CMA Workshop

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Difference between research article (primary) and meta-analysis

Content		Research article	Meta-analysis
Question			
Proposal			
Article section			
Abstract			
Introduction			
Methods	**Sample size**	People	Paper
	Sampling method		Search strategy
	Data collection		
	Statistical analysis		
	Inclusion & exclusion		Quality assessment
Results	Descriptive		
	Analytical		
Discussion		Summary, compare, justify	Summary, compare, justify

MA in RCTs

- **P**articipants?
- **I**nterventions?
- **C**omparisons?
- **O**utcomes?

MA in Observational studies

The PICO may be not applicable

There commonly are several risk factors

There commonly are several outcomes

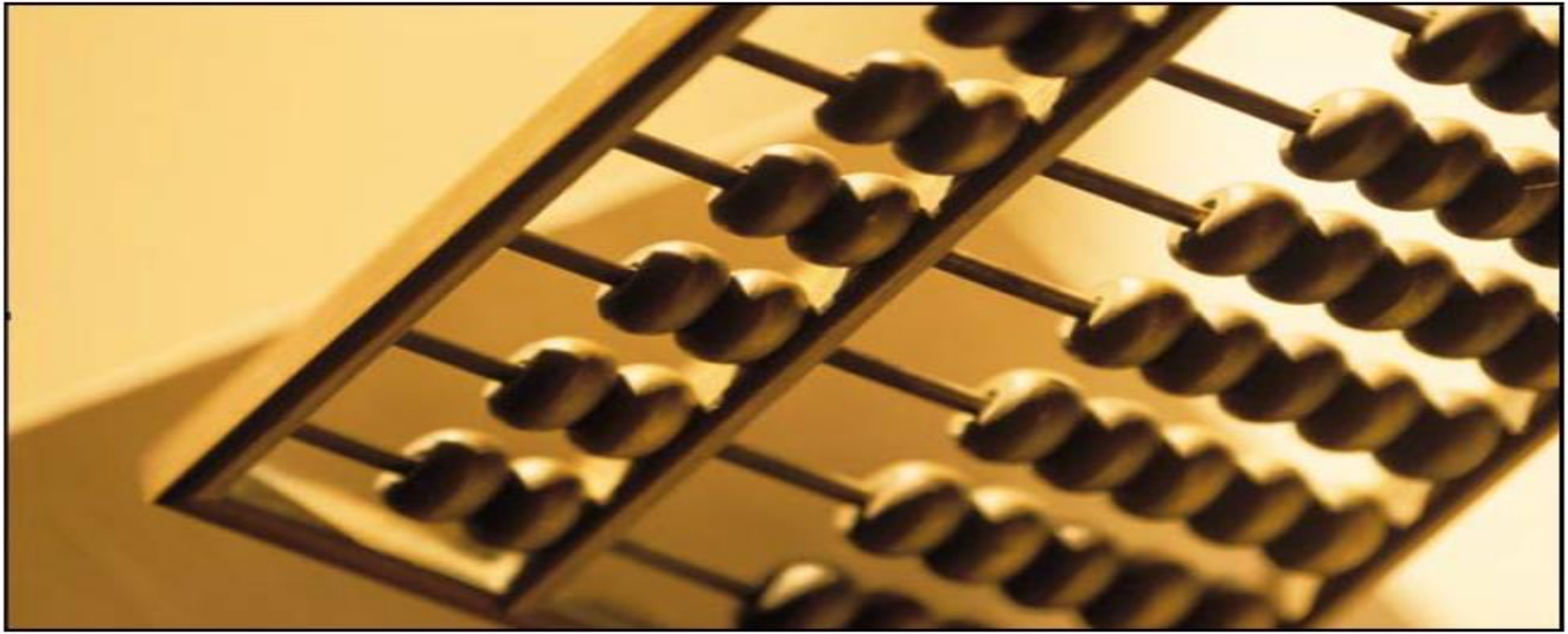
There commonly is several time-points in a study (regional, national)

Hence, we have to have specific question:

- Point estimate: Mean, Prevalence, Incidence
- Causality: Odds ratio, Risk ratio
- Risk difference

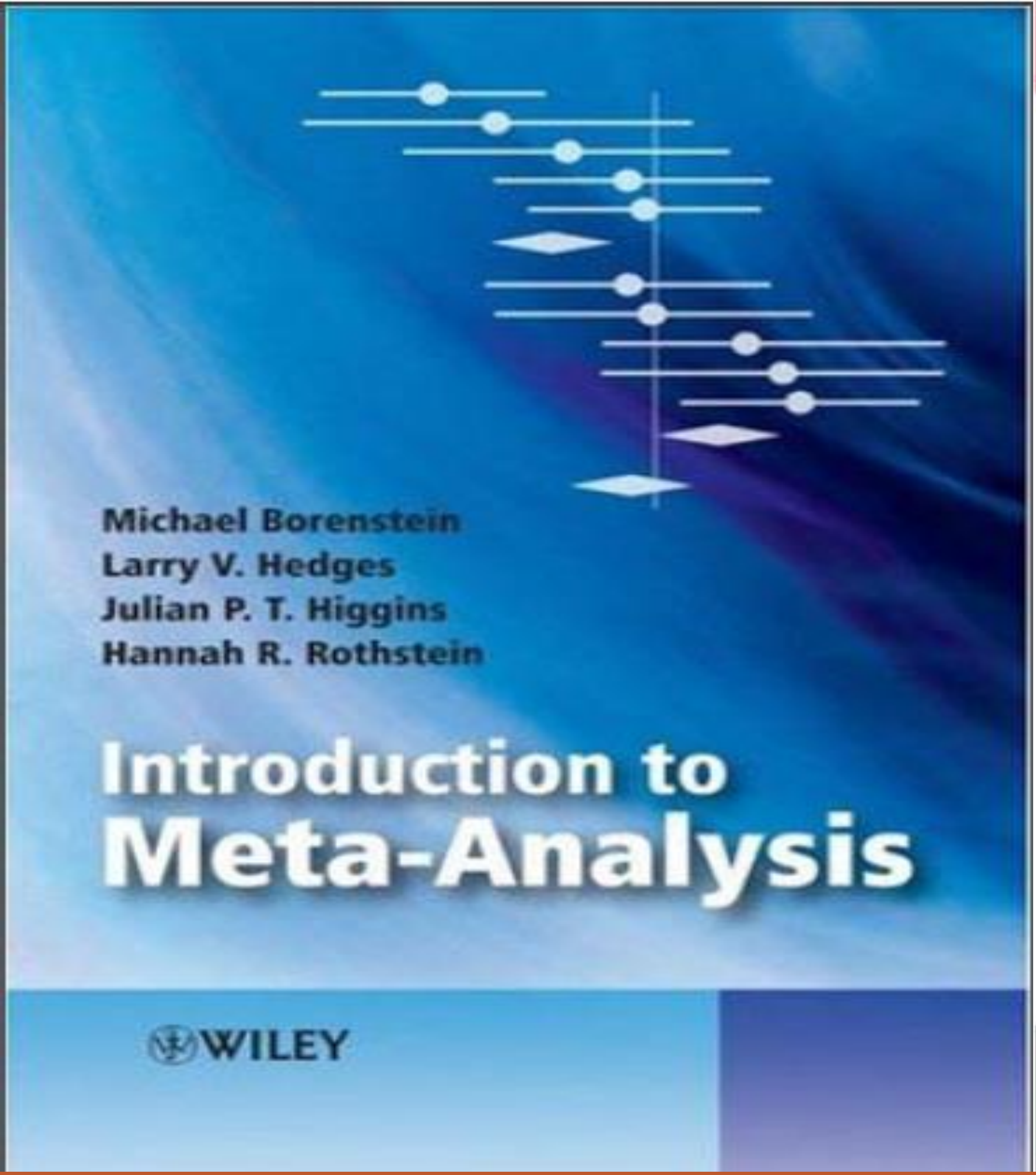
Comprehensive Meta Analysis Version 2.0

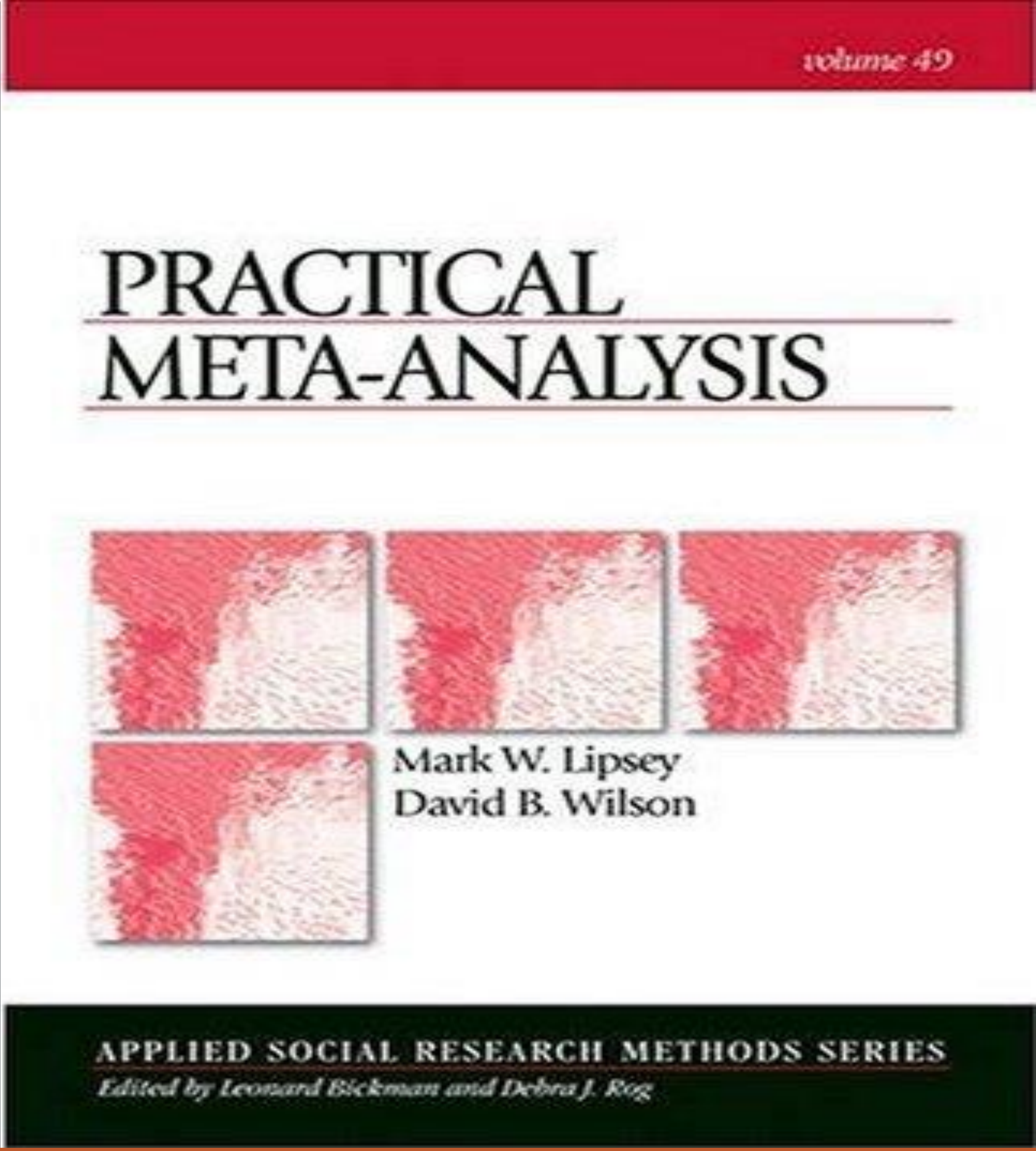
This manual will continue to be revised to reflect changes in the program. It will also be expanded to include chapters covering conceptual topics. Upgrades to the program and manual will be available on our download site.

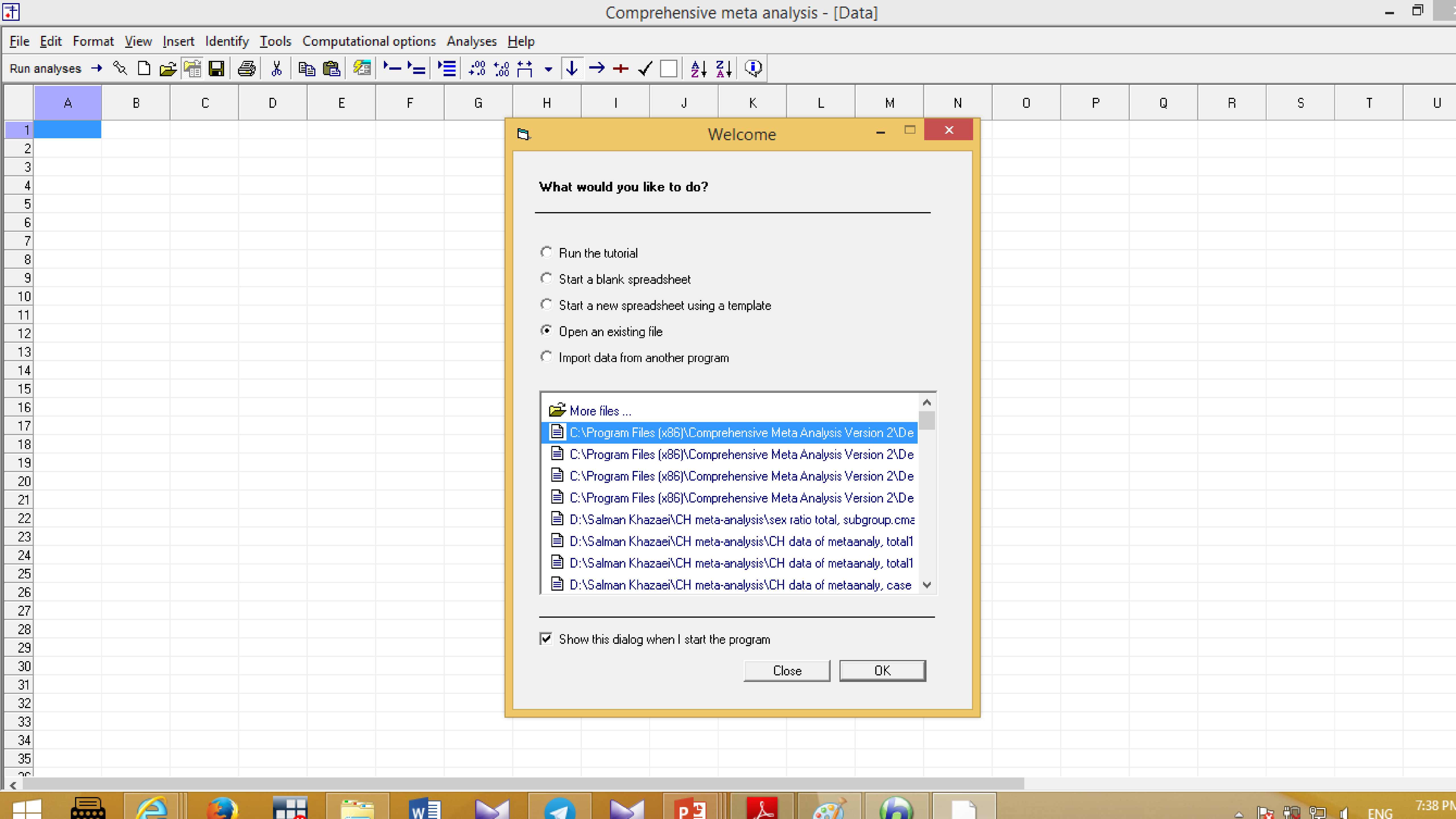


Group meetings to develop the program

July 2002. Left to right (Seated) Vish Viswesvaran, Will Shadish, Hannah Rothstein, Michael Borenstein, Fred Oswald, Terri Pigott. (Standing) Spyros Konstantopoulos, David Wilson, Alex Sutton, Jonathan Sterne, Harris Cooper, Sue Duval, Jesse Berlin, Larry Hedges, Mike McDaniel, Jack Vevea


Michael Borenstein
Larry V. Hedges
Julian P. T. Higgins
Hannah R. Rothstein
Introduction to
Meta-Analysis
WILEY


volume 49
PRACTICAL
META-ANALYSIS
Mark W. Lipsey
David B. Wilson
APPLIED SOCIAL RESEARCH METHODS SERIES
Edited by Leonard Bickman and Debra J. Rog


Comprehensive meta analysis - [Data]
File Edit Format View Insert Identify Tools Computational options Analyses Help
Run analyses
Welcome
What would you like to do?
Run the tutorial
Start a blank spreadsheet
Start a new spreadsheet using a template
Open an existing file
Import data from another program
More files ...
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C:\Program Files (x86)\Comprehensive Meta Analysis Version 2\De
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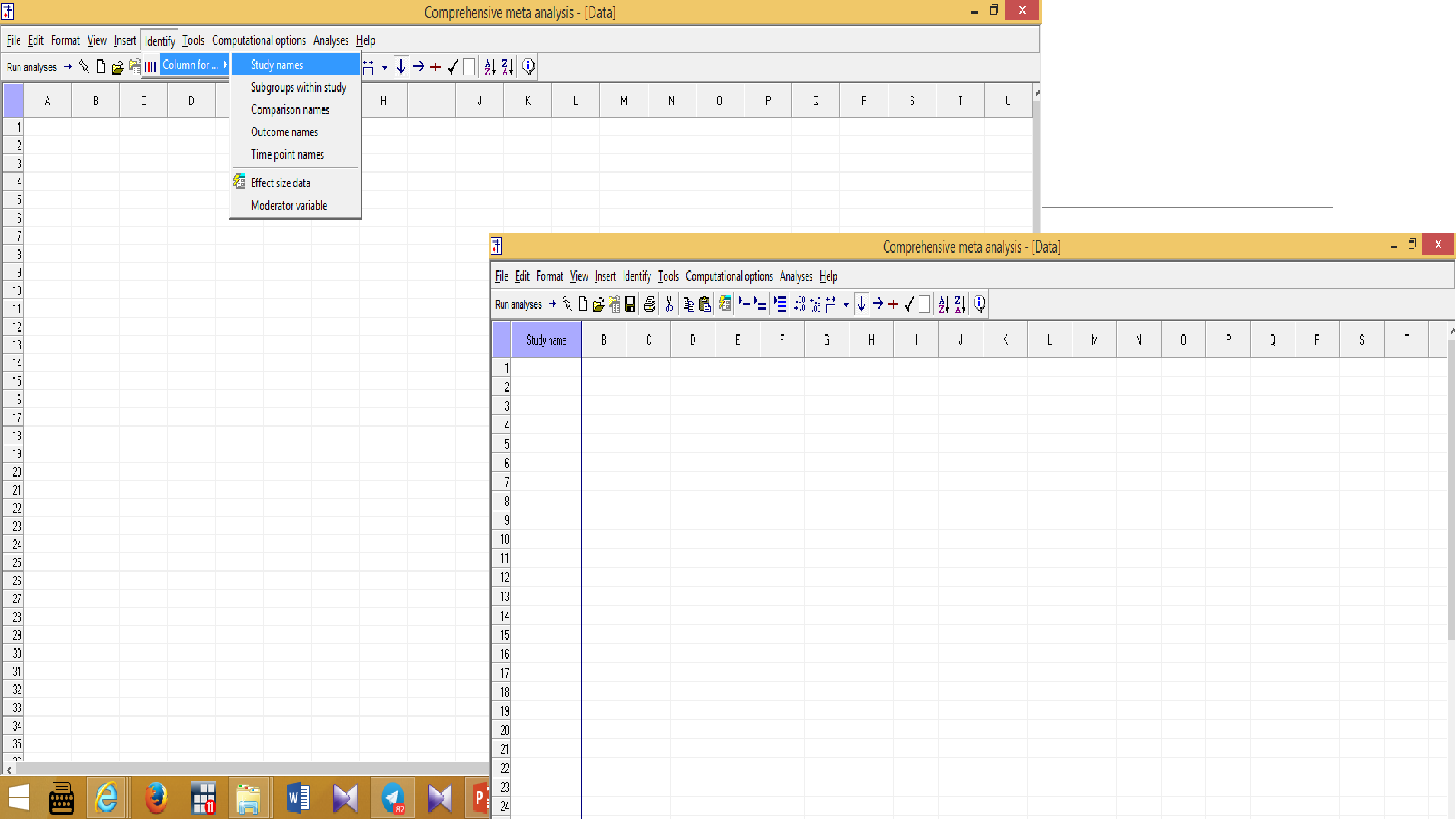
OK
ENG
7:38 PM

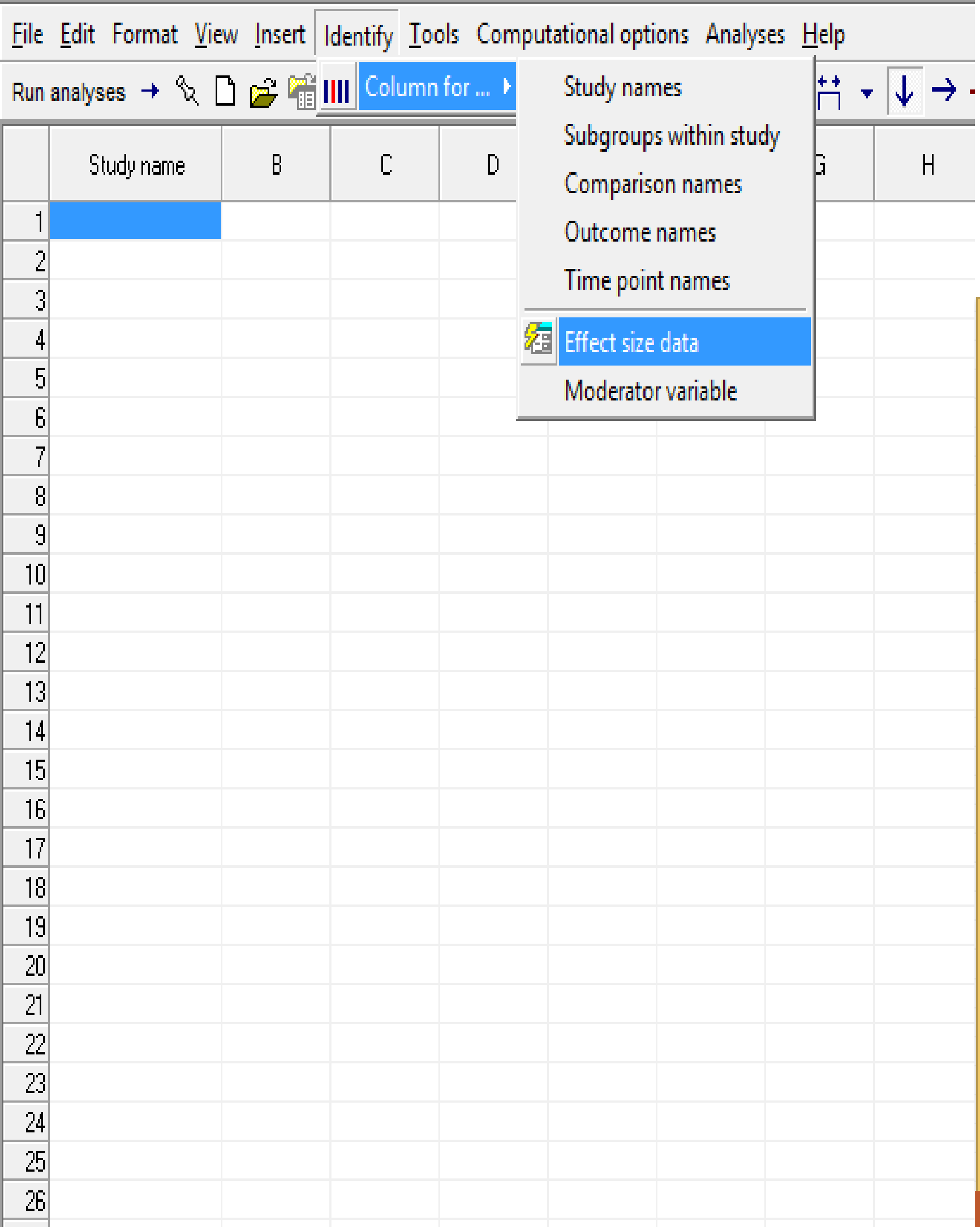
Q1: Protective vaccination against tuberculosis, with special reference to BCG vaccine

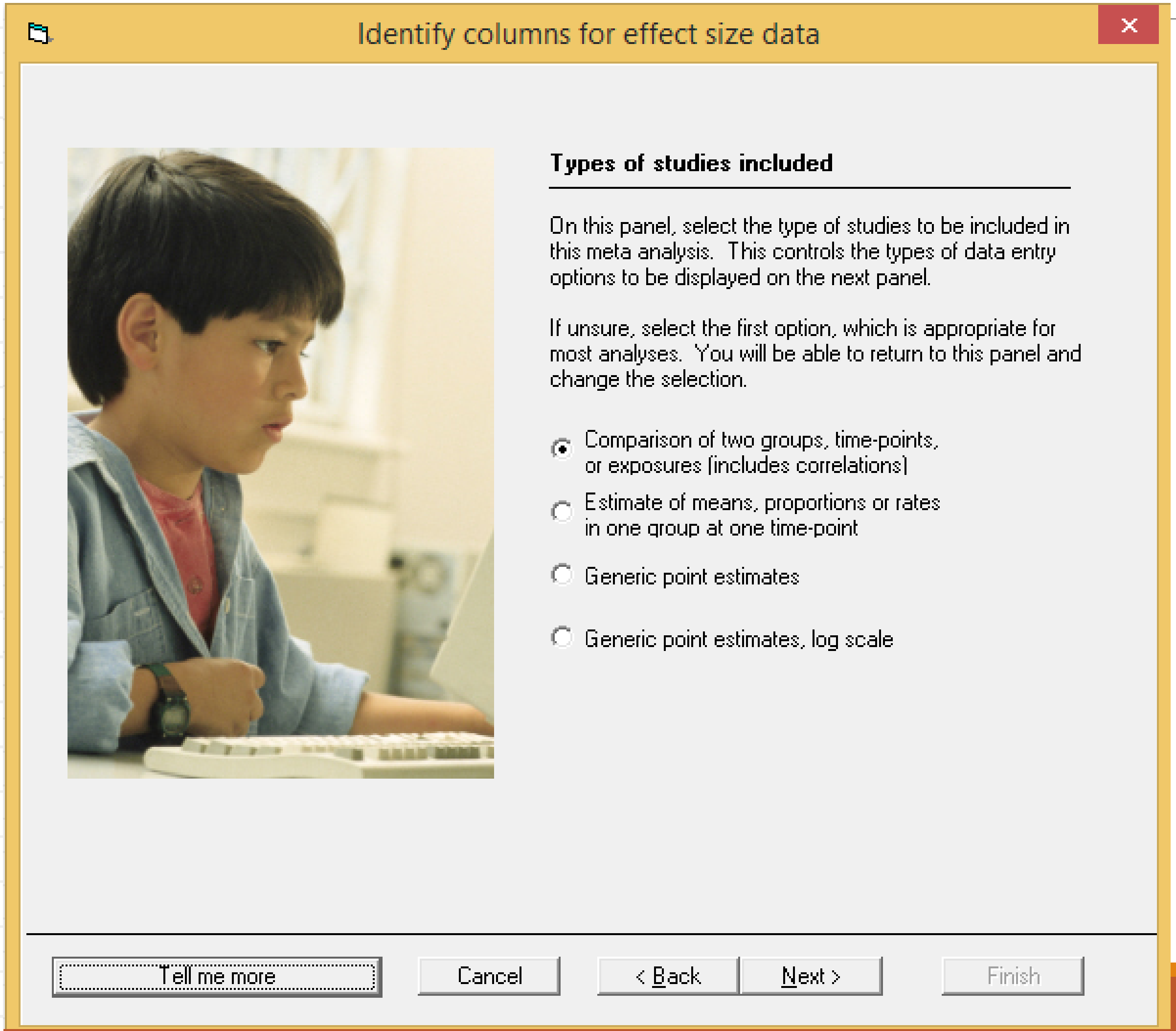
Total retrieved same studies: 13

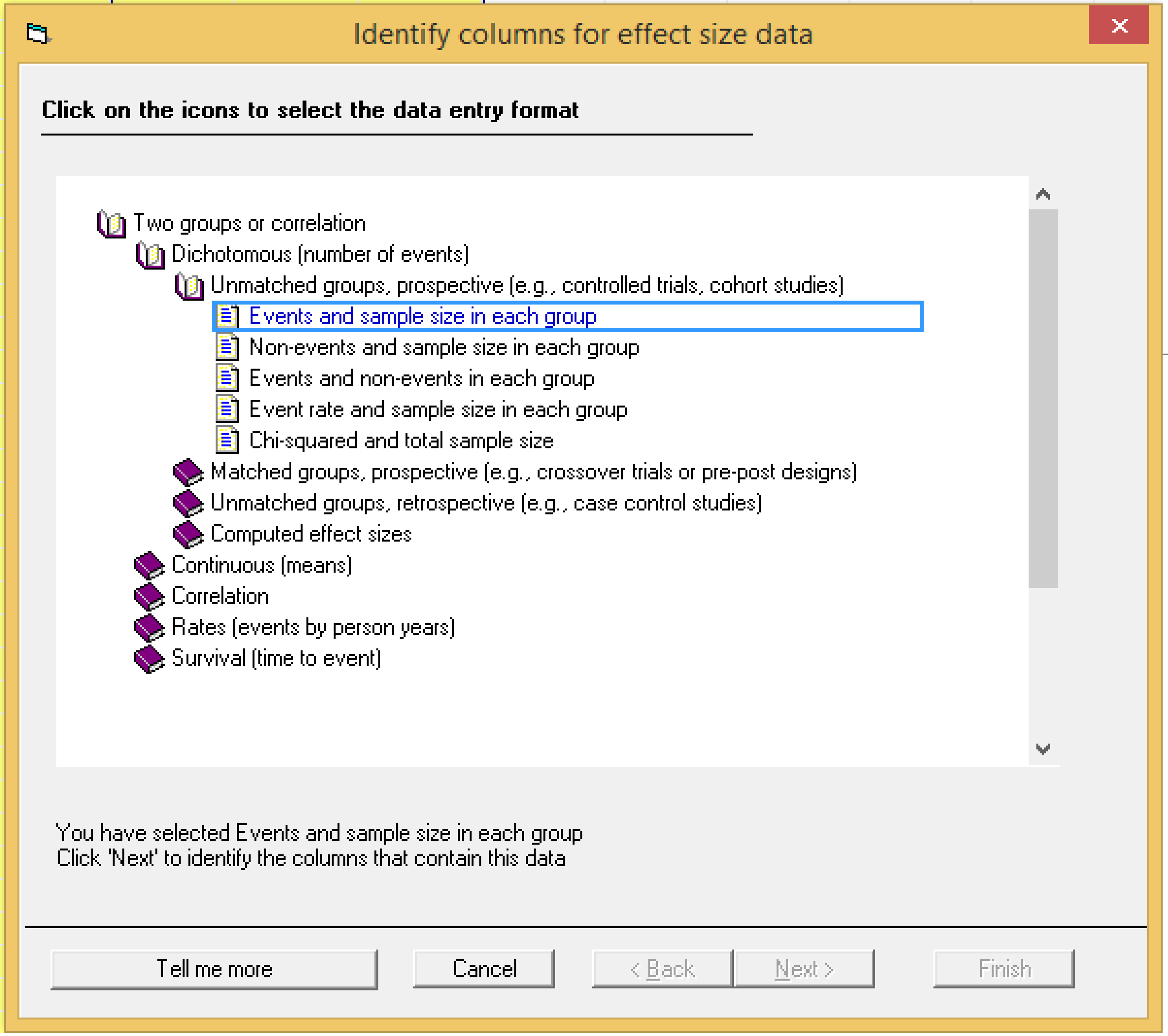
No. of events in each group

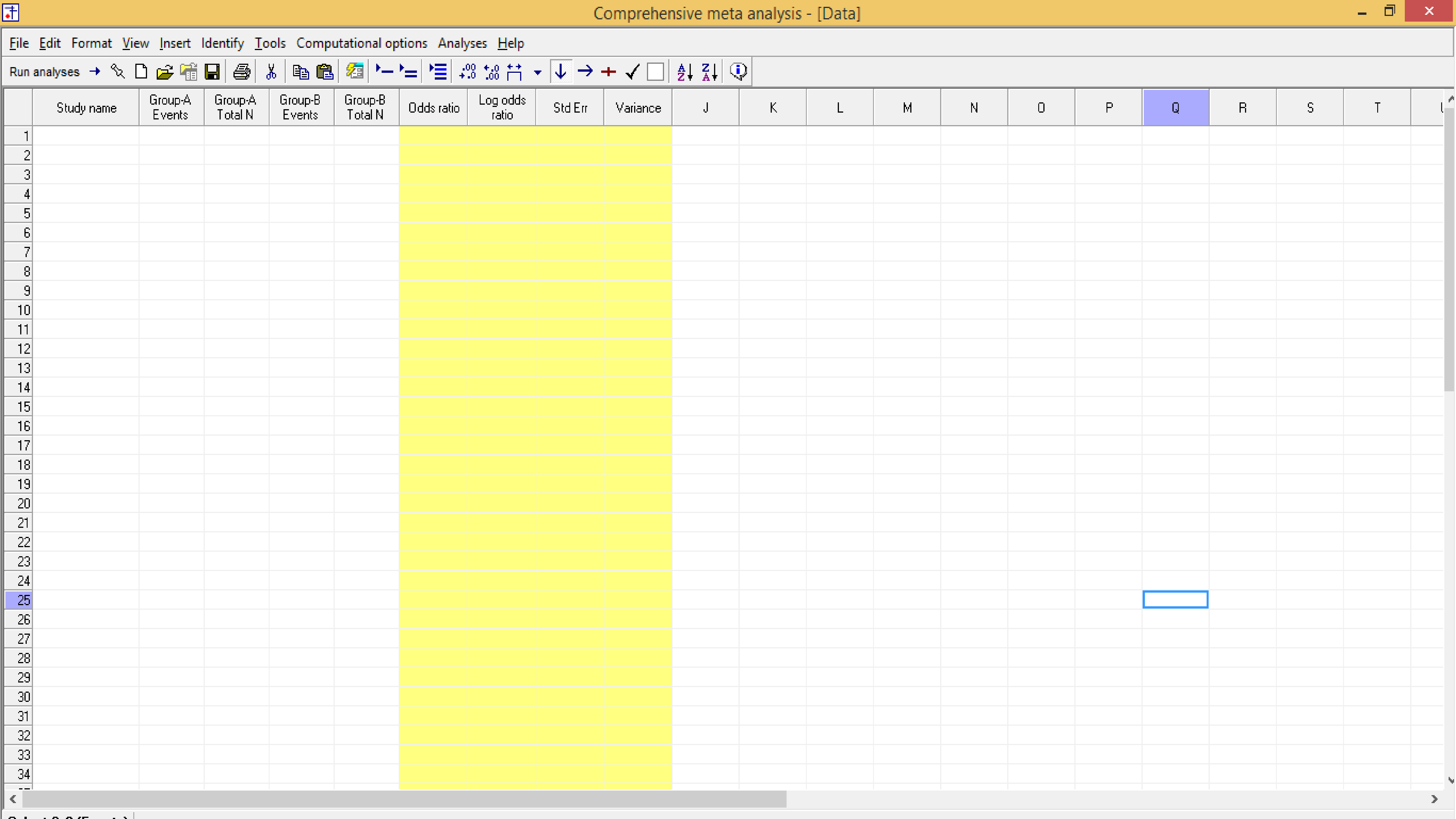
		Case	Control	N
Vaccine	+	4		123
	-	11		139


Comprehensive meta analysis - [Data]
File Edit Format View Insert Identify Tools Computational options Analyses Help
Run analyses
Column for ...
Study names
Subgroups within study
Comparison names
Outcome names
Time point names
Effect size data
Moderator variable
Comprehensive meta analysis - [Data]
File Edit Format View Insert Identify Tools Computational options Analyses Help
Run analyses
Study name


File Edit Format View Insert Identify Tools Computational options Analyses Help
Run analyses
Column for ...
Study names
Subgroups within study
Comparison names
Outcome names
Time point names
Effect size data
Moderator variable
Study name
B
C
D
G
H


Identify columns for effect size data
Types of studies included
On this panel, select the type of studies to be included in this meta analysis. This controls the types of data entry options to be displayed on the next panel.
If unsure, select the first option, which is appropriate for most analyses. You will be able to return to this panel and change the selection.
Comparison of two groups, time-points, or exposures (includes correlations)
Estimate of means, proportions or rates in one group at one time-point
Generic point estimates
Generic point estimates, log scale
Tell me more
Cancel
< Back
Next >
Finish


Identify columns for effect size data
Click on the icons to select the data entry format
Two groups or correlation
Dichotomous (number of events)
Unmatched groups, prospective (e.g., controlled trials, cohort studies)
Events and sample size in each group
Non-events and sample size in each group
Events and non-events in each group
Event rate and sample size in each group
Chi-squared and total sample size
Matched groups, prospective (e.g., crossover trials or pre-post designs)
Unmatched groups, retrospective (e.g., case control studies)
Computed effect sizes
Continuous (means)
Correlation
Rates (events by person years)
Survival (time to event)
You have selected Events and sample size in each group
Click 'Next' to identify the columns that contain this data
Tell me more
Cancel
< Back
Next >
Finish


Comprehensive meta analysis - [Data]
File Edit Format View Insert Identify Tools Computational options Analyses Help
Run analyses
Study name
Group-A Events
Group-A Total N
Group-B Events
Group-B Total N
Odds ratio
Log odds ratio
Std Err
Variance
J
K
L
M
N
O
P
Q
R
S
T

Copy and paste from excel to CMA

	A	B	C	D	E
1	study name	Vaccine	N vaccine	Control	N control
2	Aronson, 1948	4	123	11	139
3	Ferguson & Sir	6	306	29	303
4	Rosenthal, 196	3	231	11	220
5	Hart & Sutherl	62	13,598	248	12,867
6	Frimodt-Molle	33	5,069	47	5,808
7	Stein & Aronsc	180	1,541	372	1,451
8	Vandiviere, 19	8	2,545	10	629
9	Madras, 1980	505	88,391	499	88,391
10	Coetze & Berja	29	7,499	45	7,277
11	Rosenthal, 196	17	1,716	65	1,665
12	Comstock, 197	186	50,634	141	27,338
13	Comstock & W	5	2,498	3	2,341
14	Comstock, 197	27	16,913	29	17,854

	[study name]	Vaccine	N vaccine	Control	N control	Odds ratio	Log odds ratio	Std Err	Variance
1	Aronson, 1948	4	123	11	139	0.391	-0.939	0.598	0.357
2	Ferguson & Simes,	6	306	29	303	0.189	-1.666	0.456	0.208
3	Rosenthal, 1960	3	231	11	220	0.250	-1.386	0.658	0.433
4	Hart & Sutherland,	62	13598	248	12867	0.233	-1.456	0.143	0.020
5	Frimodt-Moller,	33	5069	47	5808	0.803	-0.219	0.228	0.052
6	Stein & Aronson,	180	1541	372	1451	0.384	-0.958	0.100	0.010
7	Vandiviere, 1973	8	2545	10	629	0.195	-1.634	0.476	0.227
8	Madras, 1980	505	88391	499	88391	1.012	0.012	0.063	0.004
9	Coetze & Berjak,	29	7499	45	7277	0.624	-0.472	0.239	0.057
10	Rosenthal, 1961	17	1716	65	1665	0.246	-1.401	0.275	0.075
11	Comstock, 1974	186	50634	141	27338	0.711	-0.341	0.112	0.013
12	Comstock &	5	2498	3	2341	1.563	0.447	0.731	0.534
13	Comstock, 1976	27	16913	29	17854	0.983	-0.017	0.268	0.072

How does Meta-analysis work?

File Edit Format View Insert Identify Tools Computational options Analyses Help

Run analyses

	[study name]	Vaccine	N vaccine	Control	N control	Odds ratio	Log odds ratio	Std Err	Variance
1	Ferguson & Simes,	6	306	29	303	0.189	-1.666	0.456	0.208
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11	Comstock, 1976	27	16913	29	17854	[illegible]	-0.017	0.268	0.072
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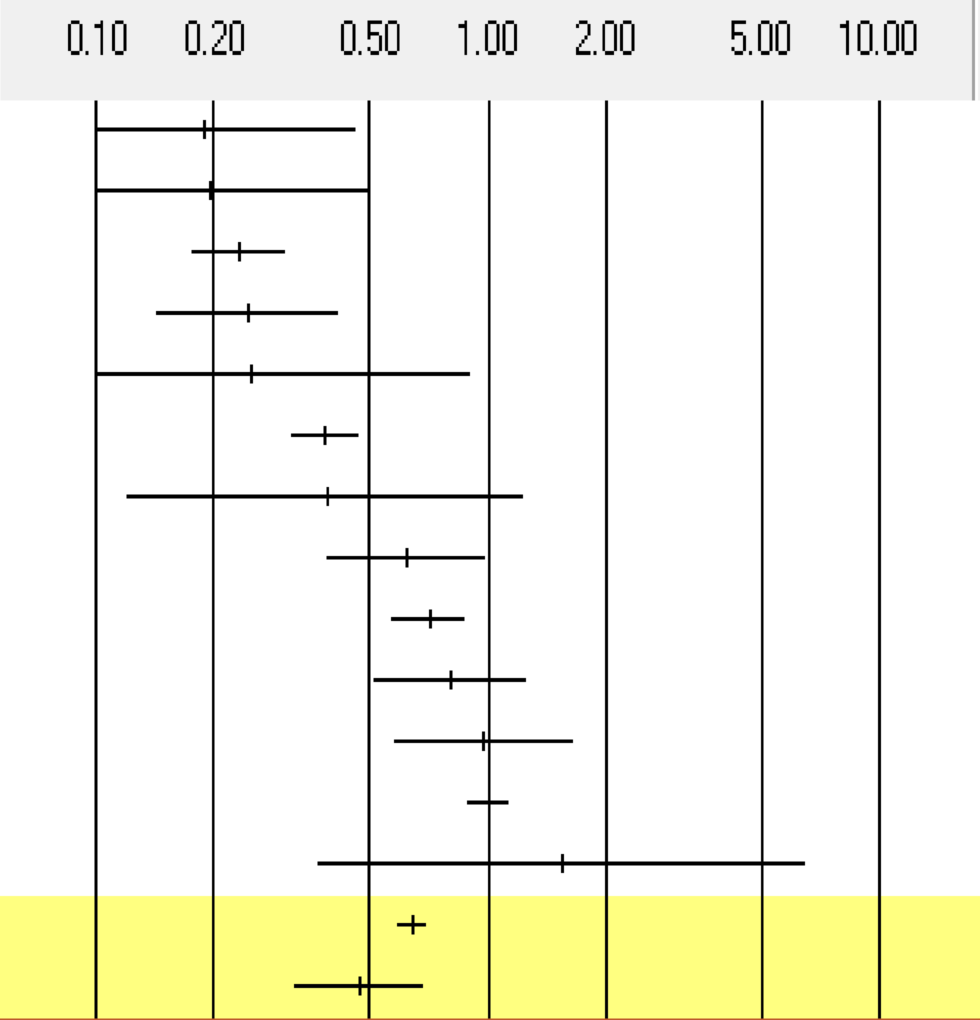
13	Comstock &	5	2498	3	2341	1.563	0.447	0.731	0.534

File Edit Format View Computational options Analyses Help

← Data entry | Next table | High resolution plot | Select by ... | + Effect measure: Odds ratio

Model	[study name]	Statistics for each study				
		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Ferguson &	0.189	0.077	0.462	-3.652	0.000
	Vandiviere,	0.195	0.077	0.497	-3.429	0.001
	Hart &	0.233	0.176	0.308	-10.219	0.000
	Rosenthal,	0.246	0.144	0.422	-5.102	0.000
	Rosenthal,	0.250	0.069	0.908	-2.106	0.035
	Stein &	0.384	0.316	0.466	-9.627	0.000
	Aronson,	0.391	0.121	1.262	-1.571	0.116
	Coetze &	0.624	0.391	0.996	-1.976	0.048
	Comstock,	0.711	0.571	0.886	-3.046	0.002
	Frimodt-Moll	0.803	0.514	1.256	-0.961	0.336
	Comstock,	0.983	0.582	1.661	-0.065	0.948
	Madras,	1.012	0.894	1.146	0.190	0.849
	Comstock &	1.563	0.373	6.548	0.611	0.541
Fixed		0.647	0.595	0.702	-10.319	0.000
Random		0.474	0.325	0.690	-3.887	0.000

Odds ratio and 95% CI



Model	[study name]	Statistics for each study					Odds ratio and 95% CI
		Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
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	Rosenthal, 1960	0.250	0.069	0.908	-2.106	0.035	
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	Comstock & Webster, 1969	1.563	0.373	6.548	0.611	0.541	
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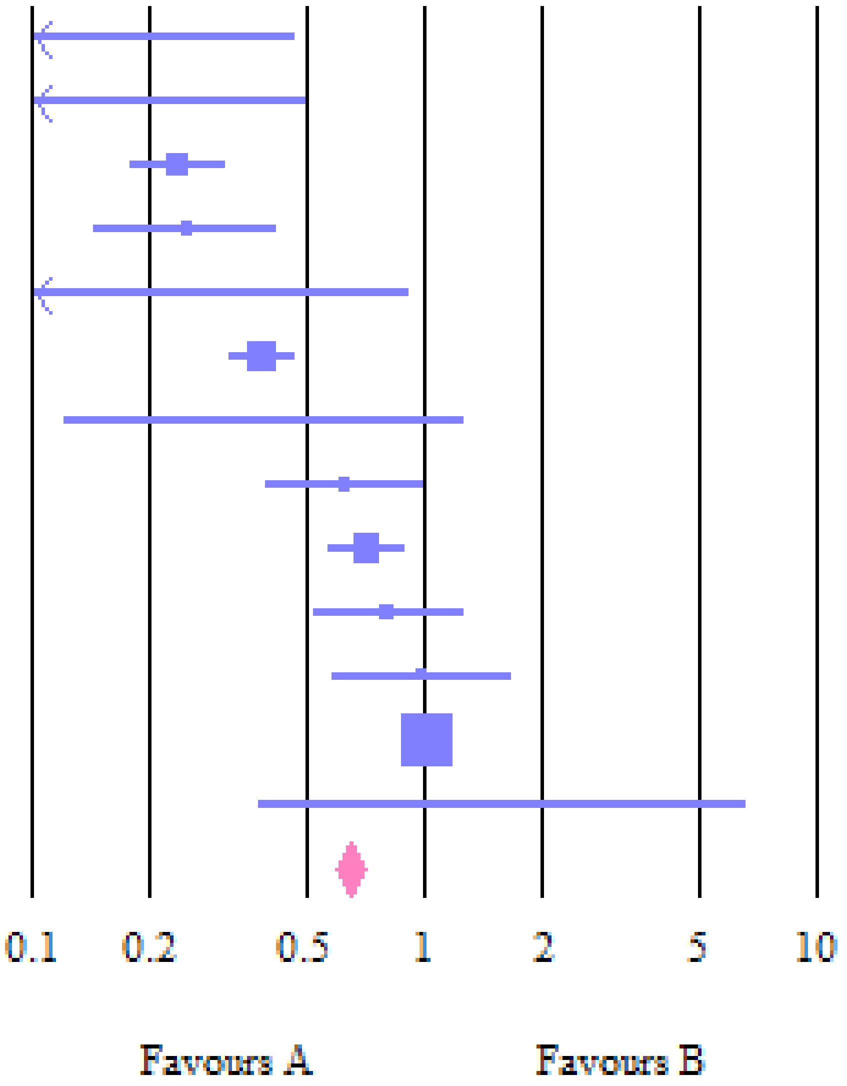


Fixed vs. Random effect

FE. Assumes a common underlying effect behind every trial

One source of variation:

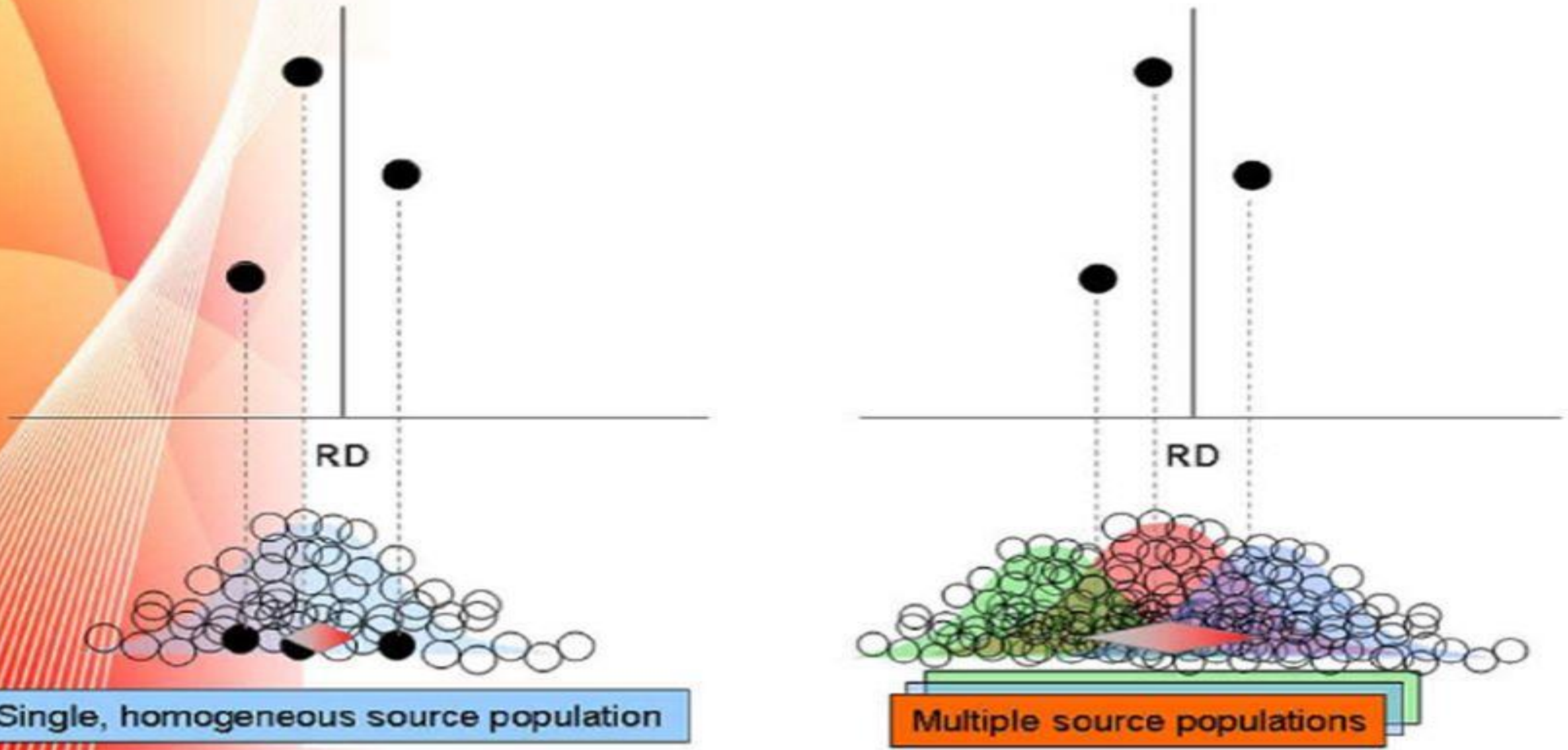
- **within studies (between patients)**

RE. Assume true effect estimates really vary across studies

Two sources of variation:

- **within studies (between patients)**
- **between studies (heterogeneity)**

Fixed and random effects models



Courtesy: Leon Bax, http://www.mix-for-meta-analysis.info/index.html#

Selection of the Model

- The selection of a model must be based solely on the question of which model fits the distribution of effect sizes, and takes account of the relevant source(s) of error.
- When studies are gathered from the published literature, the random effects model is generally a more plausible match
- The strategy of starting with a fixed-effect model and then moving to a random-effects model if the test for heterogeneity is significant is a mistake, and should be strongly discouraged

File Edit Format View Computational options Analyses Help

Data entry | Next table | High resolution plot | Select by ... | Effect measure: Odds ratio

Model		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	13	0.647	0.595	0.702	-10.319	0.000	163.165	12	0.000	92.645	0.366	0.266	0.071	0.605
Random	13	0.474	0.325	0.690	-3.887	0.000								

H_0: Odds ratio=1

H_1: Odds ratio≠1

Assessing statistical heterogeneity

If there is substantial heterogeneity among studies in a systematic review, it might be inappropriate to do a meta-analysis

How do we know if there is ‘substantial’ heterogeneity?

- 1. Visual inspection of a forest plot of studies included in the review;
- 2. Assessment of results of tests for statistical heterogeneity.

Statistical tests for heterogeneity

Cochran Q (Chi-square, X^2)

I^2

Tau^2

$$Q = \sum_{i=1}^{k} W_i (Y_i - M)^2$$

Cochran Q (Chi-square, X^2)

Under null, it is approximately distributed as a chi-square with k-1 degrees of freedom

Not powerful when number of studies is small or within study variance is large

It can not be used to estimate the magnitude of true variance

Quantifying heterogeneity, I

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%,$$

- **Q-df is the excess variation. The part that will be attributed to differences in the true effects from study to study**
- **The ratio of true heterogeneity to total observed variation**
- **Describes the percentage of total variation across studies that is due to heterogeneity rather than chance**
- **Not directly affect by the number of studies**
- **A value of 0% indicates no observed heterogeneity**
- **Low, moderate, large and very large for 0-25%, 25-50%, 50-75% and >75%**

Model		Effect size and 95% interval			Test of null (2-Tail)		Heterogeneity				Tau-squared			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Q-value	df (Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
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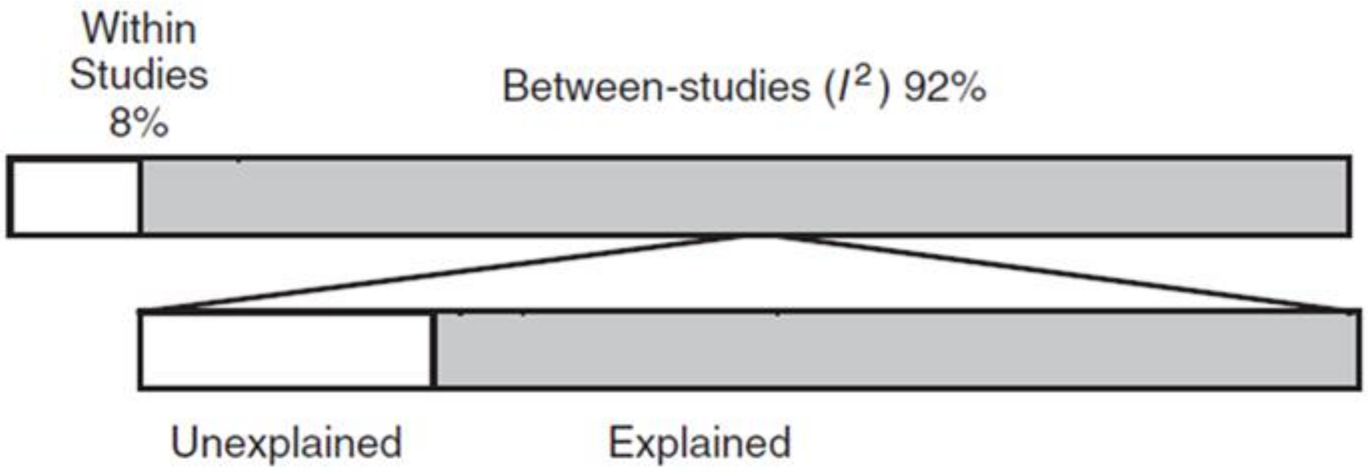


Figure Proportion of variance explained by latitude.

Tau (τ^2)

The variance of the true effect sizes, where τ^2 refers to the actual variance and T^2 is our estimate of this parameter

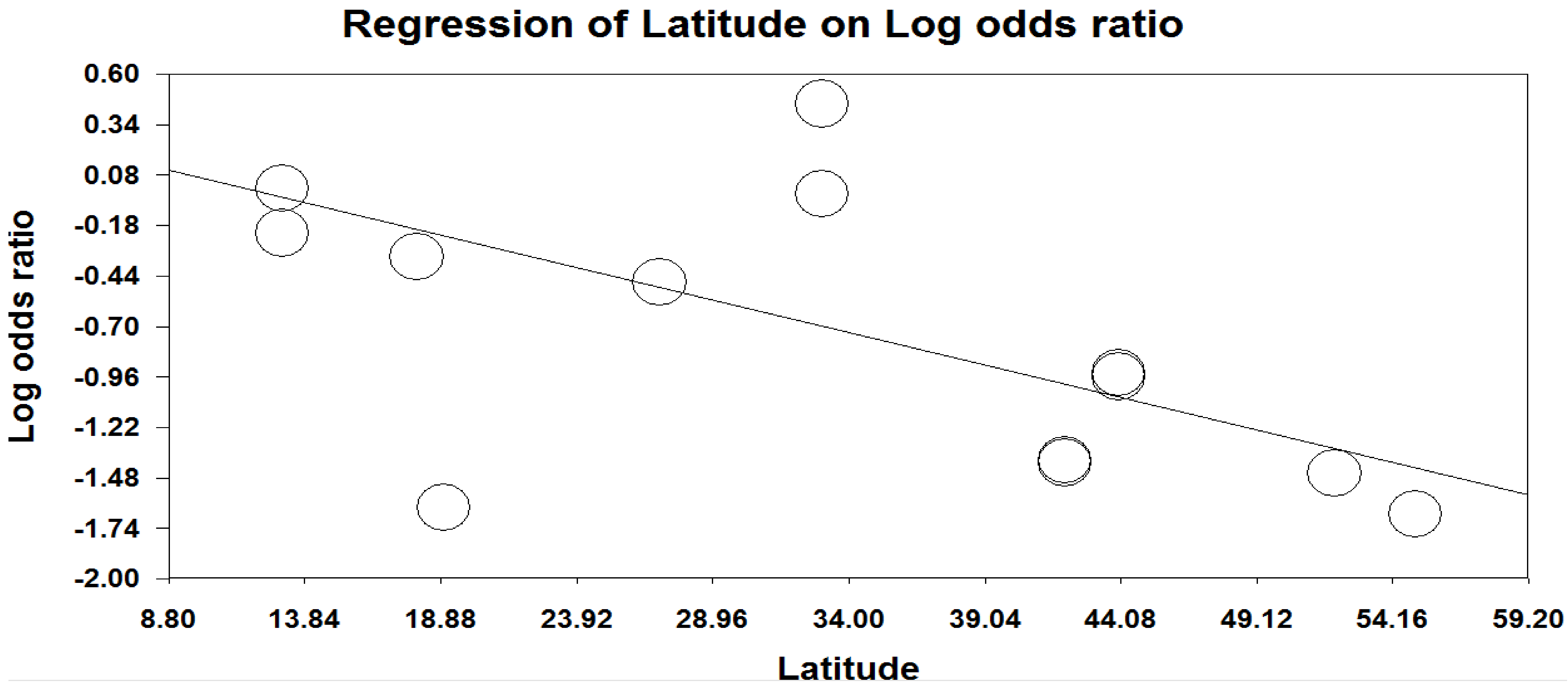
Factors affecting measures of dispersion.

	Range of possible values	Depends on number of studies	Depends on scale
Q	$0 \leq Q$	✓	
p	$0 \leq p \leq 1$	✓	
T^2	$0 \leq T^2$		✓
T	$0 \leq T$		✓
I^2	$0\% \leq I^2 < 100\%$		

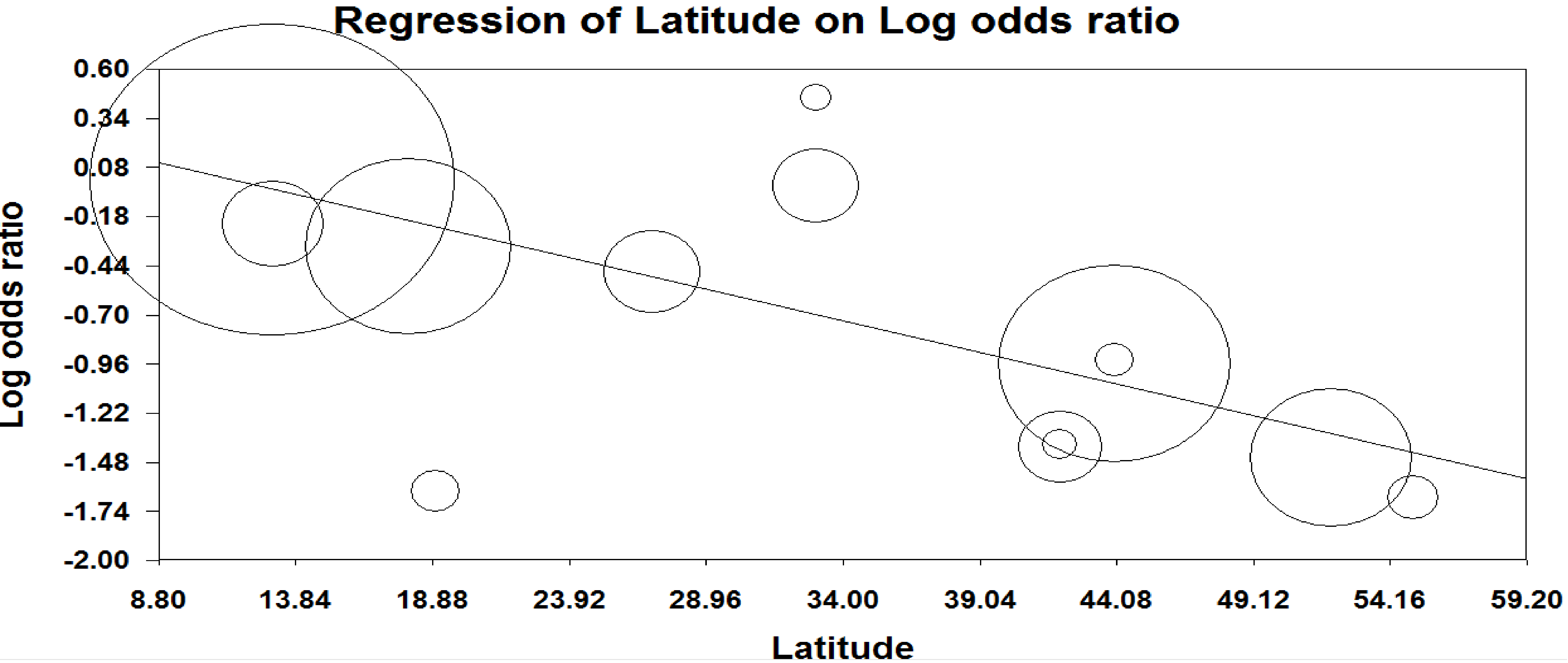
Q5. Meta regression
BCG vaccine and prevent of tuberculosis

This module allows you to run a regression analysis to estimate the impact of continuous study moderators on overall heterogeneity

In this example, there is a numeric variable as latitude



- In the default presentation, all studies are represented by circles of identical size, regardless of their individual weighting in the analysis



Proportional option identifies which studies have the greatest impact on the slope of the regression line.

Fixed effect regression

	Point estimate	Standard error	Lower limit	Upper limit	Z-value	p-Value
Slope	-0.03310	0.00282	-0.03862	-0.02758	-11.75030	0.00000
Intercept	0.39490	0.08239	0.23342	0.55639	4.79296	0.00000
Tau-squared	0.04799					

	Q	df	p-value
Model	138.06950	1.00000	0.00000
Residual	25.09542	11.00000	0.00883
Total	163.16492	12.00000	0.00000

The regression coefficient for latitude is -0.0331, which means that every one degree of latitude corresponds to a decrease of 0.0331 units in effect size

The null hypothesis for Z:

- H0: Coefficient=0

Q_{model} is the dispersion explained by the covariates.

Q_{res} means that even with latitude in the model, some of the between-studies variance remains unexplained.

The proportion of variance explained

$$R^2 = 1 - \left(\frac{\sigma^2_{unexplained}}{\sigma^2_{total}} \right)$$

$R^2 = 1 - \frac{0.04799}{0.366}$=0.87

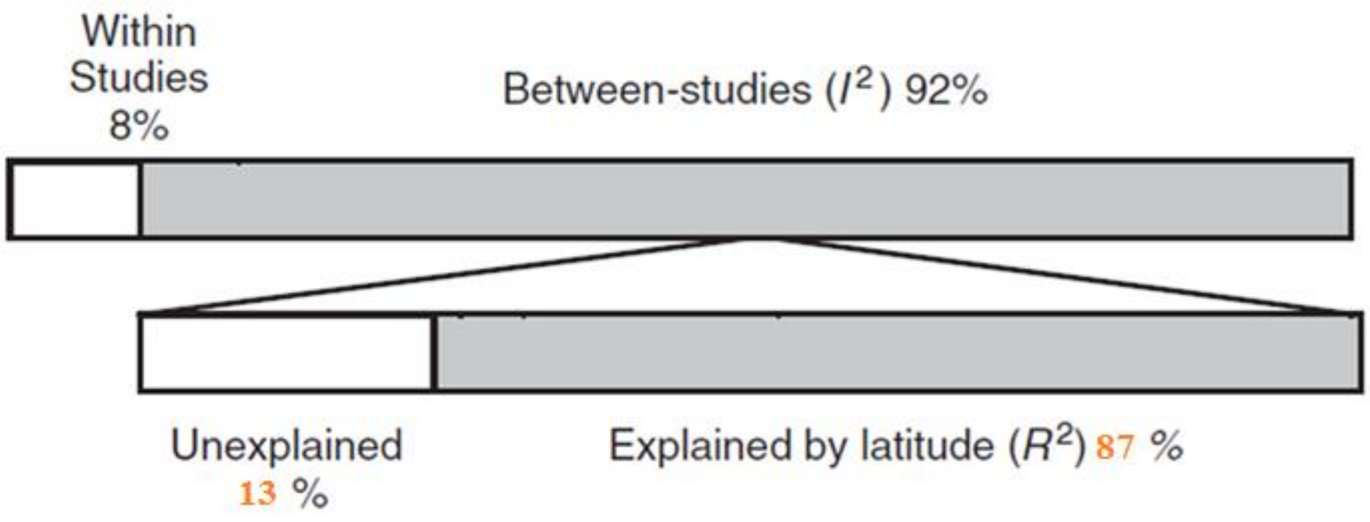


Figure Proportion of variance explained by latitude.

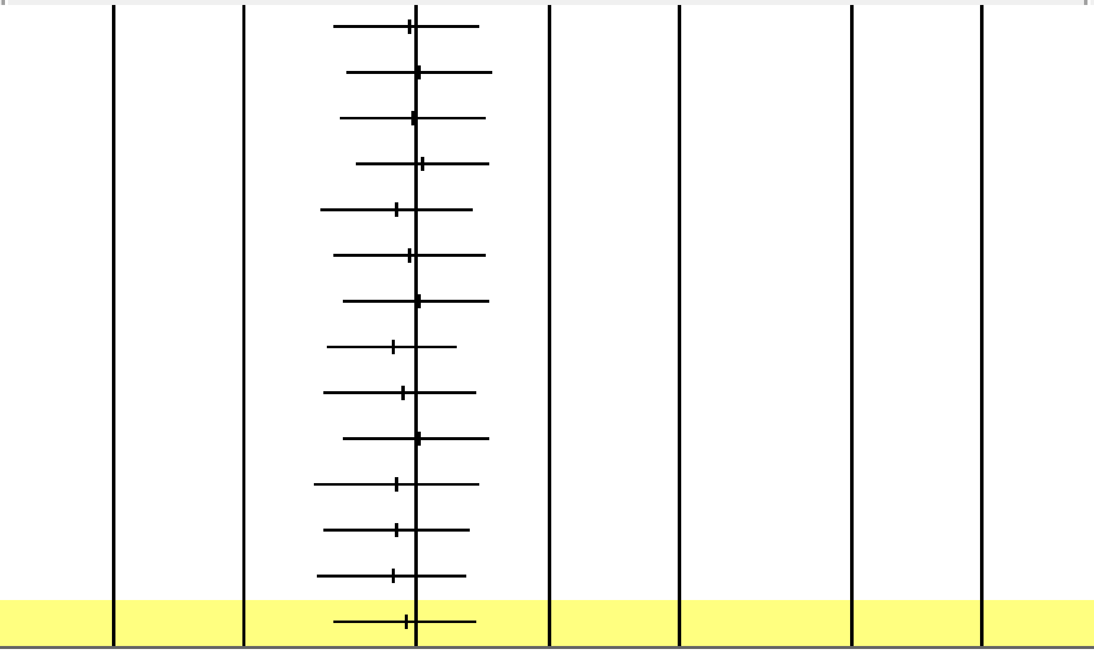
One-study removed

It will also run a one-study removed analysis to show the impact of each study on the combined effect

File Edit Format View Computational options Analyses Help

Data entry | Next table | High resolution plot | Select by ... | Effect measure: Odds ratio

Model	Study name	Summary statistics with one study removed					Odds ratio (95% CI) with study removed
		Point	Lower limit	Upper limit	Z-Value	p-Value	0.10 0.20 0.50 1.00 2.00 5.00 10.00
	Aronson,	0.478	0.324	0.706	-3.720	0.000	
	Ferguson &	0.505	0.343	0.742	-3.480	0.001	
	Rosenthal,	0.488	0.332	0.718	-3.639	0.000	
	Hart &	0.517	0.364	0.736	-3.670	0.000	
	Frimodt-Moll	0.449	0.300	0.673	-3.878	0.000	
	Stein &	0.483	0.321	0.727	-3.489	0.000	
	Vandiviere,	0.503	0.342	0.739	-3.499	0.000	
	Madras,	0.438	0.311	0.617	-4.717	0.000	
	Coetze &	0.461	0.307	0.690	-3.759	0.000	
	Rosenthal,	0.503	0.342	0.741	-3.473	0.001	
	Comstock,	0.451	0.291	0.700	-3.555	0.000	
	Comstock &	0.450	0.306	0.661	-4.063	0.000	
	Comstock,	0.442	0.297	0.659	-4.005	0.000	
Random		0.474	0.325	0.690	-3.887	0.000	



Format: Abstract ▾ Send to ▾

Proc Biol Sci. 2004 Sep 22;271(1551):1961-6.

Cumulative meta-analysis: a new tool for detection of temporal trends and publication bias in ecology.

Leimu R[1], Koricheva J.

Author information

Abstract

Temporal changes in the magnitude of research findings have recently been recognized as a general phenomenon in ecology, and have been attributed to the delayed publication of non-significant results and disconfirming evidence. Here we introduce a method of cumulative meta-analysis which allows detection of both temporal trends and publication bias in the ecological literature. To illustrate the application of the method, we used two datasets from recently conducted meta-analyses of studies testing two plant defence theories. Our results revealed three phases in the evolution of the treatment effects. Early studies strongly supported the hypothesis tested, but the magnitude of the effect decreased considerably in later studies. In the latest studies, a trend towards an increase in effect size was observed. In one of the datasets, a cumulative meta-analysis revealed publication bias against studies reporting disconfirming evidence; such studies were published in journals with a lower impact factor compared to studies with results supporting the hypothesis tested. Correlation analysis revealed neither temporal trends nor evidence of publication bias in the datasets analysed. We thus suggest that cumulative meta-analysis should be used as a visual aid to detect temporal trends and publication bias in research findings in ecology in addition to the correlative approach.

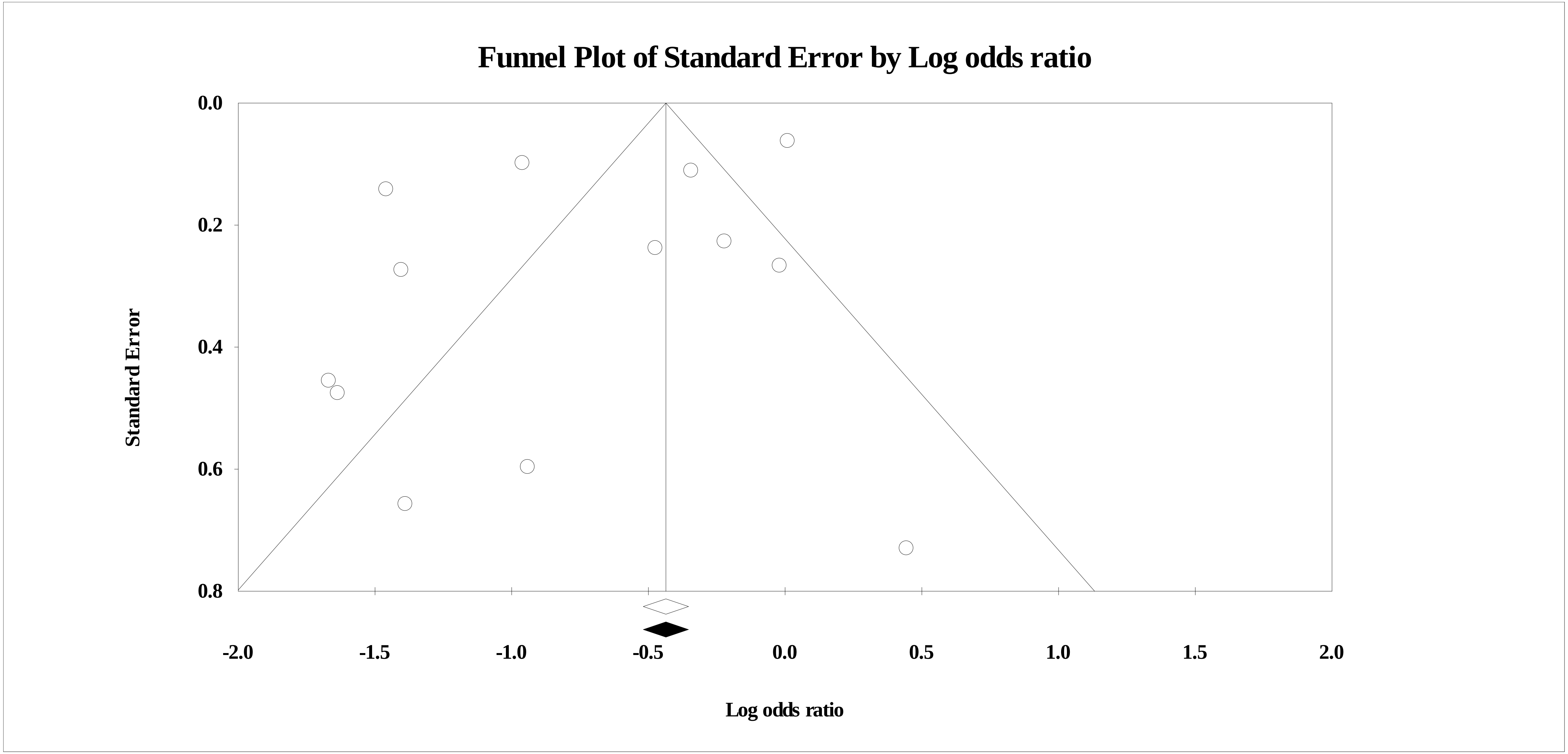
PMID: 15347521 PMCID: PMC1691819 DOI: 10.1098/rspb.2004.2828

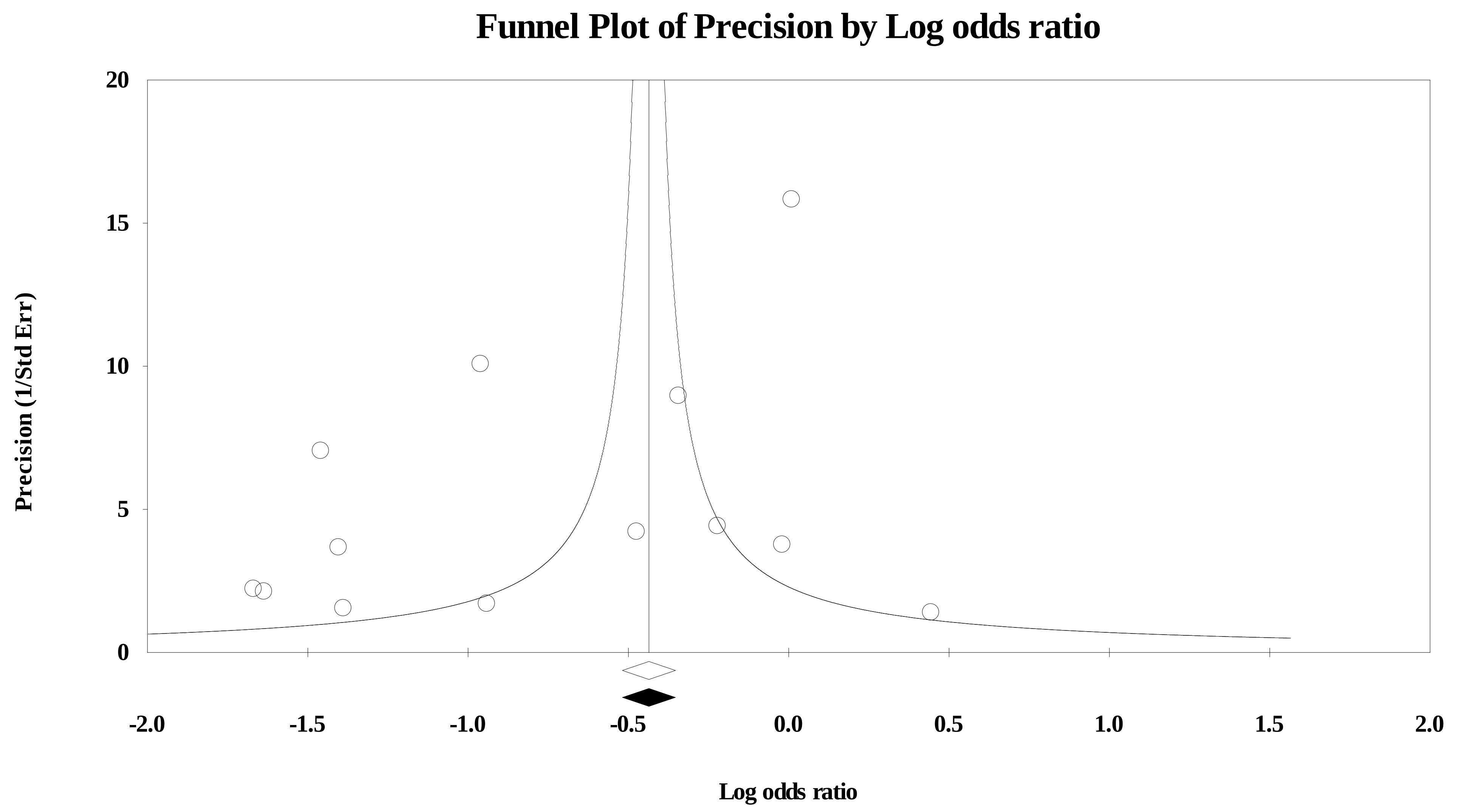
[Indexed for MEDLINE] Free PMC Article

How to check publication bias?

Graphical

Statistical test


Funnel Plot of Standard Error by Log odds ratio
Standard Error
0.0
0.2
0.4
0.6
0.8
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
Log odds ratio


Funnel Plot of Precision by Log odds ratio
20
15
10
5
0
Precision (1/Std Err)
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
2.0
Log odds ratio

Publication bias: Classic fail-safe N

Classic fail-safe N

Z-value for observed studies	-11.35821
P-value for observed studies	0.00000
Alpha	0.05000
Tails	2.00000
Z for alpha	1.95996
Number of observed studies	13.00000
Number of missing studies that would bring p-value to > alpha	424.00000

Edit

Orwin's fail-safe N

Odds ratio in observed studies	0.64653
Criterion for a 'trivial' odds ratio	0.70000
Mean odds ratio in missing studies	1.00000
Number missing studies needed to bring odds ratio over 0.7	3.00000

Edit

One concern of publication bias is that some non-significant studies are missing from our analysis and that these studies, if included, would nullify the observed effect

The fail-safe N is 424. This means that we would need to locate and include 424 'null' studies in order for the combined 2-tailed p-value to exceed 0.050

Publication bias: Begg and Mazumdar Rank Correlation Test

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	2.00000
Kendall's tau without continuity correction	
Tau	0.02564
z-value for tau	0.12202
P-value (1-tailed)	0.45144
P-value (2-tailed)	0.90288
Kendall's tau with continuity correction	
Tau	0.01282
z-value for tau	0.06101
P-value (1-tailed)	0.47568
P-value (2-tailed)	0.95135

The correlation (Kendall's tau) between the treatment effect and the standard error

A significant correlation suggests that bias exists

Conversely, a non-significant correlation may be due to low statistical power, and cannot be taken as evidence that bias is absent.

Publication Bias: Egger's Test of the Intercept

Egger's regression intercept

Intercept	-2.34534
Standard error	1.55635
95% lower limit (2-tailed)	-5.77084
95% upper limit (2-tailed)	1.08016
t-value	1.50695
df	11.00000
P-value (1-tailed)	0.08000
P-value (2-tailed)	0.15999

Egger suggests that we assess this same bias by using precision (the inverse of the standard error) to predict the standardized effect (effect size divided by the standard error).

In this equation, the size of the treatment effect is captured by the slope of the regression line (B1) while bias is captured by the intercept (B0).

Publication bias: Duval and Tweedie's Trim and Fill

If the meta analysis had captured all the relevant studies we would expect the funnel plot to be symmetric

Duval and Tweedie developed a method that allows us to impute missed studies. That is, we determine where the missing studies are likely to fall, add them to the analysis, and then recompute the combined effect

In our example, using Trim and Fill these values are unchanged

Publication bias: Duval and Tweedie's Trim and Fill

Duval and Tweedie's trim and fill

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0.64653	0.59513	0.70237	0.47360	0.32490	0.69035	163.16492
Adjusted values	0	0.64653	0.59513	0.70237	0.47360	0.32490	0.69035	163.16492

Look for missing studies where?

- ○ Not specified
- ◉ To left of mean
- ○ To right of mean

Look for missing studies using which model?

- ○ Not specified
- ◉ Fixed effect model
- ○ Random effects model

Q2: Protective vaccination against tuberculosis, with special reference to BCG vaccine

Total retrieved same studies: 13

Seven studies reported No. of events in each group

Three studies reported Odds ratio and 95% CI

Three studies reported log OR and SE

How to combine these findings?

Import the data from excel (sheet Q2) to CMA

	Study name	Data format	Group-A Events	Group-A Total N	Group-B Events	Group-B Total N	Odds ratio	Lower Limit	Upper Limit	Confidence level	Odds ratio (log)	Std error (log)	Odds ratio	Log odds ratio	Std Err	Variance
1	Aronson, 1948	Cohort 2x2 (Events)	4	123	11	139							0.391	-0.939	0.598	0.357
2	Ferguson & Simes,	Cohort 2x2 (Events)	6	306	29	303							0.189	-1.666	0.456	0.208
3	Rosenthal, 1960	Cohort 2x2 (Events)	3	231	11	220							0.250	-1.386	0.658	0.433
4	Hart & Sutherland,	Cohort 2x2 (Events)	62	13598	248	12867							0.233	-1.456	0.143	0.020
5	Frimodt-Moller,	Cohort 2x2 (Events)	33	5069	47	5808							0.803	-0.219	0.228	0.052
6	Stein & Aronson,	Cohort 2x2 (Events)	180	1541	372	1451							0.384	-0.958	0.100	0.010
7	Vandiviere, 1973	Cohort 2x2 (Events)	8	2545	10	629							0.195	-1.634	0.476	0.227
8	Madras, 1980	Odds ratio					1.012	0.894	1.146	0.950			1.012	0.012	0.063	0.004
9	Coetze & Berjak,	Odds ratio					0.624	0.391	0.996	0.950			0.624	-0.472	0.239	0.057
10	Rosenthal, 1961	Odds ratio					0.246	0.144	0.422	0.950			0.246	-1.402	0.274	0.075
11	Comstock, 1974	Log OR, SE									-0.341	0.112	0.711	-0.341	0.112	0.013
12	Comstock &	Log OR, SE									0.447	0.731	1.563	0.447	0.731	0.534
13	Comstock, 1976	Log OR, SE									-0.017	0.268	0.983	-0.017	0.268	0.072

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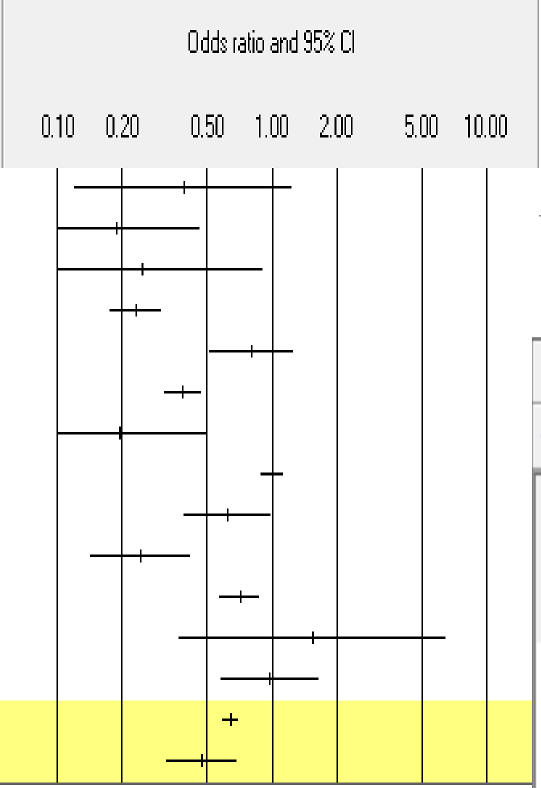
← Data entry | Next table | High resolution plot | Select by ... | + Effect measure: Odds ratio

Model	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Aronson,	0.391	0.121	1.262	-1.571	0.116
	Ferguson &	0.189	0.077	0.462	-3.652	0.000
	Rosenthal,	0.250	0.069	0.908	-2.106	0.035
	Hart &	0.233	0.176	0.308	-10.219	0.000
	Frimodt-Moll	0.803	0.514	1.256	-0.961	0.336
	Stein &	0.384	0.316	0.466	-9.627	0.000
	Vandiviere,	0.195	0.077	0.497	-3.429	0.001
	Madras,	1.012	0.894	1.146	0.188	0.851
	Coetze &	0.624	0.391	0.996	-1.977	0.048
	Rosenthal,	0.246	0.144	0.421	-5.113	0.000
	Comstock,	0.711	0.571	0.886	-3.046	0.002
	Comstock &	1.563	0.373	6.548	0.611	0.541
	Comstock,	0.983	0.582	1.661	-0.065	0.948
Fixed		0.646	0.595	0.702	-10.326	0.000
Random		0.474	0.325	0.690	-3.888	0.000

(Statistics for each study)



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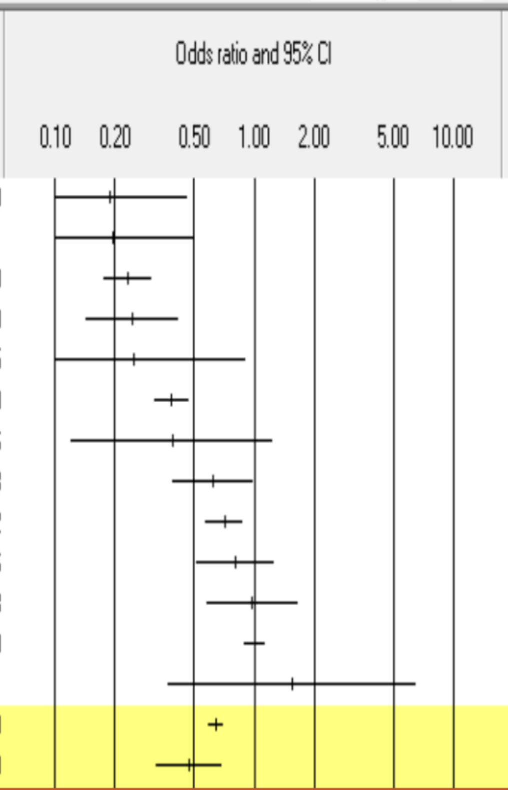
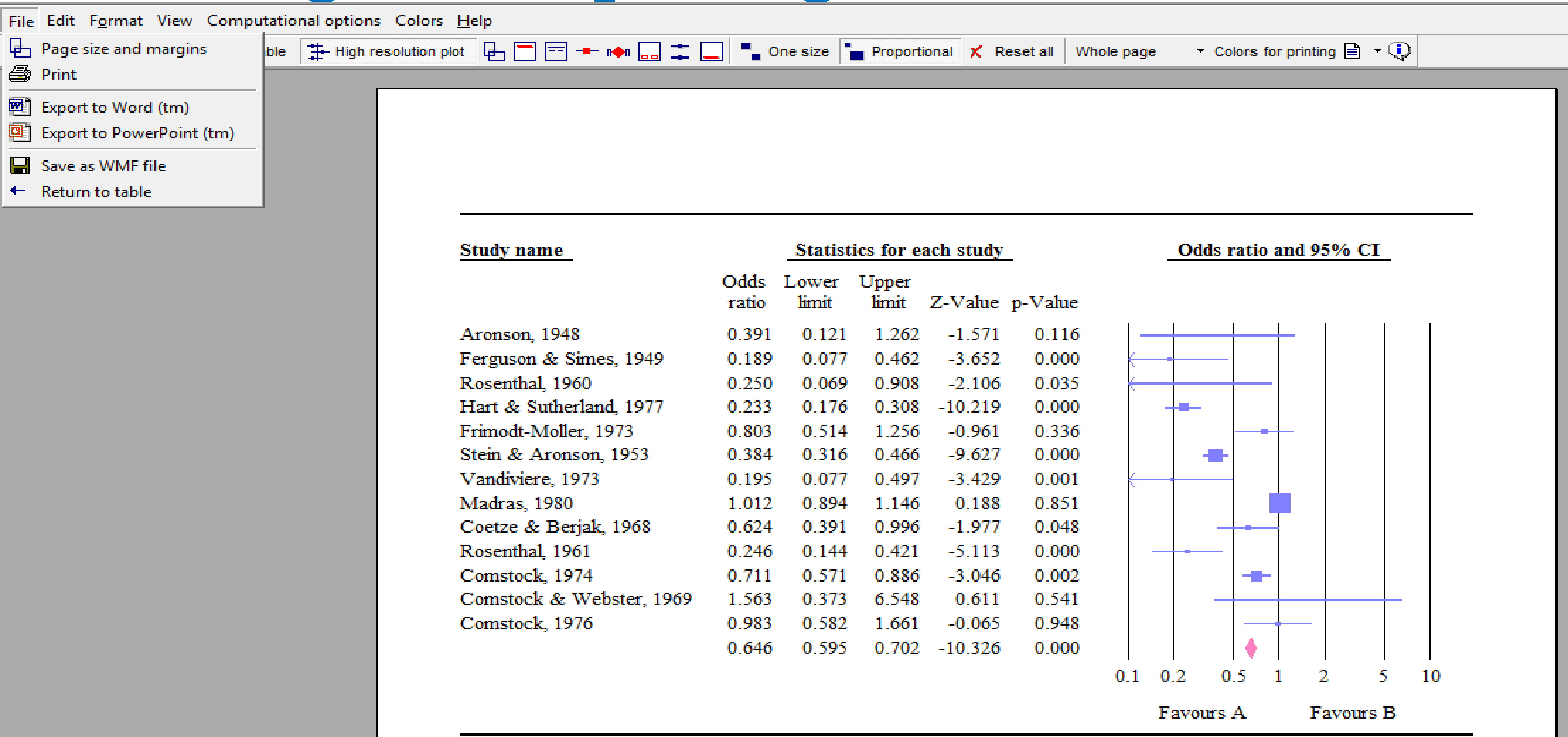
Model	[study name]	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Ferguson &	0.189	0.077	0.462	-3.652	0.000
	Vandiviere,	0.195	0.077	0.497	-3.429	0.001
	Hart &	0.233	0.176	0.308	-10.219	0.000
	Rosenthal,	0.246	0.144	0.422	-5.102	0.000
	Rosenthal,	0.250	0.069	0.908	-2.106	0.035
	Stein &	0.384	0.316	0.466	-9.627	0.000
	Aronson,	0.391	0.121	1.262	-1.571	0.116
	Coetze &	0.624	0.391	0.996	-1.976	0.048
	Comstock,	0.711	0.571	0.886	-3.046	0.002
	Frimodt-Moll	0.803	0.514	1.256	-0.961	0.336
	Comstock,	0.983	0.582	1.661	-0.065	0.948
	Madras,	1.012	0.894	1.146	0.190	0.849
	Comstock &	1.563	0.373	6.548	0.611	0.541
Fixed		0.647	0.595	0.702	-10.319	0.000
Random		0.474	0.325	0.690	-3.887	0.000

(Statistics for each study)



Saving and Exporting



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Statistics for each study				
Aronson, 1948	0.391	0.121	1.262	-1.571	0.116
Ferguson & Simes, 1949	0.189	0.077	0.462	-3.652	0.000
Rosenthal, 1960	0.250	0.069	0.908	-2.106	0.035
Hart & Sutherland, 1977	0.233	0.176	0.308	-10.219	0.000
Frimodt-Moller, 1973	0.803	0.514	1.256	-0.961	0.336
Stein & Aronson, 1953	0.384	0.316	0.466	-9.627	0.000
Vandiviere, 1973	0.195	0.077	0.497	-3.429	0.001
Madras, 1980	1.012	0.894	1.146	0.188	0.851
Coetze & Berjak, 1968	0.624	0.391	0.996	-1.977	0.048
Rosenthal, 1961	0.246	0.144	0.421	-5.113	0.000
Comstock, 1974	0.711	0.571	0.886	-3.046	0.002
Comstock & Webster, 1969	1.563	0.373	6.548	0.611	0.541
Comstock, 1976	0.983	0.582	1.661	-0.065	0.948
	0.646	0.595	0.702	-10.326	0.000

Q3. Subgroups within study

Streptokinase therapy and myocardial infarction

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Run analyses

	Study name	Subgroup within study	Treated Events	Treated Total N	Control Events	Control Total N	Odds ratio	Log odds ratio	Std Err	J
1	Fletcher	Both	1	12	4	11	0.159	-1.838	1.218	
2	Dewar	Female	2	10	4	10	0.375	-0.981	1.021	
3		Male	2	11	3	11	0.593	-0.523	1.034	
4	1st European	Female	11	40	7	42	1.897	0.640	0.545	
5		Male	9	43	8	42	1.125	0.118	0.543	
6	Heikinheimo	Female	12	100	9	105	1.455	0.375	0.465	
7		Male	10	119	8	102	1.078	0.075	0.495	
8	Italian	Both	19	164	18	157	1.012	0.012	0.350	
9	2nd European	Female	37	150	46	177	0.932	-0.070	0.255	
10		Male	32	223	48	180	0.461	-0.775	0.255	
11	2nd Frankfurt	Both	13	102	29	104	0.378	-0.973	0.369	
12	1st Australian	Female	12	135	16	124	0.659	-0.418	0.404	
13		Male	14	129	16	129	0.860	-0.151	0.389	
14	NHLBI SMIT	Both	7	53	3	54	2.587	0.950	0.719	
15	Valere	Both	11	49	9	42	1.061	0.060	0.509	
16	Frank	Both	6	55	6	53	0.959	-0.042	0.612	
17	UK Collab	Female	27	150	25	141	1.019	0.018	0.306	
18		Male	21	152	27	152	0.742	-0.298	0.317	
19	Klein	Both	4	14	1	9	3.200	1.163	1.214	
20	Austrian	Female	18	170	32	180	0.548	-0.602	0.316	
21		Male	19	182	33	196	0.576	-0.552	0.309	
22	Lasierra	Both	1	13	3	11	0.222	-1.504	1.242	
23	N German	Female	34	125	24	120	1.495	0.402	0.304	
24		Male	29	124	27	114	0.984	-0.017	0.306	
25	Witchitz	Both	5	32	5	26	0.778	-0.251	0.696	
26	2nd Australian	Both	25	112	31	118	0.806	-0.215	0.309	
27	3rd European	Both	25	156	50	159	0.416	-0.877	0.277	
28	ISAM	Both	54	859	63	882	0.872	-0.137	0.192	
29	GISSI-1	Female	321	2939	381	2922	0.818	-0.201	0.081	
30		Male	327	2921	377	2930	0.854	-0.158	0.081	

Comprehensive meta analysis - [Analysis]

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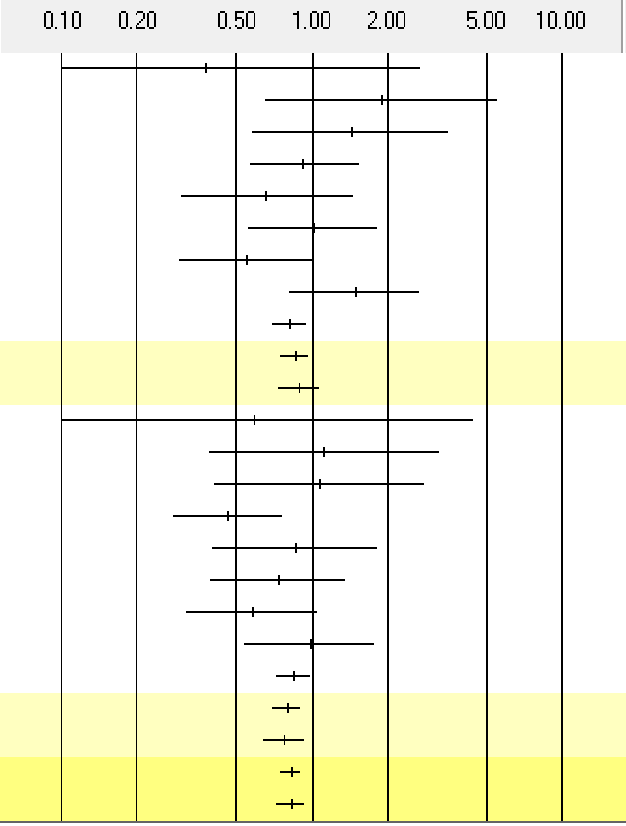
Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study				
				Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
	Female	Dewar	Female	0.375	0.051	2.772	-0.961	0.337
	Female	1st	Female	1.897	0.652	5.517	1.175	0.240
	Female	Heikinheimo	Female	1.455	0.585	3.619	0.806	0.420
	Female	2nd	Female	0.932	0.565	1.538	-0.274	0.784
	Female	1st	Female	0.659	0.298	1.454	-1.034	0.301
	Female	UK Collab	Female	1.019	0.559	1.856	0.060	0.952
	Female	Austrian	Female	0.548	0.295	1.018	-1.902	0.057
	Female	N German	Female	1.495	0.823	2.712	1.321	0.186
	Female	GISSI-1	Female	0.818	0.698	0.958	-2.493	0.013
Fixed	Female			0.858	0.751	0.980	-2.251	0.024
Random	Female			0.890	0.738	1.073	-1.220	0.223
	Male	Dewar	Male	0.593	0.078	4.498	-0.506	0.613
	Male	1st	Male	1.125	0.388	3.262	0.217	0.828
	Male	Heikinheimo	Male	1.078	0.409	2.843	0.152	0.879
	Male	2nd	Male	0.461	0.280	0.759	-3.042	0.002
	Male	1st	Male	0.860	0.401	1.844	-0.388	0.698
	Male	UK Collab	Male	0.742	0.399	1.381	-0.942	0.346
	Male	Austrian	Male	0.576	0.314	1.054	-1.789	0.074
	Male	N German	Male	0.984	0.540	1.791	-0.054	0.957
	Male	GISSI-1	Male	0.854	0.729	1.000	-1.964	0.049
Fixed	Male			0.808	0.707	0.923	-3.136	0.002
Random	Male			0.778	0.645	0.939	-2.619	0.009
Fixed	Overall			0.832	0.757	0.915	-3.810	0.000
Random	Overall			0.832	0.729	0.950	-2.714	0.007

Odds ratio and 95% CI



Computational options

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Fully random effects analysis - A random effects model is used to combine studies within each subgroup. A random effects model is used to combine subgroups and yield the overall effect. The

Fixed | Random | **Both models**

Basic stats | Calculations

Q4. Multiple outcomes within studies

Streptokinase therapy and its outcomes

	Study name	Outcome	Treated Events	Treated Total N	Control Events	Control Total N	Odds ratio	Log odds ratio	Std Err
1	Fletcher	Death	1	12	4	11	0.159	-1.838	1.218
2	Fletcher	Myocardial	2	12	4	12	0.400	-0.916	0.987
3	1st Myocardial	Myocardial	51	277	87	327	0.623	-0.474	0.199
4	Dewar	Death	4	21	7	21	0.471	-0.754	0.723
5	Dewar	Myocardial	4	24	8	22	0.350	-1.050	0.705
6	1st European	Death	20	83	15	84	1.460	0.379	0.383
7	1st European	Myocardial	18	88	14	87	1.341	0.293	0.394
8	Heikinheimo	Death	22	219	17	207	1.248	0.222	0.339
9	Heikinheimo	Myocardial	23	244	16	200	1.197	0.180	0.340
10	Italian	Death	19	164	18	157	1.012	0.012	0.350
11	Italian	Myocardial	21	177	14	147	1.279	0.246	0.365
12	2nd European	Death	69	373	94	357	0.635	-0.454	0.180
13	2nd Frankfurt	Death	13	102	29	104	0.378	-0.973	0.369
14	1st Australian	Death	26	264	32	253	0.754	-0.282	0.280
15	1st Australian	Myocardial	29	277	29	248	0.883	-0.124	0.279
16	NHLBI SMIT	Death	7	53	3	54	2.587	0.950	0.719
17	Valere	Death	11	49	9	42	1.061	0.060	0.509
18	Frank	Death	6	55	6	53	0.959	-0.042	0.612
19	UK Collab	Death	48	302	52	293	0.876	-0.133	0.219
20	UK Collab	Myocardial	44	280	51	297	0.899	-0.106	0.225
21	Klein	Death	4	14	1	9	3.200	1.163	1.214
22	Klein	Myocardial	5	15	1	8	3.500	1.253	1.201
23	Austrian	Death	37	352	65	376	0.562	-0.576	0.221
24	Austrian	Myocardial	41	341	62	388	0.719	-0.330	0.217
25	Lasierra	Death	1	13	3	11	0.222	-1.504	1.242
26	N German	Death	63	249	51	234	1.215	0.195	0.215
27	Witchitz	Death	5	32	5	26	0.778	-0.251	0.696
28	Witchitz	Myocardial	4	28	5	24	0.633	-0.457	0.738
29	2nd Australian	Death	25	112	31	118	0.806	-0.215	0.309

Thank you for your attention