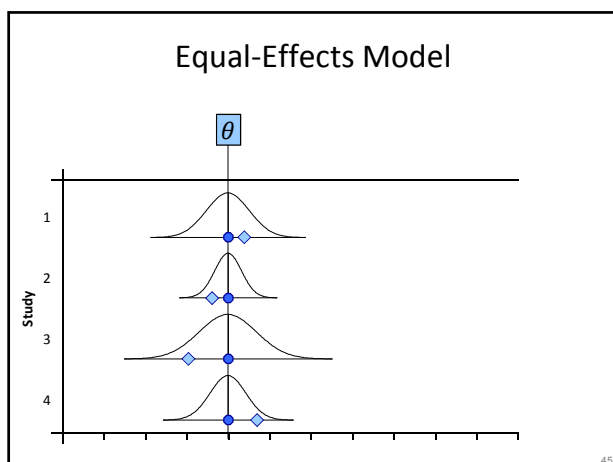


42

Equal-Effects Model



44



Equal-Effects Model

<u>Model</u>	$y_i = \theta + \epsilon_i$	$\epsilon_i \sim N(0, v_i)$
<u>Parameter Estimate</u>	$\hat{\theta} = \frac{\sum w_i y_i}{\sum w_i}$	$w_i = \frac{1}{v_i}$
<u>Var and SE of the Estimate</u>	$Var[\hat{\theta}] = \frac{1}{\sum w_i}$	$SE[\hat{\theta}] = \sqrt{\frac{1}{\sum w_i}}$
<u>Inference</u>	$z = \frac{\hat{\theta}}{SE[\hat{\theta}]}$	$\hat{\theta} \pm 1.96SE[\hat{\theta}]$

49

Example: BCG Vaccine

$\hat{\theta} = -0.4303$ (estimated log risk ratio)	$e^{-0.4303} \approx .65$ (estimated risk ratio)
$SE[\hat{\theta}] = .0405$	
$z = -10.62$	
95% CI: $(-0.5097, -0.3509)$ (95% CI for the true log risk ratio)	$(e^{-0.5097} \approx .60, e^{-0.3509} \approx .70)$ (95% CI for the true risk ratio)

50

Reverse Transformation

<ul style="list-style-type: none"> reverse the transformation when working with a transformed effect size or outcome measure for easier interpretation of results <ul style="list-style-type: none"> log risk ratio \rightarrow exponentiation log odds ratio \rightarrow exponentiation r-to-z transformed correlation $\rightarrow r = \frac{e^{2zr}-1}{e^{2zr}+1}$

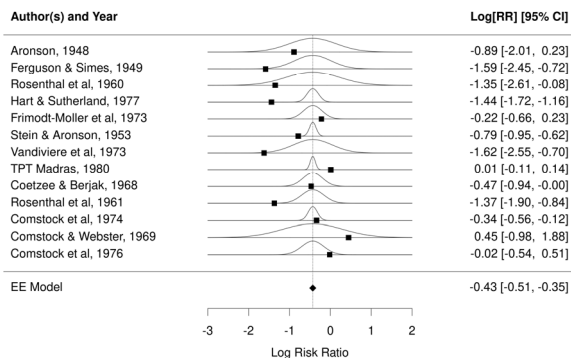
51

Testing for Heterogeneity

$H_0: \theta_1 = \theta_2 = \dots = \theta_k$
$w_i = 1/v_i$
$Q = \sum w_i (y_i - \hat{\theta})^2$
if the true outcomes are really homogeneous, then the Q -statistic follows a chi-square distribution with $k - 1$ degrees of freedom

52

Example: BCG Vaccine



Example: BCG Vaccine

$$Q = 152.23$$

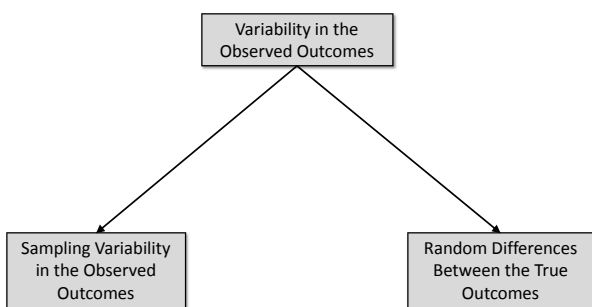
critical value (for $\alpha = .05$ and $df = 12$): 21.03

p-value: <.0001

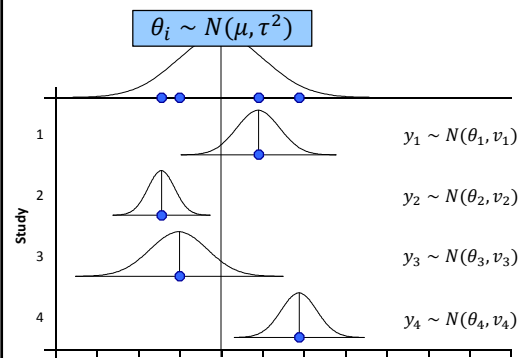
reject $H_0: \theta_1 = \theta_2 = \dots = \theta_{13}$

conclusion: the true outcomes are heterogeneous

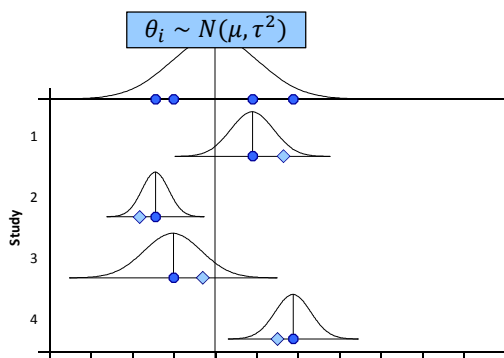
Sources of Variability



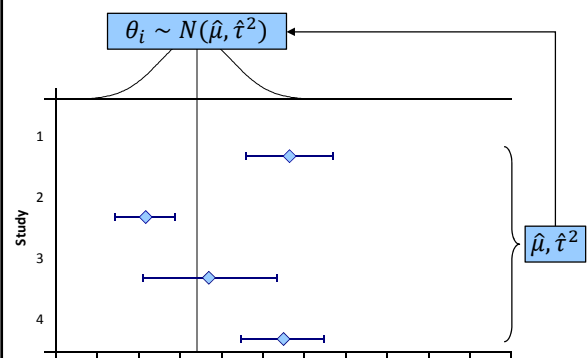
Random-Effects Model



Random-Effects Model



Random-Effects Model



Random-Effects Model

Model $y_i = \underbrace{\mu + u_i}_{\theta_i} + \epsilon_i \quad u_i \sim N(0, \tau^2)$

Parameter Estimate $\hat{\mu} = \frac{\sum w_i y_i}{\sum w_i} \quad w_i = \frac{1}{\hat{\tau}^2 + v_i}$

Var and SE of the Estimate $Var[\hat{\mu}] = \frac{1}{\sum w_i} \quad SE[\hat{\mu}] = \sqrt{\frac{1}{\sum w_i}}$

Inference $z = \frac{\hat{\mu}}{SE[\hat{\mu}]} \quad \hat{\mu} \pm 1.96SE[\hat{\mu}]$

64

Estimators for τ^2

- DerSimonian-Laird estimator
- Hedges estimator
- Hunter-Schmidt estimator
- Sidik-Jonkman estimator
- maximum likelihood estimator
- restricted maximum likelihood estimator
- empirical Bayes / Paule-Mandel estimator
- ...

65

DerSimonian-Laird Estimator for τ^2

- method of moments estimator
 - can show $E[Q] = c\tau^2 + (k-1)$
 - solve for τ^2 and then substitute Q for $E[Q]$

$$\hat{\tau}^2 = \frac{Q - (k-1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}} \quad w_i = \frac{1}{v_i}$$

- if estimate is negative, set to 0

66

Example: BCG Vaccine

$$\hat{\tau}^2 = \frac{Q - (k-1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}} = \frac{152.23 - (13-1)}{609.7007 - \frac{94820.58}{609.7007}} = 0.3088$$

estimated variance in the true log risk ratios

67

Example: BCG Vaccine

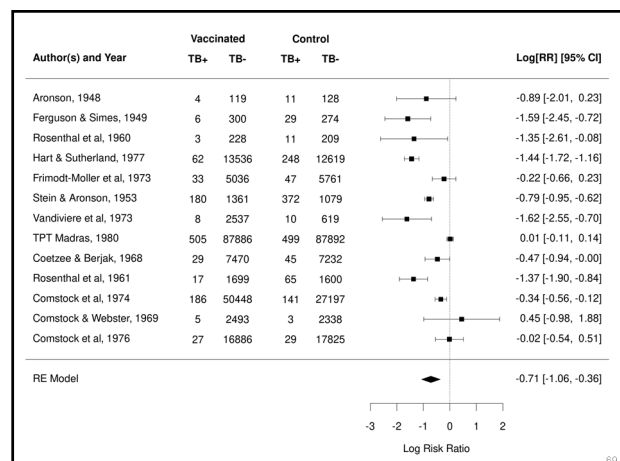
$\hat{\mu} = -0.7141$ $e^{-0.7141} \approx .49$
(estimated average log risk ratio) (estimated average risk ratio)

$SE[\hat{\mu}] = .1787$

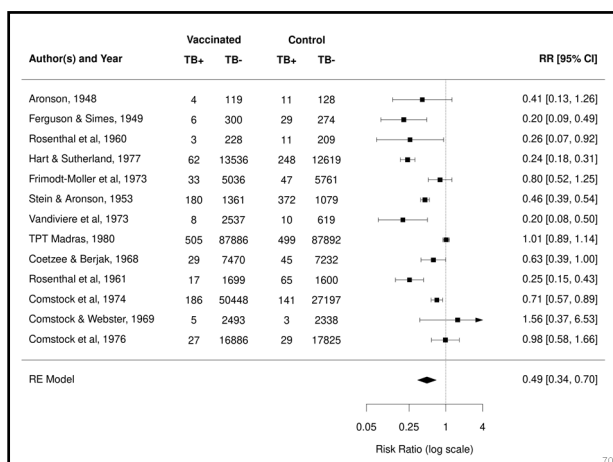
$z = -4.00$

95% CI: $(-1.0644, -0.3638)$ ($e^{-1.0644} \approx .34, e^{-0.3638} \approx .70$)
(95% CI for the true average log risk ratio) (95% CI for the true average risk ratio)

68

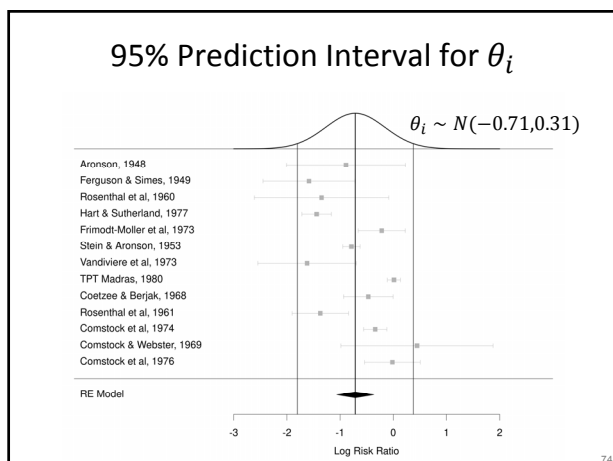
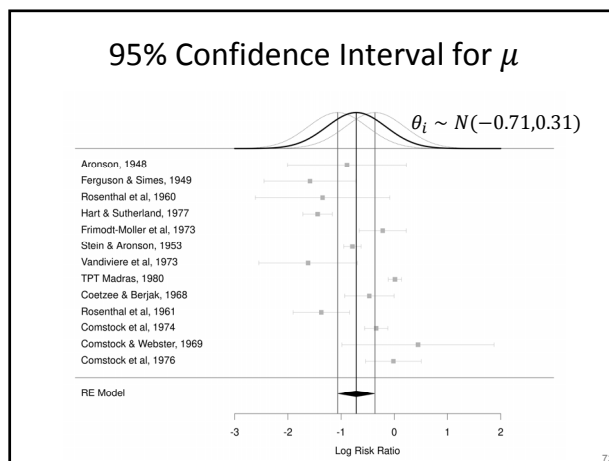
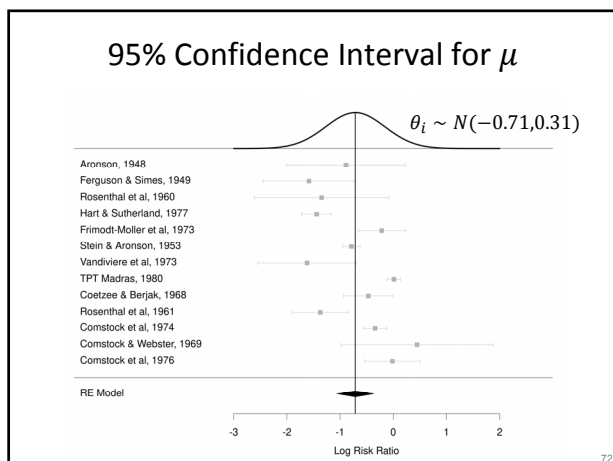


69



Interpreting $\hat{\mu}$ and $\hat{\tau}^2$ in the RE Model

- $\hat{\mu}$ is the estimated **average** outcome (while $\hat{\theta}$ in the EE model is **the** estimated outcome)
- $\hat{\tau}^2$ estimates the **total** amount of variability (heterogeneity) among the true outcomes
- heterogeneity may be due to random or systematic differences between the θ_i 's
- $\hat{\tau}^2$ does not differentiate between sources



Prediction Interval for θ_i

- interval where approximately 95% of the true outcomes are estimated/predicted to fall:

$$\hat{\mu} \pm 1.96\sqrt{\hat{\tau}^2}$$

- example:

$$-0.71 \pm 1.96\sqrt{0.31} = -1.80 \text{ to } 0.37$$

$$\text{back-transformed: } 0.16 \text{ to } 1.45$$

Prediction Interval for θ_i

- interval ignores uncertainty in $\hat{\mu}$ (i.e., $Var[\hat{\mu}]$)
- an improved 95% interval:

$$\hat{\mu} \pm 1.96\sqrt{\hat{\tau}^2 + Var[\hat{\mu}]}$$

- example:
 $-0.71 \pm 1.96\sqrt{0.31 + 0.032} = -1.86 \text{ to } 0.43$
 back-transformed: 0.16 to 1.54

76

Quantifying Heterogeneity

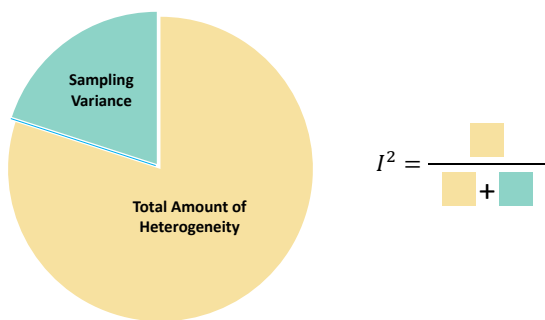
I^2 estimates (in %) how much of the total variability in the observed outcomes is due to heterogeneity among the true outcomes

$$I^2 = 100\% \times \frac{\hat{\tau}^2}{\hat{\tau}^2 + \tilde{v}} \quad \tilde{v} = \frac{(k-1)\sum w_i}{(\sum w_i)^2 - \sum w_i^2} \quad w_i = 1/v_i$$

$$= 100\% \times \frac{Q - (k-1)}{Q} \quad \text{(when estimating } \tau^2 \text{ with the DL estimator)}$$

77

Quantifying Heterogeneity



78

Example: BCG Vaccine

$$k = 13 \quad \hat{\tau}^2 = 0.3088$$

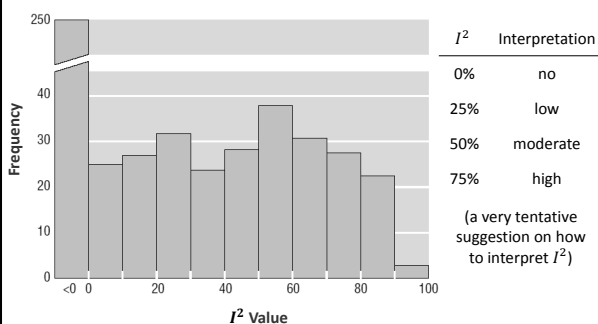
$$Q = 152.23 \quad \tilde{v} = 0.0264$$

$$I^2 = 100\% \times \frac{0.3088}{0.3088 + 0.0264}$$

$$= 100\% \times \frac{152.23 - (13 - 1)}{152.23} \quad \left. \vphantom{\frac{152.23 - (13 - 1)}{152.23}} \right\} = 92\%$$

79

Quantifying Heterogeneity



80

Relative vs. Absolute Heterogeneity

- I^2 is a relative measure of heterogeneity (but is often interpreted as an absolute measure)
- it can also be thought of as a measure to what extent the CIs in the forest plot do not overlap
- if you want to know in absolute terms how much heterogeneity there is, look at the prediction interval

81

Literature

- Colditz, G. A., Brewer, T. F., Berkey, C. S., Wilson, M. E., Burdick, E., Fineberg, H. V., et al. (1994). Efficacy of BCG vaccine in the prevention of tuberculosis: Meta-analysis of the published literature. *Journal of the American Medical Association*, 271(9), 698-702.
- Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *British Medical Journal*, 327(7414), 557-560.
- Normand, S. T. (1999). Meta-analysis: Formulating, evaluating, combining, and reporting. *Statistics in Medicine*, 18(3), 321-359.
- Riley, R. D., Higgins, J. P., & Deeks, J. J. (2011). Interpretation of random effects meta-analyses. *British Medical Journal*, 342, d549.

82

Meta-Analysis Software

- MA not typically available in general purpose statistical software (SPSS, Stata, SAS, ...) (but there were add-ons and now SPSS and Stata do include routines)
- specialized software: CMA, MetaWin, ...
- we will use R

83

What is R? Why use it?

- R is a software package for the manipulation, statistical analysis, and graphical display of data
<https://www.r-project.org>
- a (statistical) programming language
- freely available under the GNU General Public License (GPL) → open-source
- cross-platform (can be used under Windows, macOS, Unix/Linux, ...)
- extremely powerful, huge/active/enthusiastic user community, 'lingua franca' of statistics

84

Meta-Analysis with R

- several R packages for meta-analysis exist:
 - meta (Guido Schwarzer)
 - rmeta (Thomas Lumley)
 - metafor (Wolfgang Viechtbauer)
 - ...
- meta-analysis 'task view' on CRAN:
<https://cran.r-project.org/view=MetaAnalysis>
- we will work with the metafor package:
<https://www.metafor-project.org>

85

Meta-Analysis with R (metafor)

- install with: `install.packages("metafor")`
- load package with: `library(metafor)`
- **put your commands in a script file!!!**
- if you are new to R, consider using RStudio
- comments start with `#` (use them!)

86

Loading External/Internal Datasets

- can use external software (Excel, SPSS, etc.) for data preparation and management
- for an external dataset, first change working directory to where the script and data file are stored (Session – Set Working Directory)
- can read in external data with `read.table()` (plain text files), `readxl::read_excel()` (Excel files), `haven::read_sav()` (SPSS files), ...
- metafor also comes with a bunch of datasets we can make use of (and we mostly will!)

87

Loading the BCG Data

- set the working directory to where the data file is stored (RStudio: Menu Session → Set Working Directory → To Source File Location)

```
> # read in data from data_bcg.txt
> dat <- read.table("data_bcg.txt", header=TRUE)
>
> # examine data
> dat
```

- header=TRUE** indicates that the first row of the dataset includes the variables names

88

```
> # or use the built-in dataset
> # copy BCG vaccine data to 'dat'
> dat <- dat.bcg
> dat
```

				TB+		TB-			
				treated	control	tpos	tneg	cpos	cneg
trial	author	year		tpos	tneg	cpos	cneg	ablat	alloc
1	1	Aronson	1948	4	119	11	128	44	random
2	2	Ferguson & Simes	1949	6	300	29	274	55	random
3	3	Rosenthal et al	1960	3	228	11	209	42	random
4	4	Hart & Sutherland	1977	62	13536	248	12619	52	random
5	5	Frimodt-Moller et al	1973	33	5036	47	5761	13	alternate
6	6	Stein & Aronson	1953	180	1361	372	1079	44	alternate
7	7	Vandiviere et al	1973	8	2537	10	619	19	random
8	8	TPT Madras	1980	505	87886	499	87892	13	random
9	9	Coetzee & Berjak	1968	29	7470	45	7232	27	random
10	10	Rosenthal et al	1961	17	1699	65	1600	42	systematic
11	11	Comstock et al	1974	186	50448	141	27197	18	systematic
12	12	Comstock & Webster	1969	5	2493	3	2338	33	systematic
13	13	Comstock et al	1976	27	16886	29	17825	33	systematic

89

Calculate Outcome Measures

- to compute outcomes: **escalc()** command
- basic syntax (see **help(escalc)** for details):

```
dat <- escalc(measure="", ..., data=dat)
```

to specify the outcome measure (RD, RR, OR, MD, SMD, ROM, ...)

to specify the variables needed to compute the observed outcomes

name of data frame containing the variables

- this will add variables **yi** (observed outcomes) and **vi** (sampling variances) to the dataset

90

```
> # calculate log risk ratios and sampling variances
> dat <- escalc(measure="RR", ai=tpos, bi=tneg, ci=cpos, di=cneg, data=dat)
> dat
```

trial	author	year	...	yi	vi
1	1	Aronson	1948	...	-0.8893 0.3256
2	2	Ferguson & Simes	1949	...	-1.5854 0.1946
3	3	Rosenthal et al	1960	...	-1.3481 0.4154
4	4	Hart & Sutherland	1977	...	-1.4416 0.0200
5	5	Frimodt-Moller et al	1973	...	-0.2175 0.0512
6	6	Stein & Aronson	1953	...	-0.7861 0.0069
7	7	Vandiviere et al	1973	...	-1.6209 0.2230
8	8	TPT Madras	1980	...	0.0120 0.0040
9	9	Coetzee & Berjak	1968	...	-0.4694 0.0564
10	10	Rosenthal et al	1961	...	-1.3713 0.0730
11	11	Comstock et al	1974	...	-0.3394 0.0124
12	12	Comstock & Webster	1969	...	0.4459 0.5325
13	13	Comstock et al	1976	...	-0.0173 0.0714

log risk ratios and sampling variances

91

Drawing Forest Plots

- to draw forest plots: **forest()** command
- basic syntax:

```
forest(dat$yi, dat$vi)
```

specify variable with the observed outcomes

specify variable with the sampling variances

- the look of the plot can be heavily customized (see **help(forest.default)** for details)

92

Equal-Effects Model

- basic syntax:

```
res <- rma(yi, vi, method="EE", data=dat)
```

name of variable for the observed outcomes

name of variable for the corresponding sampling variances

to fit an equal-effects model (EE=equal-effects)

name of data frame containing the variables

- to print results, type: **res**
- or use: **print(res, digits=2)**

93

Equal-Effects Model

- use `predict()` to apply back-transformation
 - for exponentiation: `transf=exp`
 - for z-to-r transformation: `transf=transf.ztor`

```
predict(res, transf=<>, digits=2)
```
- use `forest(res)` to obtain a forest plot with the results from the model added

94

```
> # fit equal-effects model
> res <- rma(yi, vi, method="EE", data=dat)
> res
```

Equal-Effects Model (k = 13)

I² (total heterogeneity / total variability): 92.12%
H² (total variability / sampling variability): 12.69

Test for Heterogeneity:

Q(df = 12) = 152.2330, p-val < .0001

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
-0.4303	0.0405	-10.6247	<.0001	-0.5097	-0.3509

```
> # back-transform results to the risk ratio scale
> predict(res, transf=exp, digits=2)
```

pred	ci.lb	ci.ub
0.65	0.60	0.70

95

Random-Effects Model

- basic syntax:

```
res <- rma(yi, vi, method="DL", data=dat)
```

name of variable for the observed outcomes → yi
name of variable for the corresponding sampling variances → vi
to select the τ^2 estimator (DL, ML, REML, PM, EB, ...) → method="DL"
name of data frame containing the variables → data=dat

- to print results, type: `res`
- or use: `print(res, digits=2)`

96

Random-Effects Model

- default is `method="REML"`
- use `predict()` to get prediction interval (and apply back-transformation)

```
predict(res, digits=2)
predict(res, transf=<>, digits=2)
```

- use `level` argument to change the CI/PI level (the default is 95 for a 95% CI/PI)
- again use `forest(res)` to obtain a forest plot

97

```
> # fit random-effects model
> res <- rma(yi, vi, method="DL", data=dat)
> res
```

Random-Effects Model (k = 13; tau² estimator: DL)

tau² (estimated amount of total heterogeneity): 0.3088
tau (square root of estimated tau² value): 0.5557
I² (total heterogeneity / total variability): 92.12%
H² (total variability / sampling variability): 12.69

Test for Heterogeneity:

Q(df = 12) = 152.2330, p-val < .0001

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
-0.7141	0.1787	-3.9952	<.0001	-1.0644	-0.3638

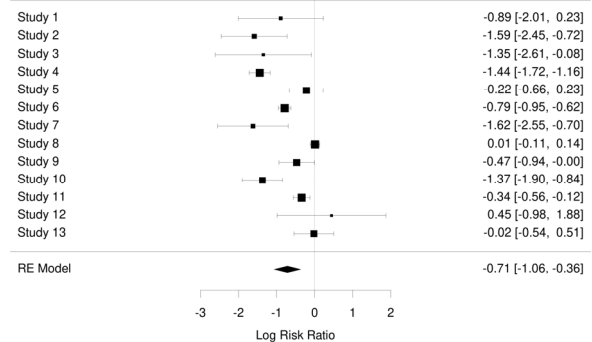
```
> # estimated average risk ratio (and 95% CI/PI)
```

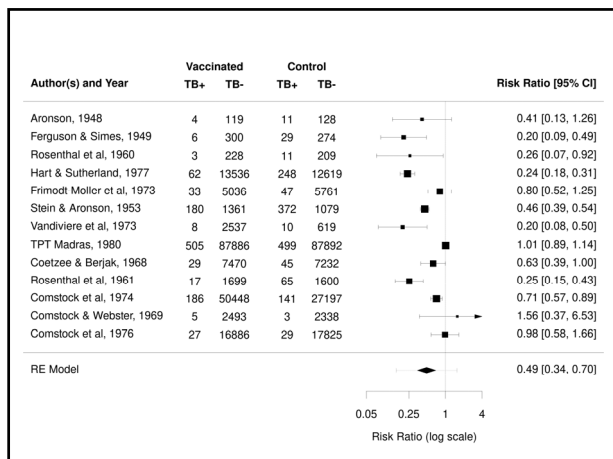
```
> predict(res, transf=exp, digits=2)
```

pred	ci.lb	ci.ub	pi.lb	pi.ub
0.49	0.34	0.70	0.16	1.54

→ pi.lb/pi.ub = bounds of the 95% prediction interval

98





Confidence Intervals for τ^2 and I^2

`confint(res)`

a random-effects
model object

```
> res <- rma(yi, vi, method="DL", data=dat)
> confint(res)
```

	estimate	ci.lb	ci.ub
tau^2	0.3088	0.1197	1.1115
tau	0.5557	0.3460	1.0543
I^2(%)	92.1173	81.9177	97.6781
H^2	12.6861	5.5303	43.0680

101

Literature

- Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software*, 36(3), 1-48. <https://doi.org/10.18637/jss.v036.i03>
- package website: <https://www.metafor-project.org>

102

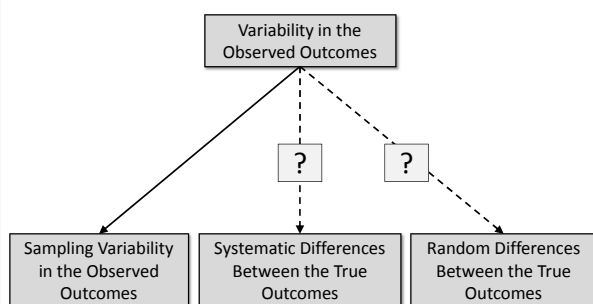
Exercises

- look at: **exercises.r**
- complete the syntax and think about the interpretation of the results (writing the syntax is the easy part!)
- have not yet covered 'meta-regression' so skip those parts

Meta-Analysis	Outcome Measure
effectiveness of writing-to-learn interventions on academic achievement (Bangert-Drowns et al., 2004)	standardized mean differences
relationship between class attendance and class performance in college students (Credé et al., 2010)	correlation coefficients (r-to-z transformed)

103

Sources of Variability



104

Moderator Variables

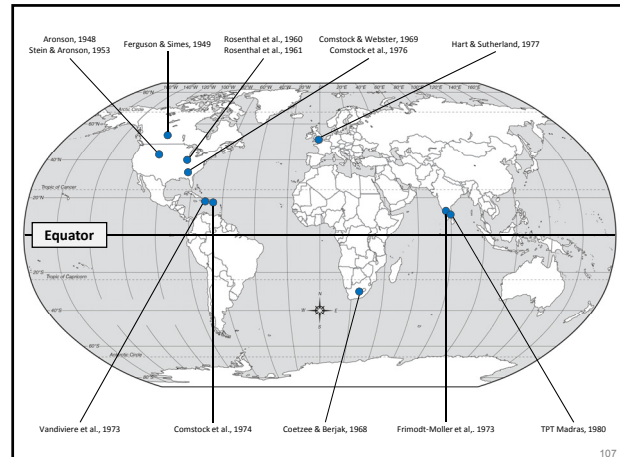
- study-level variables that may be associated with the size of the outcomes
- these may be:
 - substantive variables (characteristics of the treatment, context, subjects)
 - methodological variables (e.g., randomized versus non-randomized study)
 - 'extrinsic' variables (e.g., publication year, published/unpublished)

105

Example: BCG Vaccine

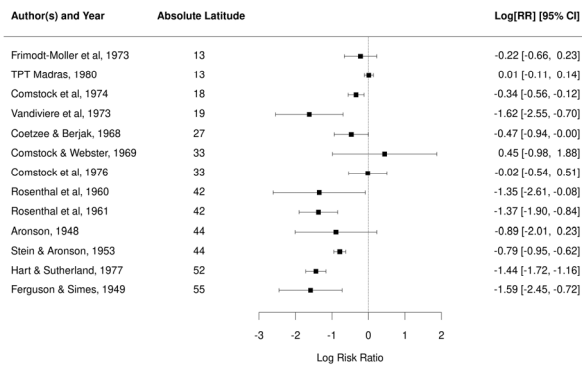
- nonpathogenic environmental mycobacteria
 - may provide a natural immunity against TB
 - are more prevalent closer to the equator
- therefore, BCG vaccine may appear to be less effective when closer to the equator
- absolute latitude of study site may therefore be a moderator of BCG vaccine efficacy

106



107

Example: BCG Vaccine



Mixed-Effects Meta-Regression Model

Model $y_i = \beta_0 + \beta_1 x_{1i} + \dots + \beta_p x_{pi} + u_i + \varepsilon_i$

Parameter Estimates $b = (X'WX)^{-1}X'Wy$ $w_i = \frac{1}{v_i + \hat{\tau}^2}$

Var and SE of the Estimates $Var[b] = (X'WX)^{-1}$ square root of the diagonal elements of $Var[b] = SE[b_j]$

Inference $z = \frac{b_j}{SE[b_j]}$ $b_j \pm 1.96SE[b_j]$

109

DerSimonian-Laird Estimator for τ^2

$$P = W - WX(X'WX)^{-1}X'W \quad w_i = 1/v_i$$

$$\hat{\tau}^2 = \frac{y'Py - (k - p - 1)}{tr[P]}$$

(if the estimate is negative, then set it equal to 0)

110

Example: BCG Vaccine

$$\hat{\tau}^2 = \frac{y'Py - (k - p - 1)}{tr[P]} = \frac{30.7331 - (13 - 2)}{311.7367} = 0.0633$$

estimated variance in the true log risk ratios not accounted for by absolute latitude

111

Example: BCG Vaccine

$$y = \begin{bmatrix} -.89 \\ -1.59 \\ \vdots \\ -.02 \end{bmatrix} \quad X = \begin{bmatrix} 1 & 44 \\ 1 & 55 \\ \vdots & \vdots \\ 1 & 33 \end{bmatrix} \quad W = \begin{bmatrix} \frac{1}{.326+.0633} & & \\ & \frac{1}{.195+.0633} & \\ & & \ddots \\ & & & \frac{1}{.071+.0633} \end{bmatrix}$$

$$b = \begin{bmatrix} .25954 \\ -.02923 \end{bmatrix} \quad SE[b_0] = \sqrt{.05396676} = .2323 \quad SE[b_1] = \sqrt{.00004533} = .0067$$

$$Var[b] = \begin{bmatrix} .05396676 & -.00141159 \\ -.00141159 & .00004533 \end{bmatrix}$$

112

Example: BCG Vaccine

	estimate	SE	z	p-value	95% CI
intercept	.2595	.2323	1.12	.26	(-.20, .71)
absolute latitude	-.0292	.0067	-4.34	<.0001	(-.04, -.02)

$$\hat{\mu}_i = .2595 - .0292(\text{absolute latitude}_i)$$

113

Predicted Average Outcome

$$x_i = [1 \quad x_{1i} \quad \cdots \quad x_{pi}] \quad b = \begin{bmatrix} b_0 \\ b_1 \\ \vdots \\ b_p \end{bmatrix}$$

Predicted Average Outcome

$$\hat{\mu}_i = b_0 + b_1 x_{1i} + \cdots + b_p x_{pi} \\ \hat{\mu}_i = x_i b$$

Variance of Predicted Average Outcome

$$Var[\hat{\mu}_i] = x_i Var[b] x_i'$$

95% CI for the True Average Outcome

$$\hat{\mu}_i \pm 1.96 \sqrt{Var[\hat{\mu}_i]}$$

114

Example: BCG Vaccine

$$x_i = [1 \quad 44]$$

$$b = \begin{bmatrix} .25954 \\ -.02923 \end{bmatrix}$$

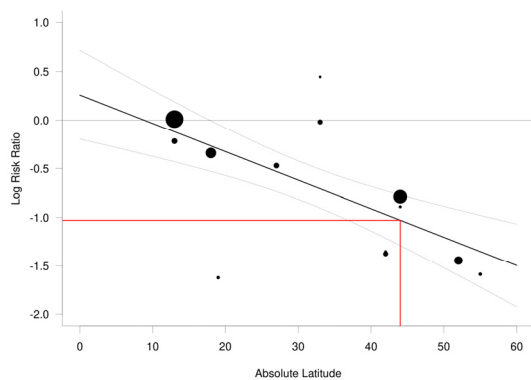
$$\hat{\mu}_i = .25954 + (-.02923)44 = -1.0265 \quad (e^{-1.0265} \approx .36)$$

$$Var[\hat{\mu}_i] = [1 \quad 44] \begin{bmatrix} .05396676 & -.00141159 \\ -.00141159 & .00004533 \end{bmatrix} \begin{bmatrix} 1 \\ 44 \end{bmatrix} = .017512$$

$$-1.0265 \pm 1.96 \sqrt{.017512} = (-1.2859, -.7672) \\ (e^{-1.2859} \approx .28, e^{-.7672} \approx .46)$$

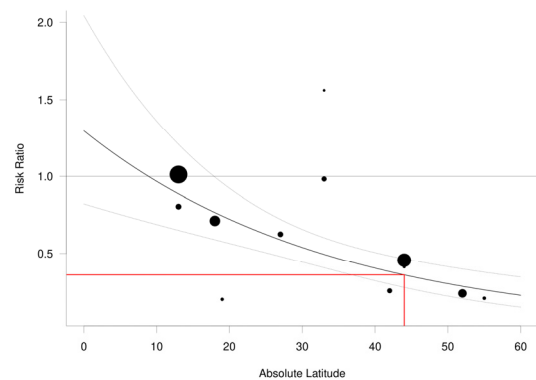
115

Example: BCG Vaccine



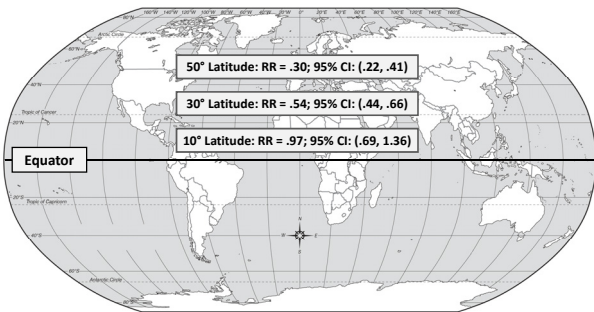
116

Example: BCG Vaccine



117

Example: BCG Vaccine



118

Interpreting $\hat{\mu}_i$ and $\hat{\tau}^2$ in the ME Model

- $\hat{\tau}^2$ estimates the **residual** amount of heterogeneity among the true outcomes
- $\hat{\mu}_i$ is the estimated **average** outcome for a particular set of moderator values
- residual heterogeneity may be random or systematic but $\hat{\tau}^2$ does not differentiate between sources

119

Meta-Analytic Questions

- what is the overall/average effectiveness?
- is the effectiveness the same for all studies?
- if the effectiveness is not the same, then:
 - how much does it vary?
 - is that variability a result of systematic differences between the characteristics of the studies?

120

Mixed-Effects Meta-Regression Model

- basic syntax:

name of variable to use as moderator
↑
`res <- rma(yi, vi, mods = ~ var, method="DL", data=dat)`

- single moderator: `mods = ~ var`
- multiple moderators: `mods = ~ var1 + var2 + ...`
- moderators can be categorical (→ dummy coded)
- treat numerical variables categorically: `factor(var)`
- can also examine interactions, polynomial terms, etc.

121

```
> # fit mixed-effects meta-regression model
> res <- rma(yi, vi, mods = ~ ablat, method="DL", data=dat)
> res
```

Mixed-Effects Model (k = 13; tau² estimator: DL)

tau² (estimated amount of residual heterogeneity): 0.0633
tau (square root of estimated tau² value): 0.2516
I² (residual heterogeneity / unaccounted variability): 64.21%
H² (unaccounted variability / sampling variability): 2.79
R² (amount of heterogeneity accounted for): 79.50%

Test for Residual Heterogeneity:
QE(df = 11) = 30.7331, p-val = 0.0012

Test of Moderators (coefficient 2):
QM(df = 1) = 18.8452, p-val < .0001

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	0.2595	0.2323	1.1172	0.2639	-0.1958	0.7149
ablat	-0.0292	0.0067	-4.3411	<.0001	-0.0424	-0.0160

122

Pseudo R² Value

estimates the proportion of heterogeneity in the true outcomes that is accounted for by the moderator(s) included in the model

$$R^2 = \frac{\hat{\tau}_{RE}^2 - \hat{\tau}_{ME}^2}{\hat{\tau}_{RE}^2}$$

123

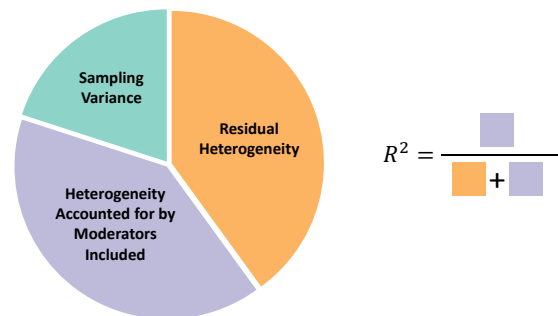
Example: BCG Vaccine

$$\hat{\tau}_{RE}^2 = 0.3088 \quad \hat{\tau}_{ME}^2 = 0.0633$$

$$R^2 = \frac{0.3088 - 0.0633}{0.3088} = .80$$

124

Decomposing Heterogeneity



125

Predicted Values with CIs

```
res <- rma(yi, vi, mods = ~ var,
           method="DL", data=dat)
predict(res)
predict(res, newmods=<value>)
```

- by default the function provides the predicted/fitted values for all of the studies included in the analysis
- use **newmods** to specify the value of the moderator
- use **transf** as before to transform values

126

```
> # fit mixed-effects meta-regression model
> res <- rma(yi, vi, mods = ~ ablat, method="DL", data=dat)

> # predicted average log risk ratio at 44 degrees
> predict(res, newmods=44)

    pred    se  ci.lb  ci.ub  pi.lb  pi.ub
-1.0265 0.1323 -1.2859 -0.7672 -1.5837 -0.4694

> # predicted average risk ratio at 44 degrees
> predict(res, newmods=44, digits=2, transf=exp)

    pred ci.lb ci.ub pi.lb pi.ub
    0.36  0.28  0.46  0.21  0.63
```

127

```
> # mixed-effects meta-regression model with 2 moderators
> res <- rma(yi, vi, mods = ~ ablat + year, method="DL", data=dat)
> res
```

Mixed-Effects Model (k = 13; tau² estimator: DL)

tau² (estimated amount of residual heterogeneity): 0.0790
tau (square root of estimated tau² value): 0.2811
I² (residual heterogeneity / unaccounted variability): 64.70%
H² (unaccounted variability / sampling variability): 2.83
R² (amount of heterogeneity accounted for): 74.40%

Test for Residual Heterogeneity:
QE(df = 10) = 28.3251, p-val = 0.0016

Test of Moderators (coefficients 2:3):
QM(df = 2) = 15.9314, p-val = 0.0003

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-1.2798	25.7550	-0.0497	0.9604	-51.7586	49.1990
ablat	-0.0288	0.0090	-3.2035	0.0014	-0.0464	-0.0112
year	0.0008	0.0130	0.0594	0.9526	-0.0247	0.0262

128

Omnibus Test of Moderators

$$H_0: \beta_1 = \dots = \beta_p = 0$$

$$Q_M = \mathbf{b}_{[2]}' (\text{Var}[\mathbf{b}]_{[2]})^{-1} \mathbf{b}_{[2]}$$

if the moderators included in the model are not at all related to the outcomes, then Q_M follows a chi-square distribution with p degrees of freedom

129

Example: BCG Vaccine

$$H_0: \beta_1 = \beta_2 = 0$$

$$\mathbf{b}_{[2]} = \begin{bmatrix} -0.0288 \\ 0.0008 \end{bmatrix} \quad \text{Var}[\mathbf{b}]_{[2]} = \begin{bmatrix} 0.000081 & 0.000068 \\ 0.000068 & 0.000169 \end{bmatrix}$$

$$Q_M = [-0.0288 \quad 0.0008] \begin{bmatrix} 0.000081 & 0.000068 \\ 0.000068 & 0.000169 \end{bmatrix}^{-1} \begin{bmatrix} -0.0288 \\ 0.0008 \end{bmatrix} = 15.93$$

critical value (for $\alpha = .05$ and $df = 2$): 5.99
 p-value for $Q_M = 15.93$: .0003
 reject $H_0: \beta_1 = \beta_2 = 0$
 conclusion: the outcomes are associated with
 absolute latitude, year, or both

130

`newmods=c()` with comma-separated
 values for the moderator variables

```
> predict(res, newmods=c(10, 1970), digits=2, transf=exp)

    pred ci.lb ci.ub pi.lb pi.ub
    0.95  0.63  1.44  0.48  1.90

> predict(res, newmods=c(30, 1970), digits=2, transf=exp)

    pred ci.lb ci.ub pi.lb pi.ub
    0.54  0.43  0.66  0.30  0.97

> predict(res, newmods=c(50, 1970), digits=2, transf=exp)

    pred ci.lb ci.ub pi.lb pi.ub
    0.30  0.20  0.45  0.15  0.60
```

131

Subgrouping

- often interested in subgroups
- two options:
 - fit RE model within subgroups
 - fit ME model with categorical moderator
- difference: whether we want to allow for different τ^2 values within subgroups or not

132

```
> # create dummy variable (1 for random, 0 otherwise)
> dat$random <- ifelse(dat$alloc=="random", 1, 0)
>
> res <- rma(yi, vi, method="DL", subset=c(random==0), data=dat)
> res
```

Random-Effects Model (k = 6; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.1357
 tau (square root of estimated tau^2 value): 0.3684
 I^2 (total heterogeneity / total variability): 82.33%
 H^2 (total variability / sampling variability): 5.66

Test for Heterogeneity:
 Q(df = 5) = 28.2980, p-val < .0001

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
-0.4947	0.1819	-2.7194	0.0065	-0.8512	-0.1381

133

```
> res <- rma(yi, vi, method="DL", subset=c(random==1), data=dat)
> res
```

Random-Effects Model (k = 7; tau^2 estimator: DL)

tau^2 (estimated amount of total heterogeneity): 0.7631
 tau (square root of estimated tau^2 value): 0.8735
 I^2 (total heterogeneity / total variability): 94.56%
 H^2 (total variability / sampling variability): 18.37

Test for Heterogeneity:
 Q(df = 6) = 110.2133, p-val < .0001

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
-1.0042	0.3621	-2.7731	0.0056	-1.7139	-0.2944

134

```
> # mixed-effects meta-regression model with dummy variable
> res <- rma(yi, vi, mods = ~ random, method="DL", data=dat)
> res
```

Mixed-Effects Model (k = 13; tau^2 estimator: DL)

tau^2 (estimated amount of residual heterogeneity): 0.4137
 tau (square root of estimated tau^2 value): 0.6432
 I^2 (residual heterogeneity / unaccounted variability): 92.06%
 H^2 (unaccounted variability / sampling variability): 12.59
 R^2 (amount of heterogeneity accounted for): 0.00%

Test for Residual Heterogeneity:
 QE(df = 11) = 138.5113, p-val < .0001

Test of Moderators (coefficient 2):
 QM(df = 1) = 1.6422, p-val = 0.2000

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.4578	0.2881	-1.5889	0.1121	-1.0224	0.1069
random	-0.5164	0.4030	-1.2815	0.2000	-1.3062	0.2734

135

```
> # predicted average log risk ratio for random=0
> predict(res, newmods=0)
```

	pred	se	ci.lb	ci.ub	pi.lb	pi.ub
	-0.4578	0.2881	-1.0224	0.1069	-1.8391	0.9236

```
> # predicted average log risk ratio for random=1
> predict(res, newmods=1)
```

	pred	se	ci.lb	ci.ub	pi.lb	pi.ub
	-0.9741	0.2817	-1.5263	-0.4220	-2.3504	0.4021

```
> # predicted average risk ratio for random=0
> predict(res, newmods=0, digits=2, transf=exp)
```

	pred	ci.lb	ci.ub	pi.lb	pi.ub
	0.63	0.36	1.11	0.16	2.52

```
> # predicted average risk ratio for random=1
> predict(res, newmods=1, digits=2, transf=exp)
```

	pred	ci.lb	ci.ub	pi.lb	pi.ub
	0.38	0.22	0.66	0.10	1.50

136

```
> # mixed-effects meta-regression model with a categorical moderator
> res <- rma(yi, vi, mods = ~ alloc, method="DL", data=dat)
> res
```

Mixed-Effects Model (k = 13; tau² estimator: DL)

tau² (estimated amount of residual heterogeneity): 0.5596
tau (square root of estimated tau² value): 0.7480
I² (residual heterogeneity / unaccounted variability): 92.45%
H² (unaccounted variability / sampling variability): 13.24
R² (amount of heterogeneity accounted for): 0.00%

Test for Residual Heterogeneity:

QE(df = 10) = 132.3676, p-val < .0001

Test of Moderators (coefficients 2:3):

QM(df = 2) = 1.4349, p-val = 0.4880

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.5125	0.5421	-0.9454	0.3444	-1.5751	0.5500
allocrandom	-0.4780	0.6286	-0.7605	0.4470	-1.7099	0.7540
allocsystematic	0.1042	0.6822	0.1528	0.8786	-1.2329	1.4414

137

```
> # predicted average risk ratio for 'alternate'
> predict(res, newmods=c(0,0), digits=2, transf=exp)
```

	pred	ci.lb	ci.ub	pi.lb	pi.ub
	0.60	0.21	1.73	0.10	3.66

```
> # predicted average risk ratio for 'random'
> predict(res, newmods=c(1,0), digits=2, transf=exp)
```

	pred	ci.lb	ci.ub	pi.lb	pi.ub
	0.37	0.20	0.69	0.08	1.83

```
> # predicted average risk ratio for 'systematic'
> predict(res, newmods=c(0,1), digits=2, transf=exp)
```

	pred	ci.lb	ci.ub	pi.lb	pi.ub
	0.66	0.30	1.50	0.12	3.55

138

Sample Size Issues

- a FAQ: how many studies do I need to conduct a meta-regression analysis?
- some say: 5 or 10 studies per moderator [1]
- too simplistic; better would be a proper power calculation (Hedges & Pigott, 2004), but this is difficult in practice
- could also look into the metapower package:
<https://cran.r-project.org/package=metapower>

[1] <https://training.cochrane.org/handbook/current/chapter-10#section-10-11-5-1>

139

Literature

- Hedges, L. V., & Pigott, T. D. (2004). The power of statistical tests for moderators in meta-analysis. *Psychological Methods*, 9(4), 426-445.
- Raudenbush, S. W. (2009). Analyzing effect sizes: Random-effects models. In H. Cooper, L. V. Hedges, & J. C. Valentine (Eds.), *The handbook of research synthesis and meta-analysis* (2nd ed., pp. 295-315). New York: Russell Sage Foundation.
- Thompson, S. G., & Higgins, J. P. T. (2002). How should meta-regression analyses be undertaken and interpreted? *Statistics in Medicine*, 21(11), 1559-1573.
- Viechtbauer, W. (2007). Accounting for heterogeneity via random-effects models and moderator analyses in meta-analysis. *Zeitschrift für Psychologie / Journal of Psychology*, 215(2), 104-121.

140

Exercises

- back to: **exercises.r**
- conduct the suggested meta-regression analyses (or others you are interested in) for the Bangert-Drowns et al. (2004) and Credé et al. (2010) meta-analyses and think about the interpretation of the results

141

Example: Magnesium Treatment

- meta-analysis on the effectiveness of intravenous magnesium treatment in acute myocardial infarction for reducing the risk of mortality and arrhythmias



142

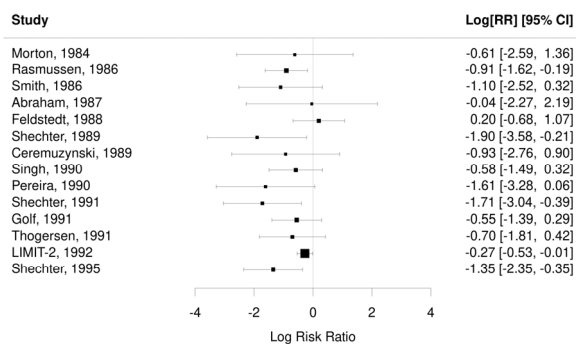
Example: Magnesium Treatment

	Heart Attack Fatal?		
	Yes	No	
Magnesium	9	126	135
Control	23	112	135
	32	238	270

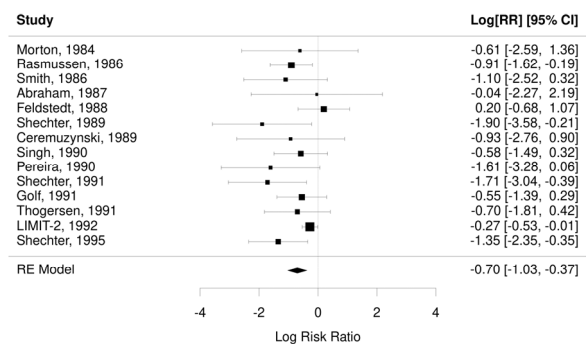
- $p_T = 9 / 135 = .067$
- $p_C = 23 / 135 = .170$
- risk ratio = $.067 / .170 = .39$

143

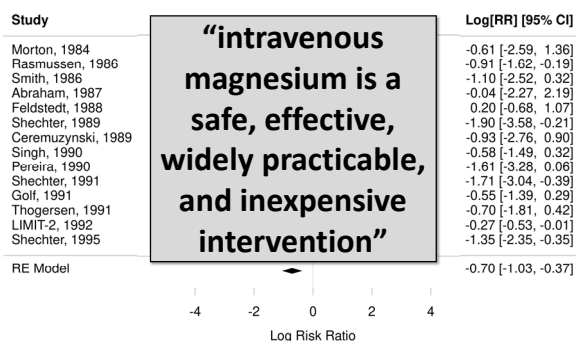
Example: Magnesium Treatment



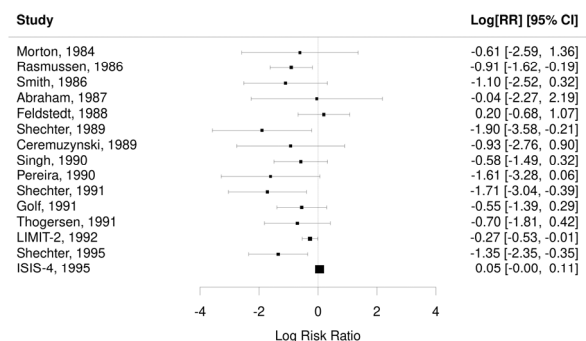
Example: Magnesium Treatment

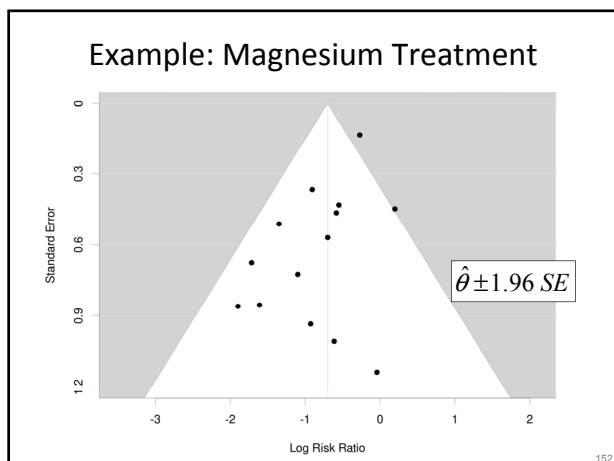
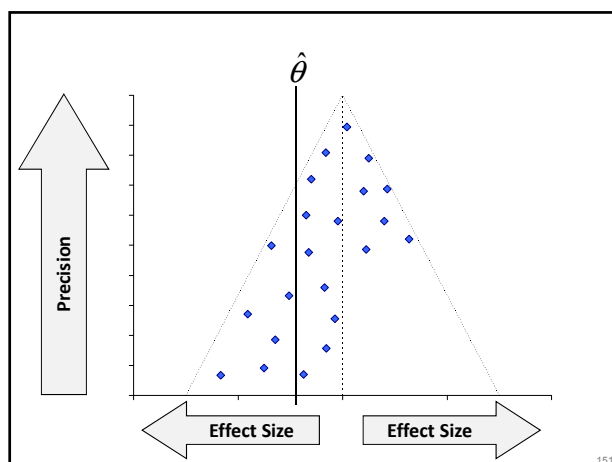
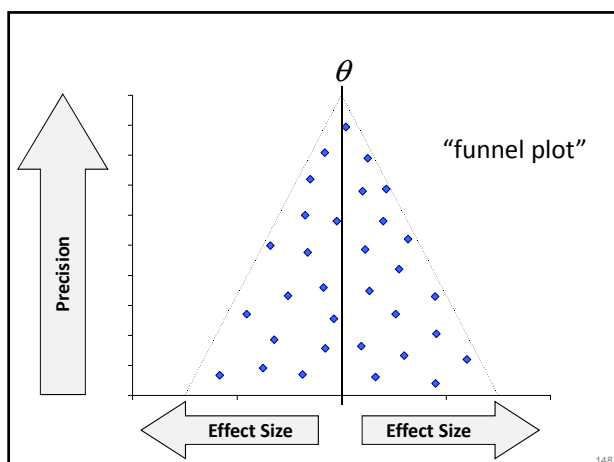


Example: Magnesium Treatment



Example: Magnesium Treatment





Software: R

```
> # copy magnesium treatment dataset to 'dat'
> dat <- dat.egger2001
>
> # remove studies 8 and 16
> dat <- dat[-c(8,16),]
>
> # compute the log risk ratios
> dat <- escalc(measure="RR", ai=ai, n1i=n1i,
               ci=ci, n2i=n2i, data=dat, to="all")
> dat
>
> # fit random-effects model
> res <- rma(yi, vi, data=dat)
> res
>
> # estimated average risk ratio (with 95% CI)
> predict(res, transf=exp, digits=2)
>
> # funnel plot
> funnel(res, ylim=c(0,1.2))
```

apply the +1/2 adjustment to all studies (not just the ones where at least one cell is equal to 0)

153

Software: R

```
Random-Effects Model (k = 14; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.1087
tau (square root of estimated tau^2 value):      0.3296
I^2 (total heterogeneity / total variability):    33.61%
H^2 (total variability / sampling variability):    1.51

Test for Heterogeneity:
Q(df = 13) = 18.1711, p-val = 0.1511

Model Results:

  estimate    se    zval    pval   ci.lb   ci.ub
-0.7011  0.1686  -4.1572 <.0001  -1.0316 -0.3706

  pred ci.lb ci.ub pi.lb pi.ub
0.50  0.36  0.69  0.24  1.02
```

154

Potential Sources of Bias

- statistically significant findings are:
 - more likely to be published
 - more likely to be published quicker
 - more likely to be cited in English journals
 - more likely to be published more than once
 - more likely to be cited by others
 - ...

155

... and this is where we put the non-significant results.



156

Dealing with Publication Bias

- getting a sense of the data
 - funnel plot (but see Terrin et al., 2005)
- assessing robustness to publication bias
 - failsafe-N (“file drawer analysis”)
- checking for evidence of publication bias
 - rank correlation test (Begg & Mazumdar)
 - regression test (Egger)
 - test of excess significance
- adjusting for publication bias
 - trim and fill method
 - selection models
 - PET and PEESE

157

Robustness to Publication Bias

- if a number of (unpublished) studies with null effects were found, they could reverse the conclusions of a meta-analysis
- how many such studies would it take?
- if this number is large, results are robust
- idea due to Rosenthal (1979), later extended by Orwin (1983) and Rosenberg (2005)
- sometimes called a ‘failsafe N’ calculation

158

Stouffer Method

test of $H_0: \theta_i = 0$
in the i th study

$$z_i = \frac{y_i}{\sqrt{v_i}}$$

test of $H_0: \theta_i = 0$
for all k studies

$$z = \frac{\sum z_i}{\sqrt{k}}$$

159

Failsafe-N (“file drawer analysis”)

$$N > k \left(\frac{z}{1.645} \right)^2 - k$$

test of $H_0: \theta_i = 0$
for all k studies

Critical z-Value
(one-tailed)

Number of Studies in
the Meta-Analysis

160

Example: Magnesium Treatment

$$z = \frac{-20.271}{\sqrt{14}} = -5.418$$

$$N > 14 \left(\frac{-5.418}{1.645} \right)^2 - 14 \approx 138$$

138 studies with null results would be needed to reverse the claim that magnesium treatment significantly reduces the risk of heart attack mortality (in at least one study)

161

Software: R

```
fns(yi, vi, data=dat)
```

yi = name of variable for the observed outcomes
vi = name of the variable for the sampling variances
data = name of data frame with the variables

```
> fns(yi, vi, data=dat)
```

Fail-safe N Calculation Using the Rosenthal Approach

Observed Significance Level: <.0001
Target Significance Level: 0.05

Fail-safe N: 138

162

Robustness to Publication Bias

- Rosenthal method: 138 studies
- Orwin method: 14 studies
- Rosenberg method: 69 studies
- discrepancies due differences in underlying methods (and their purpose)
- are these numbers 'large'?
- method not used much anymore in practice

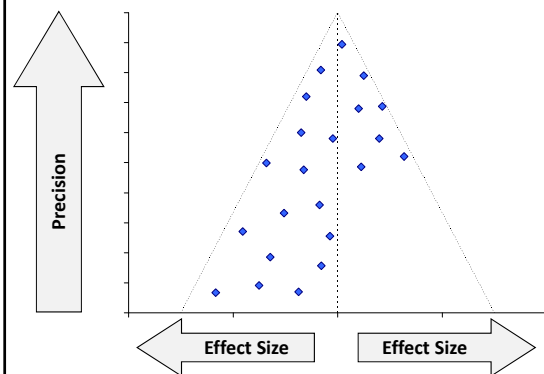
163

Dealing with Publication Bias

- getting a sense of the data
 - funnel plot
- assessing robustness to publication bias
 - failsafe-N ("file drawer analysis")
- checking for evidence of publication bias
 - rank correlation test (Begg & Mazumdar)
 - regression test (Egger)
 - test of excess significance
- adjusting for publication bias
 - trim and fill method
 - selection models
 - PET and PEESE

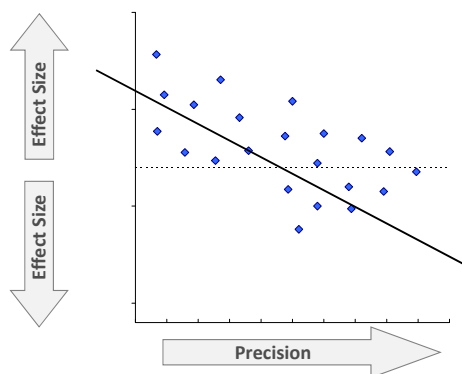
164

Regression Test



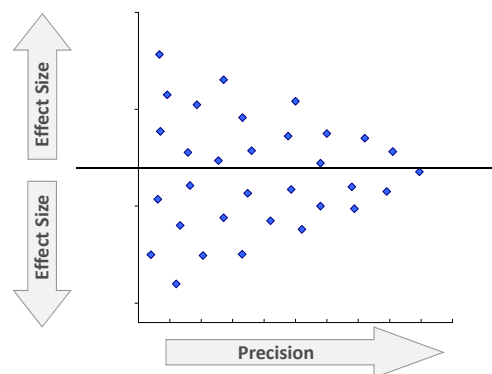
165

Regression Test



166

Regression Test



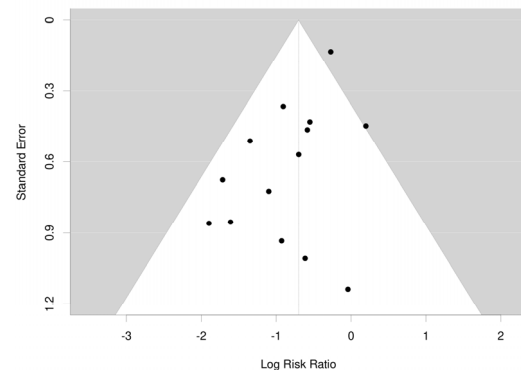
167

Regression Test

- use $se_i = \sqrt{v_i}$ as a moderator in a (mixed-effects) meta-regression model and test whether the slope of this “moderator” is significantly different from 0
- there are various versions of the regression test (all based on the same principle)
- sometimes called “Egger’s test” (Egger et al., 1997)
- it is **test for funnel plot asymmetry**, not publication bias per se; there are many possible reasons for funnel plot asymmetry (Sterne et al., 2011; Coburn & Vevea, 2015)

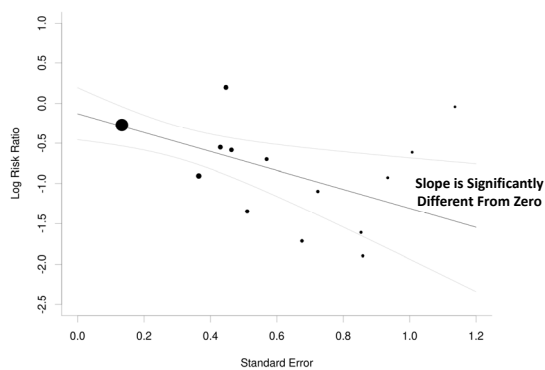
168

Example: Magnesium Treatment



169

Example: Magnesium Treatment



170

Example: Magnesium Treatment

```
dat$sei <- sqrt(dat$vi)
res <- rma(yi, vi, mods = ~ sei, data=dat)
res
```

```
> dat$sei <- sqrt(dat$vi)
> res <- rma(yi, vi, mods = ~ sei, data=dat)
> res
```

Mixed-Effects Model (k = 14; tau² estimator: REML)

tau² (estimated amount of residual heterogeneity): 0
tau (square root of estimated tau² value): 0

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.1300	0.1662	-0.7823	0.4340	-0.4557	0.1957
sei	-1.1802	0.4342	-2.7184	0.0066	-2.0312	-0.3293

171

Example: Magnesium Treatment

```
res <- rma(yi, vi, data=dat)
regtest(res)
```

```
> res <- rma(yi, vi, data=dat)
> regtest(res)
```

Regression Test for Funnel Plot Asymmetry

model: mixed-effects meta-regression model
predictor: standard error

Test for Funnel Plot Asymmetry: z = -2.7184, p = 0.0066
Limit Estimate (as sei → 0): b = -0.1300 (CI: -0.4557, 0.1957)

172

Test of Excess Significance

- recall: can test $H_0: \theta_i = 0$ with $z_i = y_i/\sqrt{v_i}$
- O : observed number of significant tests
- compute the power of each test, $1 - \beta_i$, given some (estimated) value of θ
- $E = \sum(1 - \beta_i)$: expected number of significant tests
- test if O is significantly larger than E (exact test, Pearson test, or binomial test)
- Ioannidis & Trikalinos (2007)

173

Example: Magnesium Treatment

- 5 significant findings in 14 studies
- power ranges from .07 to .95 (median = .12)
- expected number of significant findings: 2.71
- test of excess significance: $p = 0.081$

174

Example: Magnesium Treatment

```
tes(yi, vi, data=dat)
```

```
> tes(yi, vi, data=dat)
```

Test of Excess Significance

Observed Number of Significant Findings: 5 (out of 14)
 Expected Number of Significant Findings: 2.7140
 Observed Number / Expected Number: 1.8423

Estimated Power of Tests (based on $\theta = -0.4861$)

min	q1	median	q3	max
0.0712	0.0875	0.1239	0.1902	0.9542

Test of Excess Significance: $p = 0.0814$ (exact test)

Limit Estimate (θ_{lim}): -0.5111 (where $p = 0.1$)

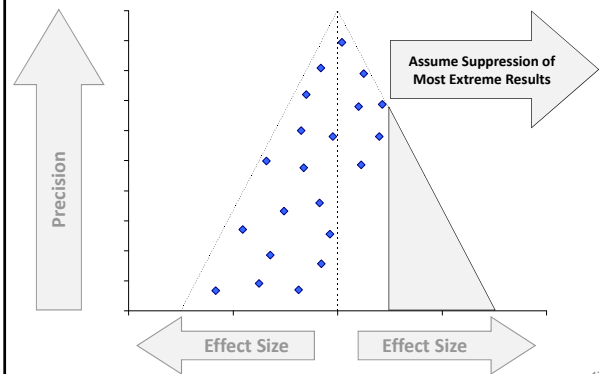
175

Dealing with Publication Bias

- getting a sense of the data
 - funnel plot
- assessing robustness to publication bias
 - failsafe-N ("file drawer analysis")
- checking for evidence of publication bias
 - rank correlation test (Begg & Mazumdar)
 - regression test (Egger)
 - test of excess significance
- adjusting for publication bias
 - trim and fill method
 - selection models
 - PET and PEESE

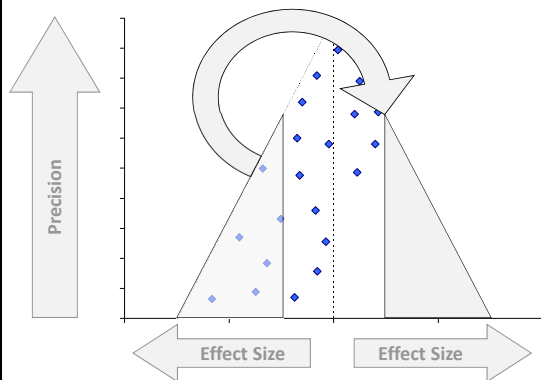
176

Trim and Fill Method



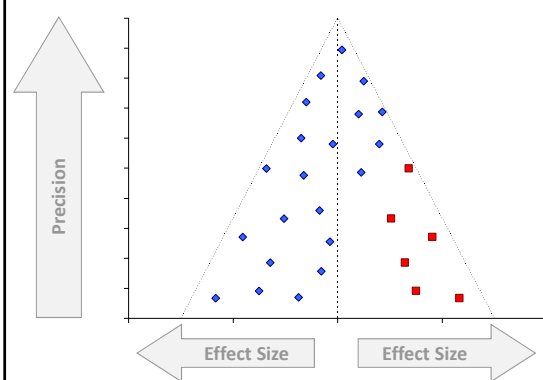
178

Trim and Fill Method



180

Trim and Fill Method



181

Example: Magnesium Treatment

```
res <- rma(yi, vi, data=dat)
taf <- trimfill(res)
taf
funnel(taf)
```

can specify the side of the funnel plot where suppression is suspected via the 'side' argument (side="right" or "left")

182

Example: Magnesium Treatment

```
> res <- rma(yi, vi, data=dat)
> taf <- trimfill(res)
> taf
```

Estimated number of missing studies on the right side: 5

Random-Effects Model (k = 19; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.2434
tau (square root of estimated tau^2 value): 0.4933
I^2 (total heterogeneity / total variability): 50.18%
H^2 (total variability / sampling variability): 2.01

Test for Heterogeneity:

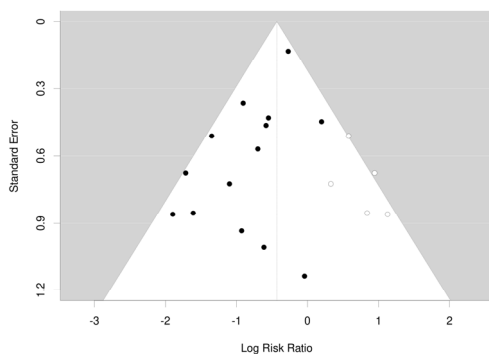
Q(df = 18) = 32.6731, p-val = 0.0183

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
-0.4318	0.1799	-2.4002	0.0164	-0.7844	-0.0792

183

Example: Magnesium Treatment



184

Example: Magnesium Treatment

- meta-analysis based on the 14 studies:
 $\hat{\mu} = -0.70$ (95% CI: -1.03 to -0.37)
- trim and fill method (14 + 5 studies):
 $\hat{\mu} = -0.43$ (95% CI: -0.78 to -0.08)

185

Selection Models

- assume an inverse relationship between the p-value of the test $H_0: \theta_i = 0$ and the probability that study is included in MA
- this induces bias in meta-analytic findings
- with enough studies, can estimate this relationship and remove the bias from the meta-analytic findings
- difficult in practice (models are complicated and k must be quite large, especially when using RE models)

186

Example: Magnesium Treatment

```
> res <- rma(yi, vi, method="EE", data=dat)
> sav <- selmodel(res, type="logistic", alternative="less")
> sav
```

Equal-Effects Model (k = 14)

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
-0.3184	0.1384	-2.3001	0.0214	-0.5898	-0.0471 *

Test for Selection Model Parameters:

LRT(df = 1) = 5.7300, p-val = 0.0167

Selection Model Results:

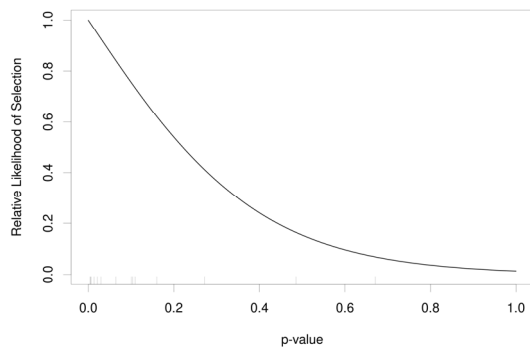
estimate	se	zval	pval	ci.lb	ci.ub
4.9703	2.1251	2.3388	0.0193	0.8051	9.1355 *

> plot(sav)

either "less", "greater", or "two.sided" depending on the expected direction of the selection

187

Example: Magnesium Treatment



188

Example: Magnesium Treatment

- meta-analysis based on the 14 studies:
 $\hat{\mu} = -0.70$ (95% CI: -1.03 to -0.37)
- selection model (based on EE model):
 $\hat{\theta} = -0.32$ (95% CI: -0.59 to -0.05)
- test of selection model: $p = .02$
- (RE selection model gives similar results with $\hat{\tau}^2 \approx 0$, but can't get the SE and CI of μ)
- see code for other selection models

189

PET and PEESE

- PET (precision-effect test) and PEESE (precision-effect estimate with SE) are methods for estimating/testing the 'true' effect in the presence of publication bias (Stanley & Doucouliagos, 2014)
- in essence: the intercept of the 'regression test' model with either se_i or v_i as moderator
- PET-PEESE: if PET estimate is not significant (at $\alpha = .10$), use it; otherwise use PEESE

190

Software: R

```
> rma(yi, vi, mods = ~ sei, data=dat)
```

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.1300	0.1662	-0.7823	0.4340	-0.4557	0.1957
sei	-1.1802	0.4342	-2.7184	0.0066	-2.0312	-0.3293

```
> rma(yi, vi, mods = ~ vi, data=dat)
```

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
intrcpt	-0.3918	0.1704	-2.2993	0.0215	-0.7259	-0.0578
vi	-0.9449	0.5035	-1.8766	0.0606	-1.9318	0.0420

191

Software: R

```
> res <- rma(yi, vi, data=dat)
> regtest(res)
```

Regression Test for Funnel Plot Asymmetry

Model: mixed-effects meta-regression model
 Predictor: standard error

Test for Funnel Plot Asymmetry: $z = -2.7184$, $p = 0.0066$
 Limit Estimate (as $sei \rightarrow 0$): $b = -0.1300$ (CI: -0.4557 , 0.1957)

```
> regtest(res, predictor="vi")
```

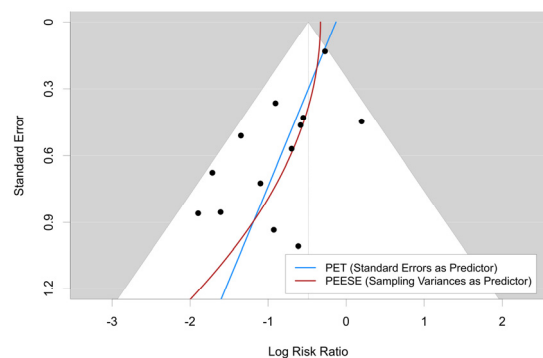
Regression Test for Funnel Plot Asymmetry

Model: mixed-effects meta-regression model
 Predictor: sampling variance

Test for Funnel Plot Asymmetry: $z = -1.8766$, $p = 0.0606$
 Limit Estimate (as $vi \rightarrow 0$): $b = -0.3918$ (CI: -0.7259 , -0.0578)

192

PET and PEESE



193

Example: Magnesium Treatment

- meta-analysis based on the 14 studies:

$$\hat{\mu} = -0.70 \text{ (95\% CI: } -1.03 \text{ to } -0.37)$$

- PET:

$$\hat{\mu} = -0.13 \text{ (95\% CI: } -0.46 \text{ to } 0.20)$$

- PEESE:

$$\hat{\mu} = -0.39 \text{ (95\% CI: } -0.73 \text{ to } -0.06)$$

194

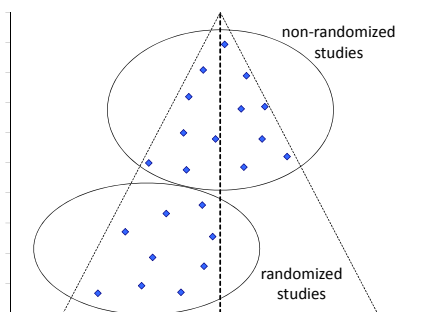
Comparison of Methods

Method/Model	Estimate	Lower	Upper
RE Model	-0.7011	-1.0316	-0.3706
Trim and Fill	-0.4318	-0.7844	-0.0792
Selection Model	-0.3184	-0.5898	-0.0471
PET	-0.1300	-0.4557	0.1957
PEESE	-0.3918	-0.7259	-0.0578
p-uniform	-0.3468	-1.2306	0.8068

- generally quite similar estimates (except for PET) and CI of p-uniform is very wide

195

Asymmetry Due to Moderators



196

Funnel Plot Variations

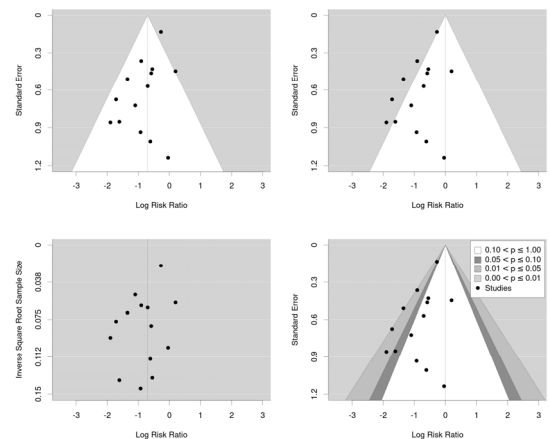
- use some other measure of precision on the y-axis besides the SE (but SE recommended)
- exception: when y_i and SE_i are known to be correlated in the absence of publication bias
- then may want to use just the sample size (or some function thereof) on the y-axis
- center the funnel plot at 0 (instead of $\hat{\theta}$ or $\hat{\mu}$)
- contour-enhanced funnel plots

197

Software: R

```
> # compute the total sample sizes of the studies
> dat$totali <- dat$ni + dat$ni2
>
> # supply this information to rma() via 'ni' argument
> res <- rma(yi, vi, ni=totali, data=dat)
>
> # four examples of other funnel plot types
> par(mfrow=c(2,2))
> funnel(res, xlim=c(-3.5,3), ylim=c(0,1.2))
> funnel(res, xlim=c(-3.5,3), ylim=c(0,1.2), refline=0)
> funnel(res, xlim=c(-3.5,3), ylim=c(0,.15), yaxis="sqrt(ninv)")
> funnel(res, xlim=c(-3.5,3), ylim=c(0,1.2), refline=0,
  level=c(90, 95, 99),
  shade=c("white", "gray55", "gray75"),
  legend=TRUE)
```

198



199

Publication Bias

- affects all review methods (not a problem specific to meta-analysis!)
- in fact, due to meta-analysis:
 - increased awareness of publication bias
 - development of systematic methods to detect and address publication bias
 - continued emphasis on the importance of trial registries and registered reports (to eliminate publication bias)

200

Gold Standard

- meta-analysis of registered reports
- same as a 'prospective meta-analysis' (Simes, 1995; Berlin & Colditz, 1999)
- if not (yet) possible, acknowledge/examine the multitude of possible results (multiverse analysis; Voracek et al., 2019)

201

Literature

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- Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal*, 315(7109), 629-634.
- Ioannidis, J. P. A. & Trikalinos, T. A. (2007). An exploratory test for an excess of significant findings. *Clinical Trials*, 4(3), 245-253.
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- Rothstein, H. R., Sutton, A. J., & Borenstein, M. (Eds.). (2005). *Publication bias in meta-analysis: Prevention, assessment, and adjustments*. Chichester, England: Wiley. (an entire book about publication bias!)
- Stanley, T. D., & Doucouliagos, H. (2014). Meta-regression approximations to reduce publication selection bias. *Research Synthesis Methods*, 5(1), 60-78.

202

Exercises

- back to: **exercises.r**
- meta-analysis of studies examining the risk of lung cancer due to environmental tobacco smoke (ETS) exposure
- conduct a meta-analysis of the studies and try out the various methods discussed in this lecture (has there been some publication bias in favor of studies showing that ETS is associated with an increased lung cancer risk?)
- note: meta-analysis is based on (log) odds ratios; in this example, you can think of these values as (log) risk ratios (but that's not true in general!)

203

Standard Random-Effects Model

$$y_i = \mu + u_i + e_i$$

average true outcome
random effect that makes the true outcome for a particular study larger/smaller by some amount (heterogeneity between studies)
sampling error

$$e_i \sim N(0, v_i) \quad u_i \sim N(0, \tau^2)$$

204

```
> # copy data into 'dat'
> dat <- dat.konstantopoulos2011
>
> # show data
> dat
```

	district	school	study	year	yi	vi
1	11	1	1	1976	-0.18	0.118
2	11	2	2	1976	-0.22	0.118
3	11	3	3	1976	0.23	0.144
4	11	4	4	1976	-0.30	0.144
5	12	1	5	1989	0.13	0.014
6	12	2	6	1989	-0.26	0.014
7	12	3	7	1989	0.19	0.015
8	12	4	8	1989	0.32	0.024
9	18	1	9	1994	0.45	0.023
10	18	2	10	1994	0.38	0.043
11	18	3	11	1994	0.29	0.012
12
56	644	4	56	1994	-0.05	0.067

standardized mean differences and sampling variances

206


```
> # fit standard random-effects model
> res <- rma(yi, vi, data = dat)
> res
```

Random-Effects Model (k = 56; tau² estimator: REML)

tau² (estimated amount of total heterogeneity): 0.0884
 tau (square root of estimated tau² value): 0.2974
 I² (total heterogeneity / total variability): 94.70%
 H² (total variability / sampling variability): 18.89

Test for Heterogeneity:
 Q(df = 55) = 578.8640, p-val < .0001

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.1279	0.0439	2.9161	0.0035	0.0419	0.2139 **

207

The rma.mv() Function

- more flexible model fitting function, but must specify random effects manually
- for now, let's replicate the previous results

```
res <- rma.mv(yi, vi, random = ~ 1 | study,
              method = "REML", data = dat)
```

- **random = ~ 1 | study** adds a random effect for each level of the study variable
- **method = "REML"** is default (other option: **ML**)

208

```
> # fit standard random-effects model with rma.mv()
> res <- rma.mv(yi, vi, random = ~ 1 | study, data = dat)
> res
```

Multivariate Meta-Analysis Model (k = 56; method: REML)

Variance Components:

	estim	sqrt	nlvis	fixed	factor
sigma ²	0.0884	0.2974	56	no	study

Test for Heterogeneity:
 Q(df = 55) = 578.8640, p-val < .0001

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.1279	0.0439	2.9161	0.0035	0.0419	0.2139 **

209

Independence Assumption

- the methods presented assume that all of the observed outcomes are independent
- this assumption may not hold, for example:
 - when there are multiple observed outcomes from the same study, article, author, or lab
 - when we calculate observed outcomes for more than one dependent variable or multiple measurement occasions in the same group
 - when there are two or more treatment groups in a single study and we contrast each treatment group against a common control group

210

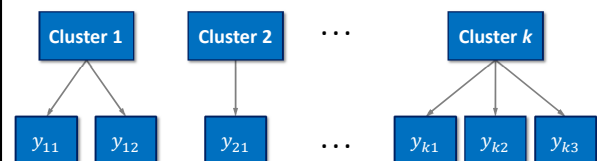
Data Reduction

- traditional approaches to handle dependencies:
 - select one observed outcome from each study or article (should be done in some reproducible way!)
 - take average of dependent outcomes
 - conduct separate analyses in subsets that only contain independent estimates
- easy to analyze, but wastes information

211

Multilevel Meta-Analytic Data

- multilevel structures can arise when we have multiple estimates for some higher clustering variable (paper, lab, research group, ...)



212

between 3 and 11
schools within 11 districts
(56 studies in total)

```
> # show data
> dat
```

	district	school	study	year	yi	vi
1	11	1	1	1976	-0.18	0.118
2	11	2	2	1976	-0.22	0.118
3	11	3	3	1976	0.23	0.144
4	11	4	4	1976	-0.30	0.144
5	12	1	5	1989	0.13	0.014
6	12	2	6	1989	-0.26	0.014
7	12	3	7	1989	0.19	0.015
8	12	4	8	1989	0.32	0.024
9	18	1	9	1994	0.45	0.023
10	18	2	10	1994	0.38	0.043
11	18	3	11	1994	0.29	0.012
12
56	644	4	56	1994	-0.05	0.067

213

Multilevel Random-Effects Model

$$y_{ij} = \mu + w_i + u_{ij} + e_{ij}$$

average true outcome

random effect that makes the true outcomes for a particular cluster larger/smaller by some amount (heterogeneity between clusters)

random effect that makes one of the true outcomes within a particular cluster larger/smaller by some amount (heterogeneity within clusters)

sampling error

$w_i \sim N(0, \sigma_B^2)$ $u_{ij} \sim N(0, \sigma_W^2)$ $e_{ij} \sim N(0, v_{ij})$

214

The rma.mv() Function

- `rma.mv()` allows for the addition of multiple nested random effects
- `random = ~ 1 | var1/var2` adds a random effect for each level of `var1` and a random effect for each level of `var2` within each level of `var1`

216

```
> # fit multilevel random-effects model
> res <- rma.mv(yi, vi, random = ~ 1 | district/school,
data = dat)
> res
```

Multivariate Meta-Analysis Model (k = 56; method: REML)

Variance Components:

	estim	sqrt	nlvls	fixed	factor
sigma^2.1	0.0651	0.2551	11	no	district
sigma^2.2	0.0327	0.1809	56	no	district/school

Test for Heterogeneity:
Q(df = 55) = 578.8640, p-val < .0001

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.1847	0.0846	2.1845	0.0289	0.0190	0.3504 *

217

Correlation due to Multilevel Structure

- the multilevel structure implies that the true outcomes within a cluster are correlated:

$$\rho = \frac{\sigma_B^2}{\sigma_B^2 + \sigma_W^2}$$

- in example:

$$\hat{\rho} = \frac{0.0651}{0.0651 + 0.0327} = .67$$

- also note: $0.0651 + 0.0327 = 0.0978$

218

```
> # variance components
> res$sigma2
[1] 0.0651 0.0327

> # within cluster correlation of true outcomes
> res$sigma2[1] / sum(res$sigma2)
[1] 0.6653

> # total heterogeneity
> sum(res$sigma2)
[1] 0.0978
```

219

A Common Error

- random effect at the level of the clustering variable **does not replace** random effect at the observation/estimate level!
- we **add** the clustering level random effect to the standard random/mixed-effects model
- (otherwise you assume that there is no heterogeneity within clusters = assuming that the within-cluster correlation is 1)

220

Multivariate Parameterization

$$y_{ij} = \mu + u_{ij} + e_{ij}$$

average true outcome
correlated random effects for the true outcomes within the same cluster
sampling error

$$\begin{bmatrix} u_{i1} \\ u_{i2} \\ u_{i3} \end{bmatrix} \sim MVN \left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \tau^2 & \rho\tau^2 & \rho\tau^2 \\ & \tau^2 & \rho\tau^2 \\ & & \tau^2 \end{bmatrix} \right) \quad e_{ij} \sim N(0, v_{ij})$$

221

The rma.mv() Function

- **rma.mv()** allows for the addition of correlated random effects within a variable
- **random = ~ var1 | var2** adds correlated random effects for each level of **var1** within each level of **var2**

223

```
> # fit multivariate random-effects model
> res <- rma.mv(yi, vi, random = ~ school | district,
               data = dat)
```

> res

Multivariate Meta-Analysis Model (k = 56; method: REML)

Variance Components:

outer factor: district (nlvls = 11)
inner factor: school (nlvls = 11)

	estim	sqr	fixed
tau^2	0.0978	0.3127	no
rho	0.6653		no

Test for Heterogeneity:
Q(df = 55) = 578.8640, p-val < .0001

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.1847	0.0846	2.1845	0.0289	0.0190	0.3504 *

$$\tau^2 = \sigma_B^2 + \sigma_W^2$$

$$\rho = \frac{\sigma_B^2}{\sigma_B^2 + \sigma_W^2}$$

224

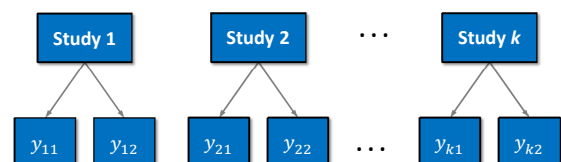
Notes

- models assume independent **sampling errors** within clusters (sensible if no overlap in the data/subjects used to compute outcomes)
- examples:
 - multiple independent studies reported in paper
 - multiple papers published by the same group
 - results reported for different subgroups
- but **true outcomes** within clusters may be more similar to each other than those from different clusters (correlated true outcomes)

225

Multiple (Correlated) Outcomes

- multivariate data also arise when multiple outcomes are measured within the studies



note: not all studies have to measure all outcomes

226

Multiple (Correlated) Outcomes

- since the outcomes are measured in the same subjects, the sampling errors are correlated
- true outcomes may also be correlated
- equations for the covariance between the sampling errors of various outcome measures can be found in Gleser & Olkin (2009), Wei & Higgins (2013), Steiger (1980), ...
- common problem: information needed to compute covariances not available

227

Multivariate Random-Effects Model

$$y_{ij} = \mu_j + u_{ij} + e_{ij}$$

average true outcome for j th outcome

correlated random effects corresponding to the true outcomes of the same study

correlated sampling errors of the observed outcomes for the same study (with known var-cov matrix)

$$Var \begin{bmatrix} u_{i1} \\ u_{i2} \end{bmatrix} = \begin{bmatrix} \tau_1^2 & \rho\tau_1\tau_2 \\ & \tau_2^2 \end{bmatrix} \quad Var \begin{bmatrix} e_{i1} \\ e_{i2} \end{bmatrix} = \begin{bmatrix} v_{i1} & cov_i \\ & v_{i2} \end{bmatrix}$$

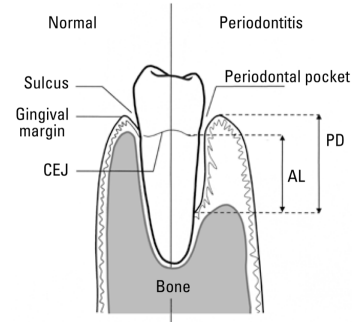
228

```
> # copy data into 'dat'
> dat <- dat.berkey1998
>
> # show data
> dat
```

mean differences
and corresponding
var-cov matrix of
the sampling errors

trial	author	year	ni	outcome	yi	v1i	v2i
1	1 Pihlstrom et al.	1983	14	PD	0.47	0.0075	0.0030
2	1 Pihlstrom et al.	1983	14	AL	-0.32	0.0030	0.0077
3	2 Lindhe et al.	1982	15	PD	0.20	0.0057	0.0009
4	2 Lindhe et al.	1982	15	AL	-0.60	0.0009	0.0008
5	3 Knowles et al.	1979	78	PD	0.40	0.0021	0.0007
6	3 Knowles et al.	1979	78	AL	-0.12	0.0007	0.0014
7	4 Ramfjord et al.	1987	89	PD	0.26	0.0029	0.0009
8	4 Ramfjord et al.	1987	89	AL	-0.31	0.0009	0.0015
9	5 Becker et al.	1988	16	PD	0.56	0.0148	0.0072
10	5 Becker et al.	1988	16	AL	-0.39	0.0072	0.0304

231



232

```
> # construct var-cov matrix of the sampling errors
> V <- vcalc(vi=1, cluster=author, rvars=c(v1i, v2i), data=dat)
> V
```

	[,1]	[,2]	[,3]	[,4]	[,5]	[,6]	[,7]	[,8]	[,9]	[,10]
[1,]	0.0075	0.0030	0.0000	0.0000
[2,]	0.0030	0.0077	0.0000	0.0000
[3,]	0.0000	0.0000	0.0057	0.0009
[4,]	0.0000	0.0000	0.0009	0.0008
[5,]
[6,]
[7,]
[8,]
[9,]	0.0148	0.0072	...
[10,]	0.0072	0.0304	...

233

The rma.mv() Function

name of object with the var-cov matrix of the sampling errors

name of factor to indicate the outcome (and remove intercept)

```
res <- rma.mv(yi, V, mods = ~ outcome - 1,
              random = ~ outcome | study,
              struct = "UN", data = dat)
```

structure of var-cov matrix of the random effects (UN = unstructured)

234

```
> # fit multivariate random-effects model
> res <- rma.mv(yi, V, mods = ~ outcome - 1, data = dat,
               random = ~ outcome | trial, struct = "UN")
> res
```

Multivariate Meta-Analysis Model (k = 10; method: REML)

Variance Components:

outer factor: trial (nlvls = 5)
inner factor: outcome (nlvls = 2)

	estim	sqr	k.lvl	fixed	level
tau^2.1	0.0327	0.1807	5	no	AL
tau^2.2	0.0117	0.1083	5	no	PD

	rho.AL	rho.PD	AL	PD
AL	1	0.6088	-	no
PD	0.6088	1	5	-

Test for Residual Heterogeneity:

QE(df = 8) = 128.2267, p-val < .0001

Test of Moderators (coefficients 1:2):

QM(df = 2) = 108.8616, p-val < .0001

Model Results:

	estimate	se	zval	pval	ci.lb	ci.ub
outcomeAL	-0.3392	0.0879	-3.8589	0.0001	-0.5115	-0.1669 ***
outcomePD	0.3534	0.0588	6.0057	<.0001	0.2381	0.4688 ***

235

```
> # contrast for differences in outcomes
> anova(res, L=c(1,-1))
```

Hypothesis:

1: outcomeAL - outcomePD = 0

Results:

	estimate	se	zval	pval
1:	-0.6926	0.0744	-9.3120	<.0001

Test of Hypothesis:

QM(df = 1) = 86.7139, p-val < .0001

236

The V Matrix

- V = var-cov matrix of the sampling errors
- roughly: whenever a subject contributes data to the computation of more than one estimate, we have correlated sampling errors
- V matrix is then not just a diagonal matrix (with the sampling variances), but also has off-diagonal elements (covariances)
- computing the covariances is often difficult

246

Alternative Methods

1. fit multilevel random-effects model ignoring the covariances in the V matrix (= assume they are 0)
 2. use cluster-robust inference methods (also known as 'robust variance estimation')
 3. approximate the V matrix, fit model, and do sensitivity analyses
 4. combine approaches 2. and 3.
- see **code_r_ml_mv.r** for an illustration of these different approaches

247

Literature

- Assink, M., & Wibbelink, C. J. M. (2016). Fitting three-level meta-analytic models in R: A step-by-step tutorial. *The Quantitative Methods for Psychology*, 12(3), 154-174.
- Berkey, C. S., Hoaglin, D. C., Antczak-Bouckoms, A., Mosteller, F., & Colditz, G. A. (1998). Meta-analysis of multiple outcomes by regression with random effects. *Statistics in Medicine*, 17(22), 2537-2550.
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- Pustejovsky, J., & Tipton, E. (in press). Meta-analysis with robust variance estimation: Expanding the range of working models. *Prevention Science*.
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- Trikalinos, T. A., & Olkin, I. (2012). Meta-analysis of effect sizes reported at multiple time points: A multivariate approach. *Clinical Trials*, 9(5), 610-620.
- van Houwelingen, H. C., Arends, L. R., & Stijnen, T. (2002). Advanced methods in meta-analysis: Multivariate approach and meta-regression. *Statistics in Medicine*, 21(4), 589-624.
- Wei, Y., & Higgins, J. P. (2013). Estimating within-study covariances in multivariate meta-analysis with multiple outcomes. *Statistics in Medicine*, 32(7), 1191-1205.

248

Exercises

- back to: **exercises.r**
- meta-analysis on relationship between class attendance and class performance in college students (Credé et al., 2010): actually has a multilevel structure
- meta-analysis on the difference between schizophrenia patients and healthy controls with respect to planning performance (Knapp et al., 2017): an example of a meta-analysis with correlated sampling errors

249