Introduction to Meta-Analysis

Michael Borenstein

Biostat, Inc, New Jersey, USA.

Larry V. Hedges

Northwestern University, Evanston, USA.

Julian P.T. Higgins

MRC, Cambridge, UK.

Hannah R. Rothstein

Baruch College, New York, USA.



Contents

Lis	t of Tables	xiii
Lis	xv	
Acl	knowledgements	xix
Pre	face	xxi
We	b site	xxix
PAR	RT 1: INTRODUCTION	
1	HOW A META-ANALYSIS WORKS	3
	Introduction	3
	Individual studies	3
	The summary effect	5
	Heterogeneity of effect sizes	6
	Summary points	7
2	WHY PERFORM A META-ANALYSIS	9
	Introduction	9
	The streptokinase meta-analysis	10
	Statistical significance	11
	Clinical importance of the effect	12
	Consistency of effects	12
	Summary points	14
PAR	T 2: EFFECT SIZE AND PRECISION	
3	OVERVIEW	17
	Treatment effects and effect sizes	17
	Parameters and estimates	18
	Outline of effect size computations	19
4	EFFECT SIZES BASED ON MEANS	21
	Introduction	21
	Raw (unstandardized) mean difference D	21
	Standardized mean difference, d and g	25
	Response ratios	30
	Summary points	32

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

vi

<u> </u>	Contents	vii
	Performing a fixed-effect meta-analysis	65
	Summary points	67
12	RANDOM-EFFECTS MODEL	69
	Introduction	69
	The true effect sizes	69
	Impact of sampling error	70
	Performing a random-effects meta-analysis	72
	Summary points	74
13	FIXED-EFFECT VERSUS RANDOM-EFFECTS MODELS	77
	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
14	WORKED EXAMPLES (PART 1)	87
	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
PAI	RT 4: HETEROGENEITY	
15	OVERVIEW	105
	Introduction	105
	Nomenclature	106
	Worked examples	106
16	IDENTIFYING AND QUANTIFYING HETEROGENEITY	107
	Introduction	107
	Isolating the variation in true effects	107
	Computing Q	109
	Estimating τ^2	114
	The I^2 statistic	117

	Comparing the measures of heterogeneity	119
	Confidence intervals for τ^2	122
	Confidence intervals (or uncertainty intervals) for I ²	124
	Summary points	125
17	PREDICTION INTERVALS	127
	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
18	WORKED EXAMPLES (PART 2)	135
	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
19	SUBGROUP ANALYSES	149
	Introduction	149
	Fixed-effect model within subgroups	151
	Computational models	161
	Random effects with separate estimates of τ^2	164
	Random effects with pooled estimate of τ^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
20	META-REGRESSION	187
	Introduction	187
	Fixed-effect model	188
	Fixed or random effects for unexplained heterogeneity	193
	Random-effects model	196
	Summary points	203
21	NOTES ON SUBGROUP ANALYSES AND META-REGRESSION	205
	Introduction	205
	Computational model	205
	Multiple comparisons	208
	Software	209
	Analyses of subgroups and regression analyses are observational	209

viii

	Contents	ix
	Statistical power for subgroup analyses and meta-regression	210
	Summary points	211
PAR	T 5: COMPLEX DATA STRUCTURES	
22	OVERVIEW	215
23	INDEPENDENT SUBGROUPS WITHIN A STUDY	217
	Introduction	217
	Combining across subgroups	218
	Comparing subgroups	222
	Summary points	223
24	MULTIPLE OUTCOMES OR TIME-POINTS WITHIN A STUDY	225
	Introduction	225
	Combining across outcomes or time-points	226
	Comparing outcomes or time-points within a study	233
	Summary points	238
25	MULTIPLE COMPARISONS WITHIN A STUDY	239
	Introduction	239
	Combining across multiple comparisons within a study	239
	Differences between treatments	240
	Summary points	241
26	NOTES ON COMPLEX DATA STRUCTURES	243
	Introduction	243
	Summary effect	243
	Differences in effect	244
PAR	T 6: OTHER ISSUES	
27	OVERVIEW	249
28	VOTE COUNTING - A NEW NAME FOR AN OLD PROBLEM	251
	Introduction	251
	Why vote counting is wrong	252
	Vote counting is a pervasive problem	253
	Summary points	255
29	POWER ANALYSIS FOR META-ANALYSIS	257
	Introduction	257
	A conceptual approach	257
	In context	261
	When to use power analysis	262

	Planning for precision rather than for power	26
	Power analysis in primary studies	26
	Power analysis for meta-analysis	26
	Power analysis for a test of homogeneity	27
	Summary points	27
30	PUBLICATION BIAS	27
	Introduction	27
	The problem of missing studies	27
	Methods for addressing bias	28
	Illustrative example	28
	The model	28
	Getting a sense of the data	28
	Is there evidence of any bias?	28
	Is the entire effect an artifact of bias?	28
	How much of an impact might the bias have?	28
	Summary of the findings for the illustrative example	28
	Some important caveats	29
	Small-study effects	29
	Concluding remarks	29
	5	
	Summary points	29
PAR	Summary points	29
PAR 31	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW	29
PAR 31 32	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES	29 29 29
PAR 31 32	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction	29 29 29 29 29
PAR 31 32	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes	29 29 29 29 29 29
PAR 31 32	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important	29 29 29 29 29 29 29 29 29
PAR 31 32	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted	29 29 29 29 29 29 29 29 29 30
PAR 31 32	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses	29 29 29 29 29 29 30 30
PAR 31 32	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses Summary points	29 29 29 29 29 30 30 30
PAF 31 32 33	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses Summary points SIMPSON'S PARADOX	29 29 29 29 30 30 30 30 30 30 30 30 30 30 30 30 30
PAR 31 32 33	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses Summary points SIMPSON'S PARADOX Introduction	29 29 29 29 29 30 30 30 30 30 30 30 30 30 30
PAR 31 32 33	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses Summary points SIMPSON'S PARADOX Introduction Circumcision and risk of HIV infection	29 29 29 29 29 29 29 30 30 30 30 30 30 30 30 30 30 30 30 30
PAF 31 32 33	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses Summary points SIMPSON'S PARADOX Introduction Circumcision and risk of HIV infection An example of the paradox	29 29 29 29 29 29 29 30 30 30 30 30 30 30 30 30 30 30 30 30
PAF 31 32 33	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses Summary points SIMPSON'S PARADOX Introduction Circumcision and risk of HIV infection An example of the paradox Summary points	29 29 29 29 29 29 29 29 29 29 30 30 30 30 30 30 30 30 30
PAR 31 32 33 33	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses Summary points SIMPSON'S PARADOX Introduction Circumcision and risk of HIV infection An example of the paradox Summary points GENERALITY OF THE BASIC INVERSE-VARIANCE METHOD	29 29 29 29 29 29 29 29 29 29 29 29 29 2
PAR 31 32 33 33	Summary points T. 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses Summary points SIMPSON'S PARADOX Introduction Circumcision and risk of HIV infection An example of the paradox Summary points GENERALITY OF THE BASIC INVERSE-VARIANCE METHOD Introduction	29 29 29 29 29 29 29 29 29 29 29 29 29 2
PAR 31 32 33 33	Summary points T. 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses Summary points SIMPSON'S PARADOX Introduction Circumcision and risk of HIV infection An example of the paradox Summary points GENERALITY OF THE BASIC INVERSE-VARIANCE METHOD Introduction Other effect sizes	29 29 29 29 29 30 30 30 30 30 30 30 30 30 30 30 30 30
PAF 31 32 33 33	Summary points T 7: ISSUES RELATED TO EFFECT SIZE OVERVIEW EFFECT SIZES RATHER THAN <i>p</i> -VALUES Introduction Relationship between <i>p</i> -values and effect sizes The distinction is important The <i>p</i> -value is often misinterpreted Narrative reviews vs. meta-analyses Summary points SIMPSON'S PARADOX Introduction Circumcision and risk of HIV infection An example of the paradox Summary points GENERALITY OF THE BASIC INVERSE-VARIANCE METHOD Introduction Other effect sizes Other methods for estimating effect sizes	29 29 29 29 29 29 29 30 30 30 30 30 30 30 30 31 31 31 31 31 31 31 31 31 31 31 31 31

	Contents	xi
	Bayesian approaches	318
	Summary points	319
PAF	RT 8: FURTHER METHODS	
35	OVERVIEW	323
36	META-ANALYSIS METHODS BASED ON DIRECTION AND <i>p</i> -VALUES	325
	Introduction	325
	Vote counting	325
	The sign test	325
	Combining <i>p</i> -values	326
	Summary points	330
37	FURTHER METHODS FOR DICHOTOMOUS DATA	331
	Introduction	331
	Mantel-Haenszel method	331
	One-step (Peto) formula for odds ratio	336
	Summary points	339
38	PSYCHOMETRIC META-ANALYSIS	341
	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
PAR	T 9: META-ANALYSIS IN CONTEXT	
39	OVERVIEW	355
40	WHEN DOES IT MAKE SENSE TO PERFORM A META-ANALYSIS?	357
	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
41	REPORTING THE RESULTS OF A META-ANALYSIS	365
-	Introduction	365
	The computational model	366

	Forest plots	366
	Sensitivity analysis	368
	Summary points	369
42	CUMULATIVE META-ANALYSIS	371
	Introduction	371
	Why perform a cumulative meta-analysis?	373
	Summary points	376
43	CRITICISMS OF META-ANALYSIS	377
	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
	Meta-analysis can disagree with randomized trials	381
	Meta-analyses are performed poorly	384
	Is a narrative review better?	385
	Concluding remarks	386
	Summary points	386
PAR	T 10: RESOURCES AND SOFTWARE	
44	SOFTWARE	391
	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
45	BOOKS, WEB SITES AND PROFESSIONAL ORGANIZATIONS	405
	Books on systematic review methods	405
	Books on meta-analysis	405
	Web sites	406
RE	FERENCES	409
INI	DEX	415

Xİİ