



**Michael Borenstein**  
**Larry V. Hedges**  
**Julian P. T. Higgins**  
**Hannah R. Rothstein**

# **Introduction to Meta-Analysis**

 **WILEY**



# Contents

List of Tables	xiii
List of Figures	xv
Acknowledgements	xix
Preface	xxi
Web site	xxix

## PART 1: INTRODUCTION

<b>1 HOW A META-ANALYSIS WORKS</b>	<b>3</b>
Introduction	3
Individual studies	3
The summary effect	5
Heterogeneity of effect sizes	6
Summary points	7
<b>2 WHY PERFORM A META-ANALYSIS</b>	<b>9</b>
Introduction	9
The streptokinase meta-analysis	10
Statistical significance	11
Clinical importance of the effect	12
Consistency of effects	12
Summary points	14

## PART 2: EFFECT SIZE AND PRECISION

<b>3 OVERVIEW</b>	<b>17</b>
Treatment effects and effect sizes	17
Parameters and estimates	18
Outline of effect size computations	19
<b>4 EFFECT SIZES BASED ON MEANS</b>	<b>21</b>
Introduction	21
Raw (unstandardized) mean difference $D$	21
Standardized mean difference, $d$ and $g$	25
Response ratios	30
Summary points	32

<b>5</b>	<b>EFFECT SIZES BASED ON BINARY DATA (<math>2 \times 2</math> TABLES)</b>	<b>33</b>
	Introduction	33
	Risk ratio	34
	Odds ratio	36
	Risk difference	37
	Choosing an effect size index	38
	Summary points	39
<b>6</b>	<b>EFFECT SIZES BASED ON CORRELATIONS</b>	<b>41</b>
	Introduction	41
	Computing $r$	41
	Other approaches	43
	Summary points	43
<b>7</b>	<b>CONVERTING AMONG EFFECT SIZES</b>	<b>45</b>
	Introduction	45
	Converting from the log odds ratio to $d$	47
	Converting from $d$ to the log odds ratio	47
	Converting from $r$ to $d$	48
	Converting from $d$ to $r$	48
	Summary points	49
<b>8</b>	<b>FACTORS THAT AFFECT PRECISION</b>	<b>51</b>
	Introduction	51
	Factors that affect precision	52
	Sample size	52
	Study design	53
	Summary points	55
<b>9</b>	<b>CONCLUDING REMARKS</b>	<b>57</b>
<b>PART 3: FIXED-EFFECT VERSUS RANDOM-EFFECTS MODELS</b>		
<b>10</b>	<b>OVERVIEW</b>	<b>61</b>
	Introduction	61
	Nomenclature	62
<b>11</b>	<b>FIXED-EFFECT MODEL</b>	<b>63</b>
	Introduction	63
	The true effect size	63
	Impact of sampling error	63

Performing a fixed-effect meta-analysis	65
Summary points	67
<b>12 RANDOM-EFFECTS MODEL</b>	<b>69</b>
Introduction	69
The true effect sizes	69
Impact of sampling error	70
Performing a random-effects meta-analysis	72
Summary points	74
<b>13 FIXED-EFFECT VERSUS RANDOM-EFFECTS MODELS</b>	<b>77</b>
Introduction	77
Definition of a summary effect	77
Estimating the summary effect	78
Extreme effect size in a large study or a small study	79
Confidence interval	80
The null hypothesis	83
Which model should we use?	83
Model should not be based on the test for heterogeneity	84
Concluding remarks	85
Summary points	85
<b>14 WORKED EXAMPLES (PART 1)</b>	<b>87</b>
Introduction	87
Worked example for continuous data (Part 1)	87
Worked example for binary data (Part 1)	92
Worked example for correlational data (Part 1)	97
Summary points	102
<b>PART 4: HETEROGENEITY</b>	
<b>15 OVERVIEW</b>	<b>105</b>
Introduction	105
Nomenclature	106
Worked examples	106
<b>16 IDENTIFYING AND QUANTIFYING HETEROGENEITY</b>	<b>107</b>
Introduction	107
Isolating the variation in true effects	107
Computing $Q$	109
Estimating $\tau^2$	114
The $I^2$ statistic	117

---

Comparing the measures of heterogeneity	119
Confidence intervals for $\tau^2$	122
Confidence intervals (or uncertainty intervals) for $I^2$	124
Summary points	125
<b>17 PREDICTION INTERVALS</b>	<b>127</b>
Introduction	127
Prediction intervals in primary studies	127
Prediction intervals in meta-analysis	129
Confidence intervals and prediction intervals	131
Comparing the confidence interval with the prediction interval	132
Summary points	133
<b>18 WORKED EXAMPLES (PART 2)</b>	<b>135</b>
Introduction	135
Worked example for continuous data (Part 2)	135
Worked example for binary data (Part 2)	139
Worked example for correlational data (Part 2)	143
Summary points	147
<b>19 SUBGROUP ANALYSES</b>	<b>149</b>
Introduction	149
Fixed-effect model within subgroups	151
Computational models	161
Random effects with separate estimates of $\tau^2$	164
Random effects with pooled estimate of $\tau^2$	171
The proportion of variance explained	179
Mixed-effects model	183
Obtaining an overall effect in the presence of subgroups	184
Summary points	186
<b>20 META-REGRESSION</b>	<b>187</b>
Introduction	187
Fixed-effect model	188
Fixed or random effects for unexplained heterogeneity	193
Random-effects model	196
Summary points	203
<b>21 NOTES ON SUBGROUP ANALYSES AND META-REGRESSION</b>	<b>205</b>
Introduction	205
Computational model	205
Multiple comparisons	208
Software	209
Analyses of subgroups and regression analyses are observational	209

Statistical power for subgroup analyses and meta-regression	210
Summary points	211

## **PART 5: COMPLEX DATA STRUCTURES**

<b>22 OVERVIEW</b>	<b>215</b>
<b>23 INDEPENDENT SUBGROUPS WITHIN A STUDY</b>	<b>217</b>
Introduction	217
Combining across subgroups	218
Comparing subgroups	222
Summary points	223
<b>24 MULTIPLE OUTCOMES OR TIME-POINTS WITHIN A STUDY</b>	<b>225</b>
Introduction	225
Combining across outcomes or time-points	226
Comparing outcomes or time-points within a study	233
Summary points	238
<b>25 MULTIPLE COMPARISONS WITHIN A STUDY</b>	<b>239</b>
Introduction	239
Combining across multiple comparisons within a study	239
Differences between treatments	240
Summary points	241
<b>26 NOTES ON COMPLEX DATA STRUCTURES</b>	<b>243</b>
Introduction	243
Summary effect	243
Differences in effect	244

## **PART 6: OTHER ISSUES**

<b>27 OVERVIEW</b>	<b>249</b>
<b>28 VOTE COUNTING – A NEW NAME FOR AN OLD PROBLEM</b>	<b>251</b>
Introduction	251
Why vote counting is wrong	252
Vote counting is a pervasive problem	253
Summary points	255
<b>29 POWER ANALYSIS FOR META-ANALYSIS</b>	<b>257</b>
Introduction	257
A conceptual approach	257
In context	261
When to use power analysis	262

---

Planning for precision rather than for power	263
Power analysis in primary studies	263
Power analysis for meta-analysis	267
Power analysis for a test of homogeneity	272
Summary points	275
<b>30 PUBLICATION BIAS</b>	<b>277</b>
Introduction	277
The problem of missing studies	278
Methods for addressing bias	280
Illustrative example	281
The model	281
Getting a sense of the data	281
Is there evidence of any bias?	283
Is the entire effect an artifact of bias?	284
How much of an impact might the bias have?	286
Summary of the findings for the illustrative example	289
Some important caveats	290
Small-study effects	291
Concluding remarks	291
Summary points	291
<b>PART 7: ISSUES RELATED TO EFFECT SIZE</b>	
<b>31 OVERVIEW</b>	<b>295</b>
<b>32 EFFECT SIZES RATHER THAN <math>p</math>-VALUES</b>	<b>297</b>
Introduction	297
Relationship between $p$ -values and effect sizes	297
The distinction is important	299
The $p$ -value is often misinterpreted	300
Narrative reviews vs. meta-analyses	301
Summary points	302
<b>33 SIMPSON'S PARADOX</b>	<b>303</b>
Introduction	303
Circumcision and risk of HIV infection	303
An example of the paradox	305
Summary points	308
<b>34 GENERALITY OF THE BASIC INVERSE-VARIANCE METHOD</b>	<b>311</b>
Introduction	311
Other effect sizes	312
Other methods for estimating effect sizes	315
Individual participant data meta-analyses	316

Bayesian approaches	318
Summary points	319
<b>PART 8: FURTHER METHODS</b>	
<b>35 OVERVIEW</b>	<b>323</b>
<b>36 META-ANALYSIS METHODS BASED ON DIRECTION AND <math>p</math>-VALUES</b>	<b>325</b>
Introduction	325
Vote counting	325
The sign test	325
Combining $p$ -values	326
Summary points	330
<b>37 FURTHER METHODS FOR DICHOTOMOUS DATA</b>	<b>331</b>
Introduction	331
Mantel-Haenszel method	331
One-step (Peto) formula for odds ratio	336
Summary points	339
<b>38 PSYCHOMETRIC META-ANALYSIS</b>	<b>341</b>
Introduction	341
The attenuating effects of artifacts	342
Meta-analysis methods	344
Example of psychometric meta-analysis	346
Comparison of artifact correction with meta-regression	348
Sources of information about artifact values	349
How heterogeneity is assessed	349
Reporting in psychometric meta-analysis	350
Concluding remarks	351
Summary points	351
<b>PART 9: META-ANALYSIS IN CONTEXT</b>	
<b>39 OVERVIEW</b>	<b>355</b>
<b>40 WHEN DOES IT MAKE SENSE TO PERFORM A META-ANALYSIS?</b>	<b>357</b>
Introduction	357
Are the studies similar enough to combine?	358
Can I combine studies with different designs?	359
How many studies are enough to carry out a meta-analysis?	363
Summary points	364
<b>41 REPORTING THE RESULTS OF A META-ANALYSIS</b>	<b>365</b>
Introduction	365
The computational model	366



---

Forest plots	366
Sensitivity analysis	368
Summary points	369
<b>42 CUMULATIVE META-ANALYSIS</b>	<b>371</b>
Introduction	371
Why perform a cumulative meta-analysis?	373
Summary points	376
<b>43 CRITICISMS OF META-ANALYSIS</b>	<b>377</b>
Introduction	377
One number cannot summarize a research field	378
The file drawer problem invalidates meta-analysis	378
Mixing apples and oranges	379
Garbage in, garbage out	380
Important studies are ignored	381
<i>Meta-analysis can disagree with randomized trials</i>	381
Meta-analyses are performed poorly	384
Is a narrative review better?	385
Concluding remarks	386
Summary points	386
 <b>PART 10: RESOURCES AND SOFTWARE</b>	
<b>44 SOFTWARE</b>	<b>391</b>
Introduction	391
The software	392
Three examples of meta-analysis software	393
Comprehensive Meta-Analysis (CMA) 2.0	395
RevMan 5.0	398
Stata macros with Stata 10.0	400
Summary points	403
<b>45 BOOKS, WEB SITES AND PROFESSIONAL ORGANIZATIONS</b>	<b>405</b>
Books on systematic review methods	405
Books on meta-analysis	405
Web sites	406
 <b>REFERENCES</b>	 <b>409</b>
<b>INDEX</b>	<b>415</b>