Meta-analysis & Systematic Review: An Introduction

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META-ANALYSIS

- **A statistical analysis of results from separate studies**, examining sources of differences in results among studies, and **leading to a quantitative summary of the results** if the results are judged sufficiently similar to support such synthesis.

Dictionary of epidemiology, 2nd edition

Systematic Review

- The application of strategies that limit bias in the assembly, critical appraisal, and synthesis of all relevant studies on a specific topic.

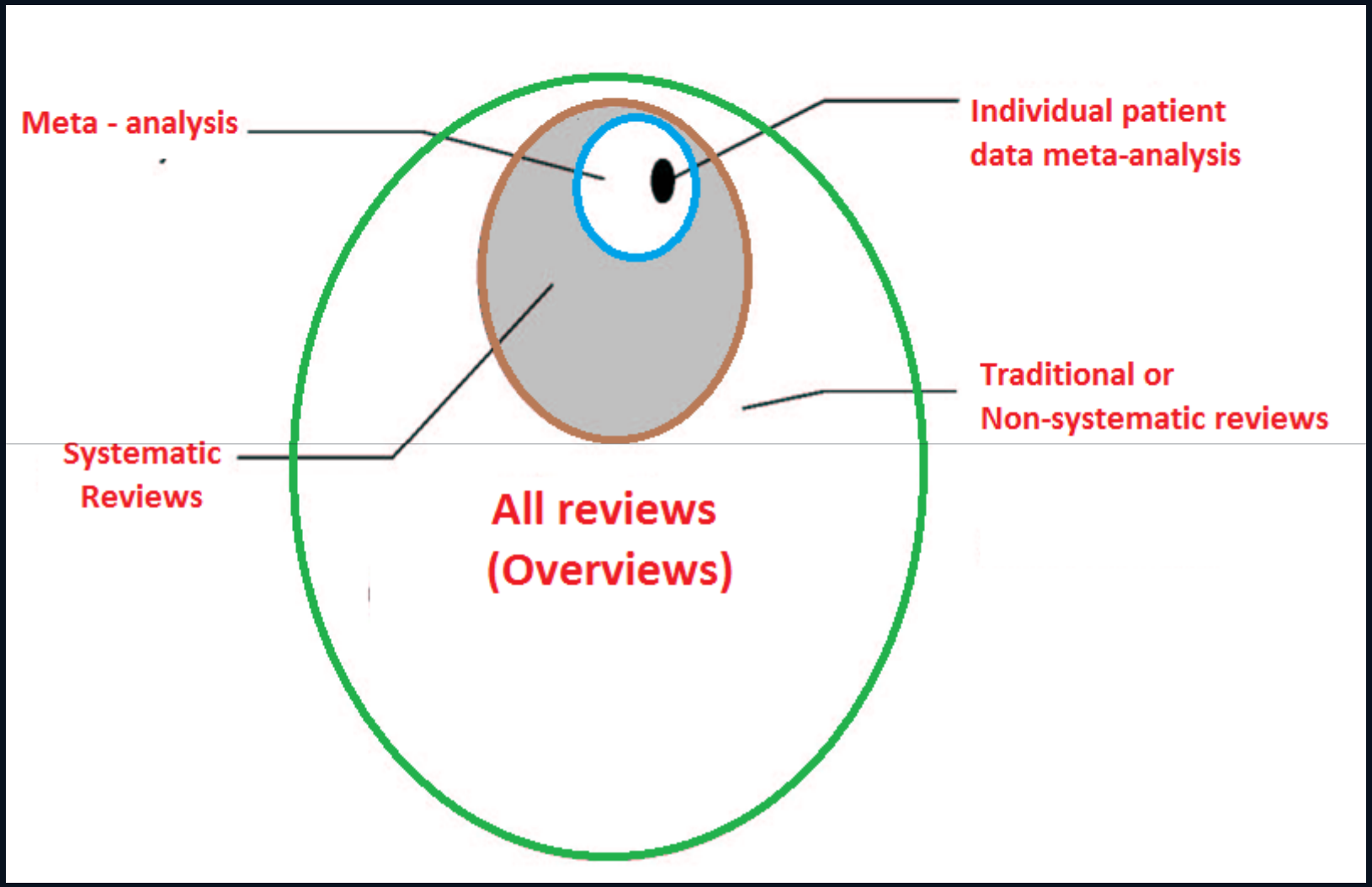
- Meta-analysis may be, but is not necessarily, used as part of this process.

Dictionary of epidemiology, 2nd edition

Cochrane Reviews

- These are systematic reviews of primary research in health care and health policy.
- They investigate the effects of interventions for prevention, treatment and rehabilitation.
- They also assess the accuracy of a diagnostic test for a given condition in a specific patient group and setting.

http://www.cochrane.org/cochrane-reviews


Meta - analysis
Individual patient
data meta-analysis
Traditional or
Non-systematic reviews
Systematic
Reviews
All reviews
(Overviews)

Hallmarks of a good systematic review

- A clearly formulated question
- A thorough search for all the existing primary research on a topic that meets certain criteria
- Assessment of the primary studies using stringent guidelines
- Establish whether or not there is conclusive evidence about a specific treatment.

http://www.cochrane.org/cochrane-reviews

WHEN to do a meta-analysis?

- When more than one study has estimated an effect
- When there are no differences in the study characteristics (patients, interventions) that may affect outcome, so that combining data will produce a clinically useful and meaningful result
- When the outcome has been measured in similar ways
- When the data are available (beware when only some data are available)
- REMEMBER, you do not need to statistically pool results to include a systematic review

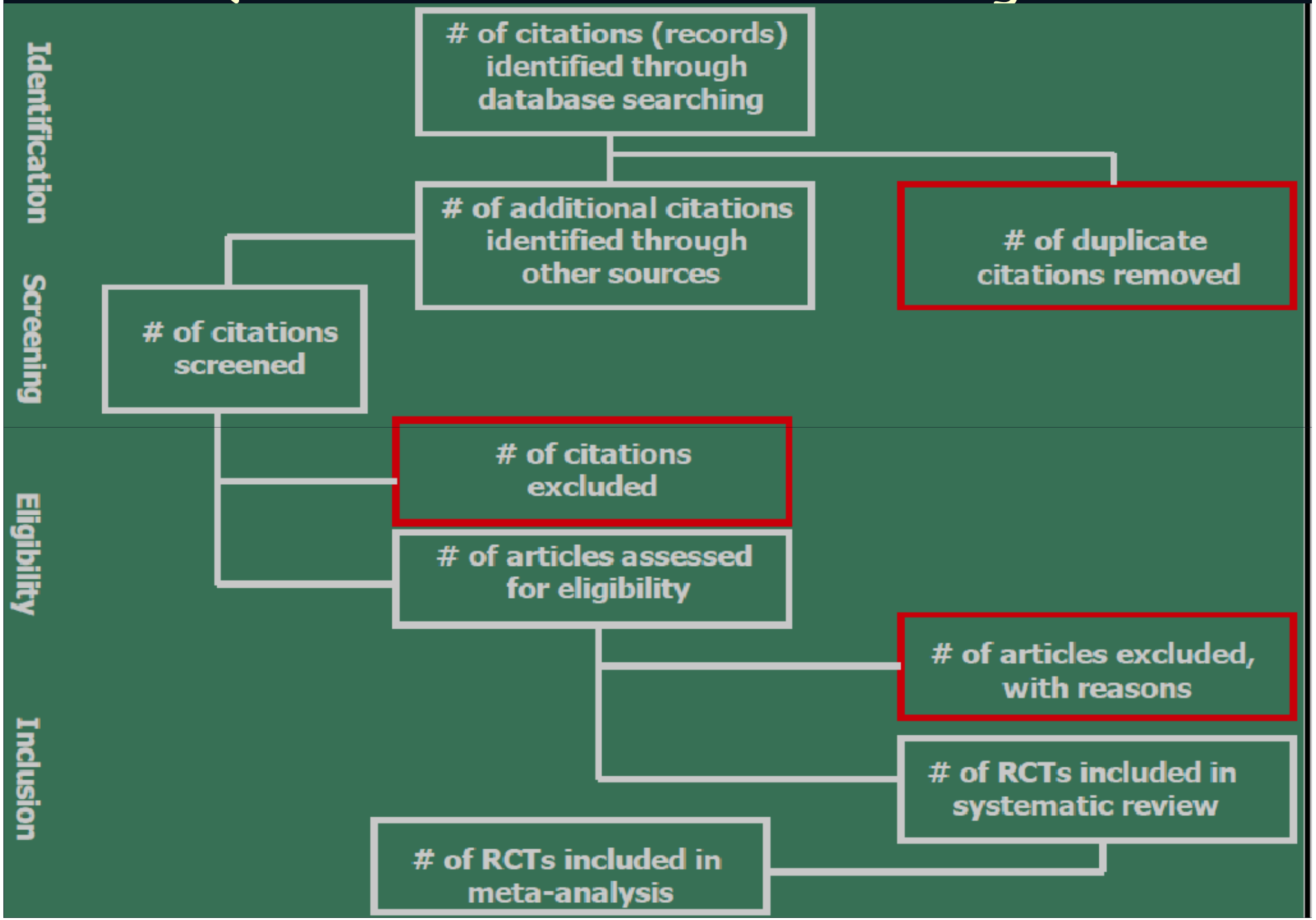
The QUOROM (Quality Of Reporting Of Meta-analyses) Statement (click)

Heading	Subheading	Descriptor
Title		Identify the report as a meta-analysis [or systematic review] of RCTs[26]
Abstract		Use a structured format[27]
		Describe
	Objectives	The clinical question explicitly
	Data sources	The databases (ie, list) and other information sources
	Review methods	The selection criteria (ie, population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie, point estimates and confidence intervals); and subgroup analyses
	Conclusion	The main results

Steps in a meta-analysis

- Define comparisons (interventions)
- Decide on appropriate study results (outcomes) for each comparison
- Select an appropriate summary statistic for each comparison
- Weight studies
- Pool results (Data synthesis/meta-analysis)
- Assess the similarity of study results within each comparison (homogeneity)
- Consider the reliability of the summaries

QUOROM statement flow diagram



Defining comparisons

- Clinically meaningful comparisons
- Specific interventions or generic ones
- Drug A vs Drug B

Combining results

- For example:
  - 6 controlled trials studying the effect of hypothermia on death rates in head injured patients
- How can we summarise the effect of hypothermia across these trials?

Summary statistic for each study

- Calculate a single summary statistic to represent the effect found in each study
- For binary data
  - Ratio of risks (risk ratio; relative risk)
  - Difference in risks (risk difference)
  - Ratio of odds (odds ratio)
- For continuous data
  - Difference between means

For example

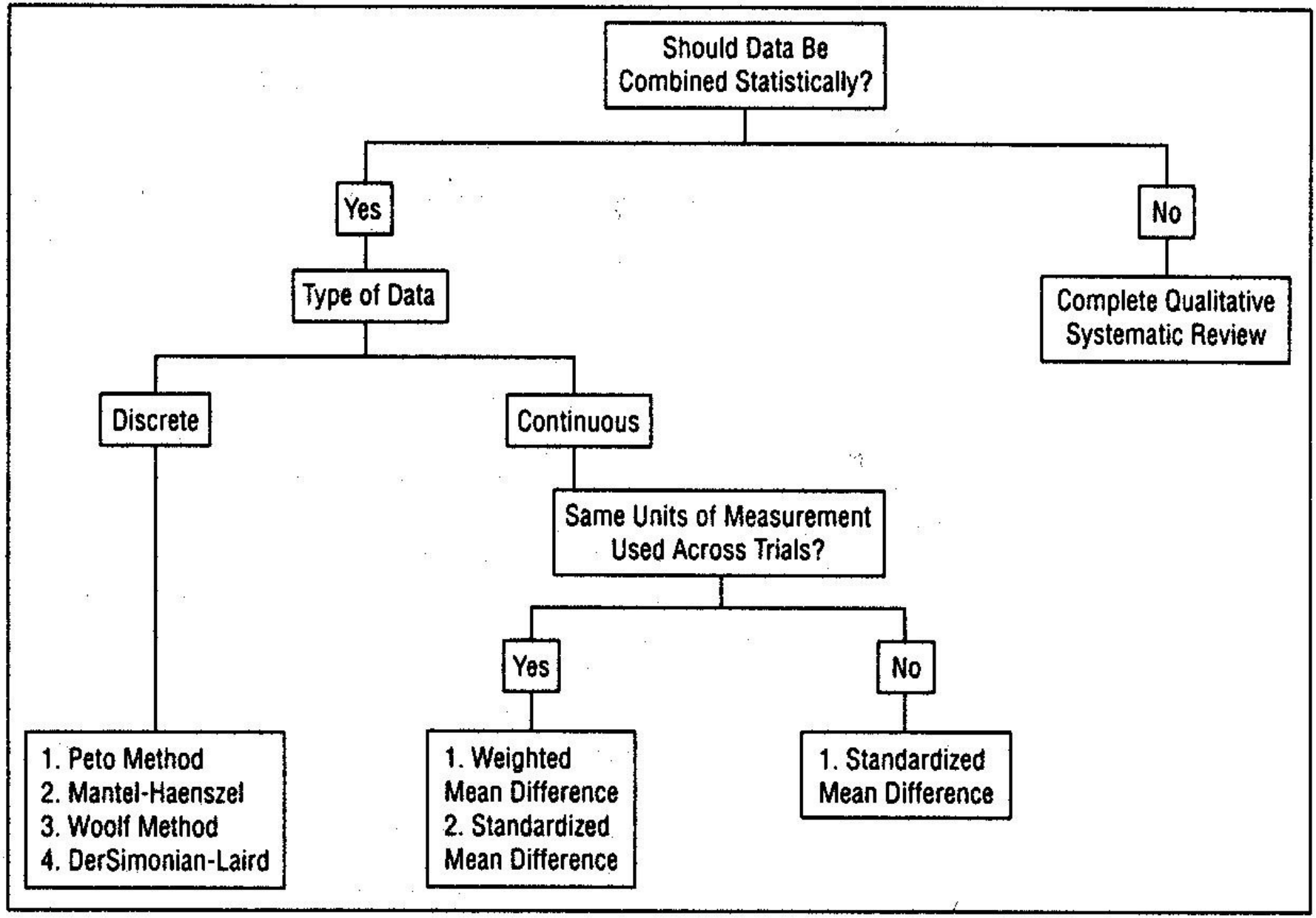
- 6 studies, hypothermia following head injury vs. no hypothermia; relative risks of death (95% CI)
  - 1.0 (0.08, 11.93)
  - 0.96 (0.44, 2.10)
  - 0.67 (0.24, 1.83)
  - 0.45 (0.21, 0.96)
  - 0.97 (0.44, 2.13)
  - 1.08 (0.27, 4.37)

Weighting studies

- More weight to the studies which give us more information
  - More participants
  - More events
  - Lower variance
- Weight is proportional to inverse variance

For example

	Deaths on hypothermia	Deaths on control	Weight (%)
Clifton 1992	1/5	1/5	2.4
Clifton 1993	8/23	8/22	20.0
Hirayama 1994	4/12	5/10	13.4
Jiang 1996	6/23	14/24	33.5
Marion 1997	9/39	10/42	23.6
Meissner 1998	3/12	3/13	7.1



Algorithm of statistical choices available to systematic reviewers.

Displaying results graphically

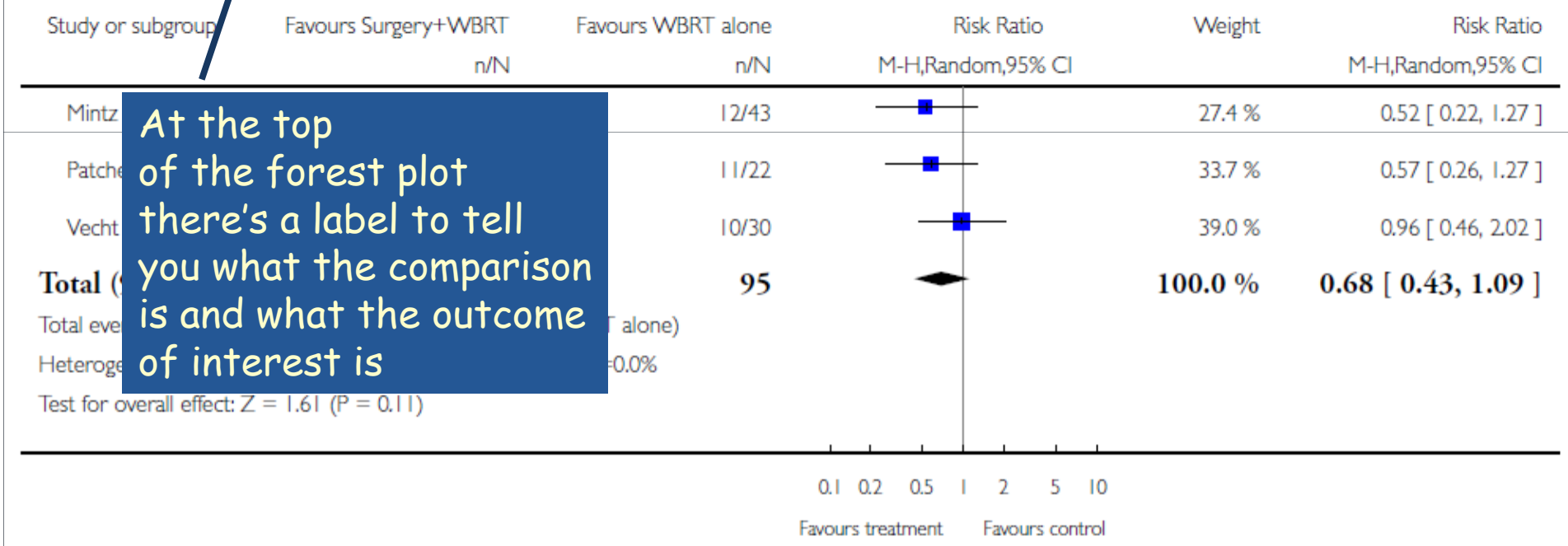
- forest plots
  - Commonly used

Analysis 1.3. Comparison 1 Surgery + Radiotherapy vs Radiotherapy, Outcome 3 Neurological Death.

Review: Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases

Comparison: 1 Surgery + Radiotherapy vs Radiotherapy

Outcome: 3 Neurological Death



At the top of the forest plot there's a label to tell you what the comparison is and what the outcome of interest is

Hart MG, Grant R, Walker M, Dickinson HO. Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases. *Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD003292. DOI:* 10.1002/14651858.CD003292.pub2.

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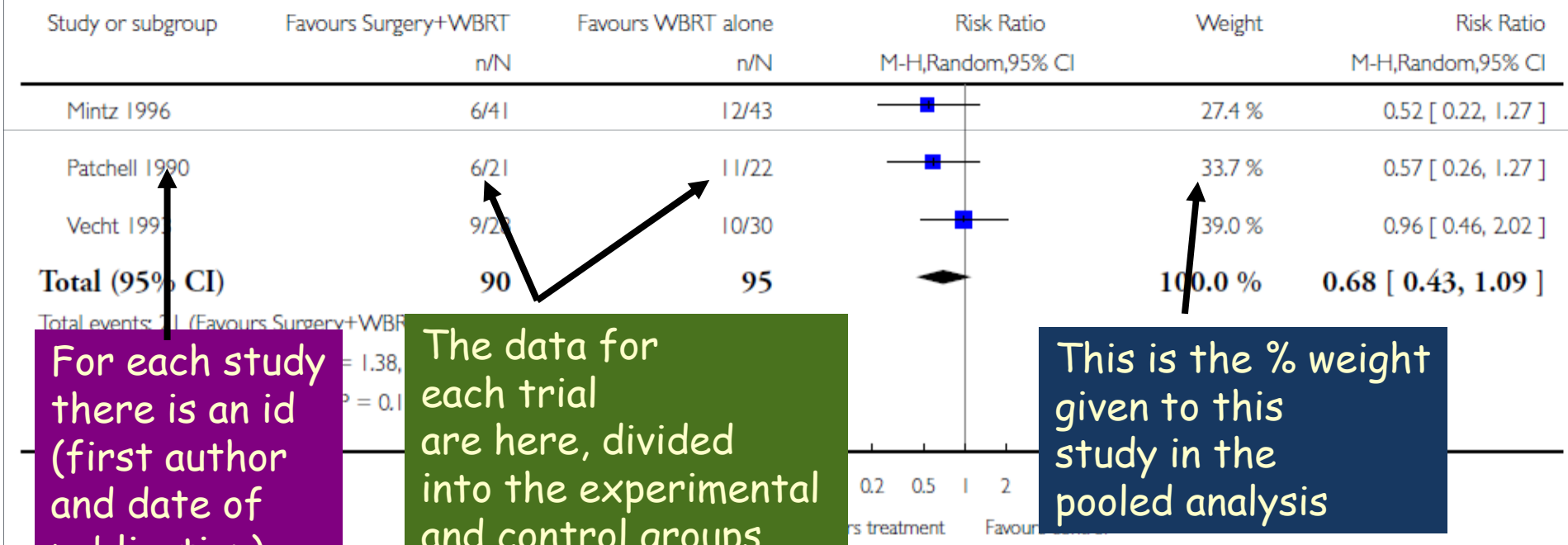

For each study there is an id (first author and date of publication)

The data for each trial are here, divided into the experimental and control groups

This is the % weight given to this study in the pooled analysis

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The label above the graph tells you what statistic has been used

The data shown in the graph are also given numerically

Study or subgroup	Favours Surgery+WBRT n/N	Favours WBRT alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Mintz 1996	6/41	12/43		27.4 %	0.52 [0.22, 1.27]
Patchell 1990	6/21	11/22		33.7 %	0.57 [0.26, 1.27]
Vecht 1993	9/28	10/30		39.0 %	0.96 [0.46, 2.02]
Total (95% CI)	**90**	**95**		**100.0 %**	**0.68 [0.43, 1.09]**

Total events: 21 (Favours Surgery+WBRT), 33 (Favours WBRT alone)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.38$, df = 2 (P = 0.50); $I^2 = 0.0\%$

Test for overall effect: Z = 1.61 (P = 0.11)

- Each study is given a blob, placed where the data measure the effect.
- The size of the blob is proportional to the % weight
- The horizontal line is called a confidence interval and is a measure of how we think the result of this study might vary with the play of chance.
- The wider the horizontal line is, the less confident we are of the observed effect.

Hart MG, Grant R, Walker M, Dickinson HO. Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases. *Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD003292. DOI:* 10.1002/14651858.CD003292.pub2.

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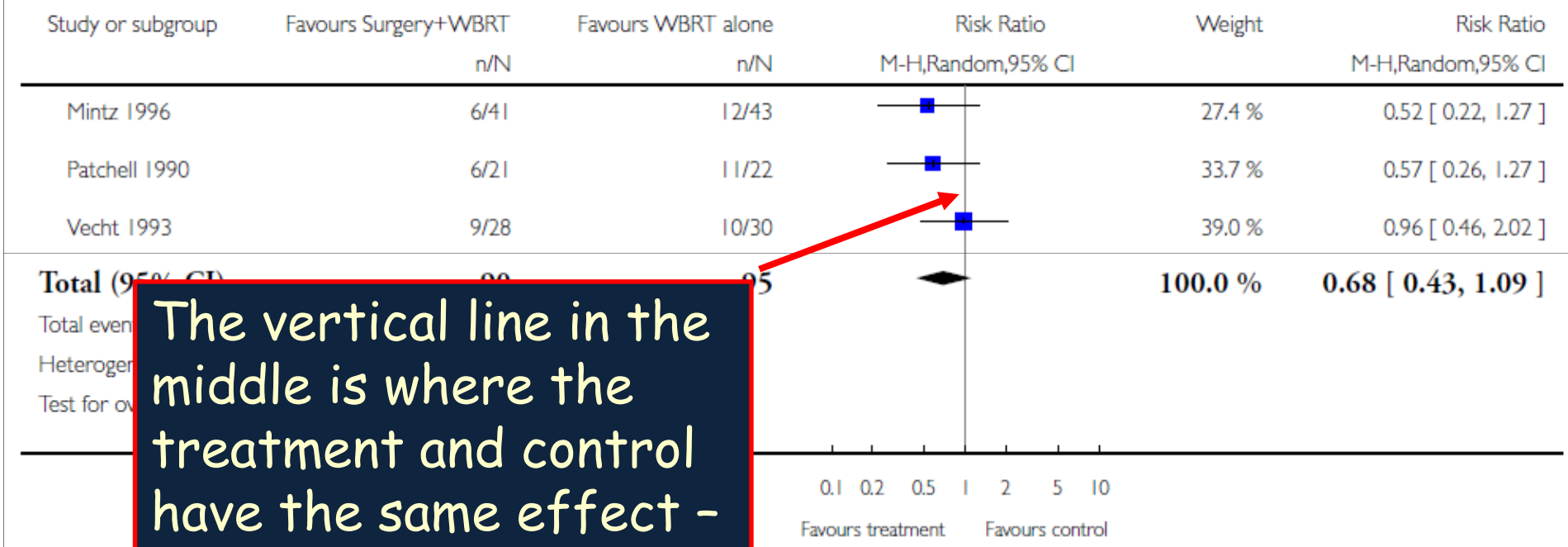

The vertical line in the middle is where the treatment and control have the same effect – there is no difference between the two

Hart MG, Grant R, Walker M, Dickinson HO. Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases. *Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD003292. DOI:* 10.1002/14651858.CD003292.pub2.

At the bottom there's a horizontal line. This is the scale measuring the treatment effect. Here the outcome is death and towards the left the scale is less than one, meaning the treatment has made death less likely.

Take care to read what the labels say – things to the left do not always mean the treatment is better than the control.

Analysis 1.3. Compa

Review: Surgical resection and whole

Comparison: 1 Surgery + Radiother

Outcome: 3 Neurological Death

Study or subgroup	Favours Sur			
Mintz 1996	6/41	12/43	27.4 %	0.52 [0.22, 1.27]
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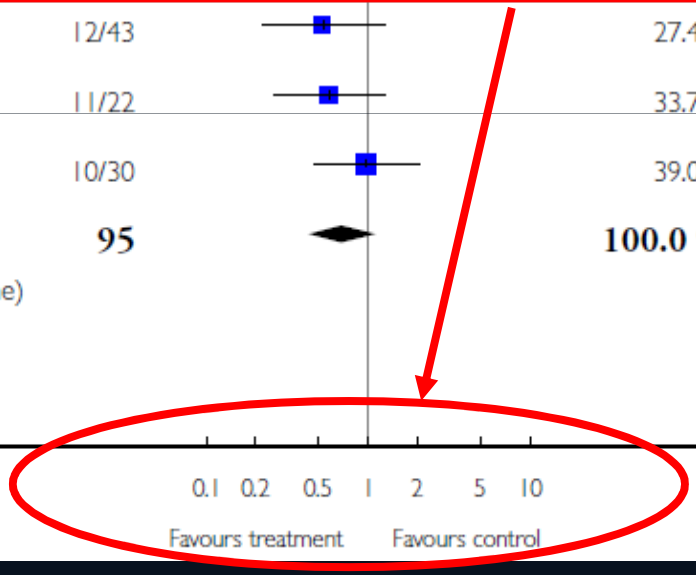

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Comparison

Outcome:

The pooled analysis is given a diamond shape where the widest bit in the middle is located at the calculated best guess (point estimate), and the horizontal width is the confidence interval

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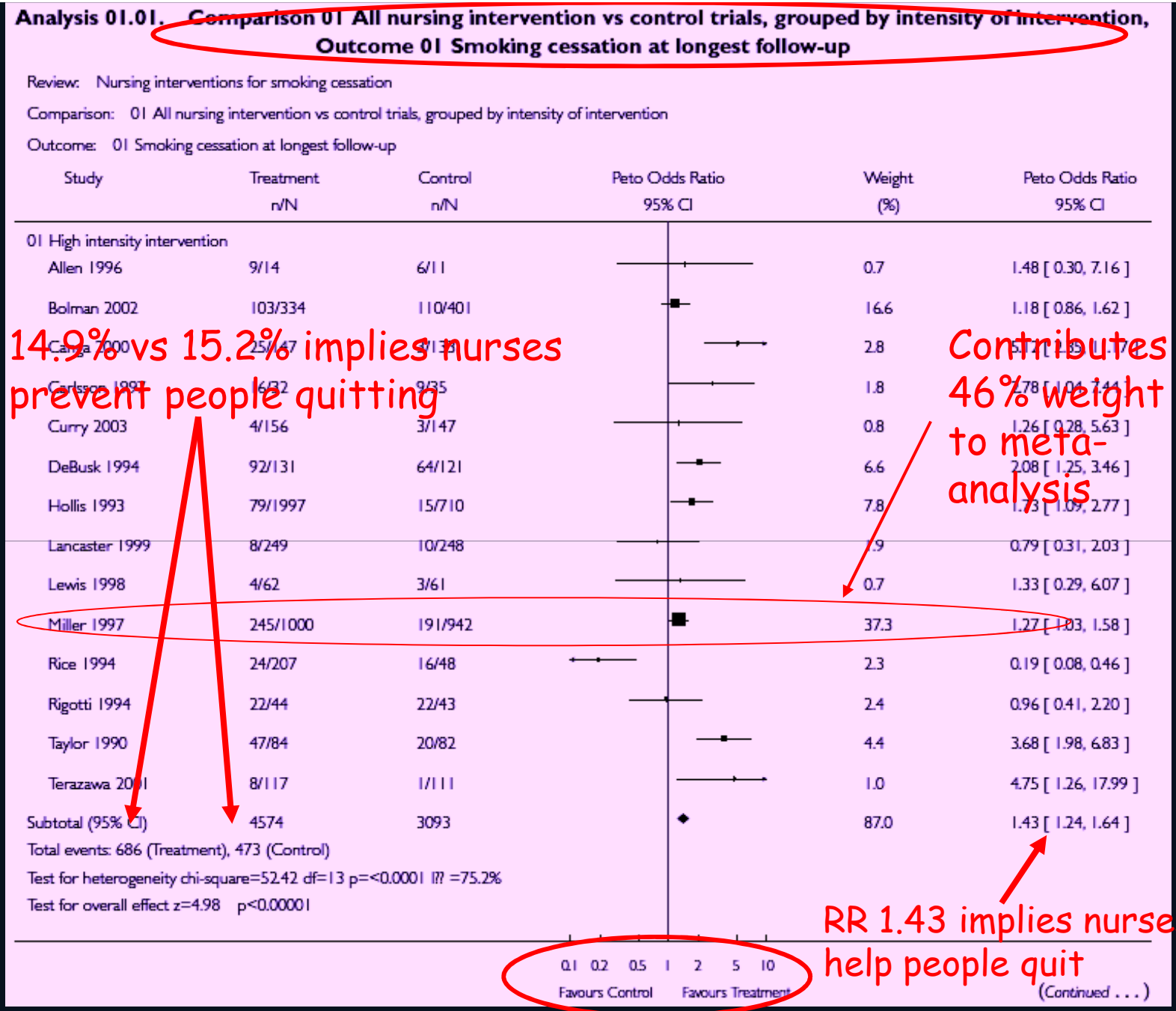
Test for overall

Note on interpretation

If the confidence interval crosses the line of no effect, this is equivalent to saying that we have found no statistically significant difference in the effects of the two interventions

Hart MG, Grant R, Walker M, Dickinson HO. Surgical resection and whole brain radiation therapy versus whole brain radiation therapy alone for single brain metastases. *Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD003292. DOI:* 10.1002/14651858.CD003292.pub2.



Rice VH, Stead LF. Nursing interventions for smoking cessation (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

Pooling continuous data: what you need

- Number of participants in each group, means and standard deviations
- Each trial will present, or allow you to calculate a *mean difference.*
- Mean difference is the difference between the means of the two groups

When to use MD / SMD

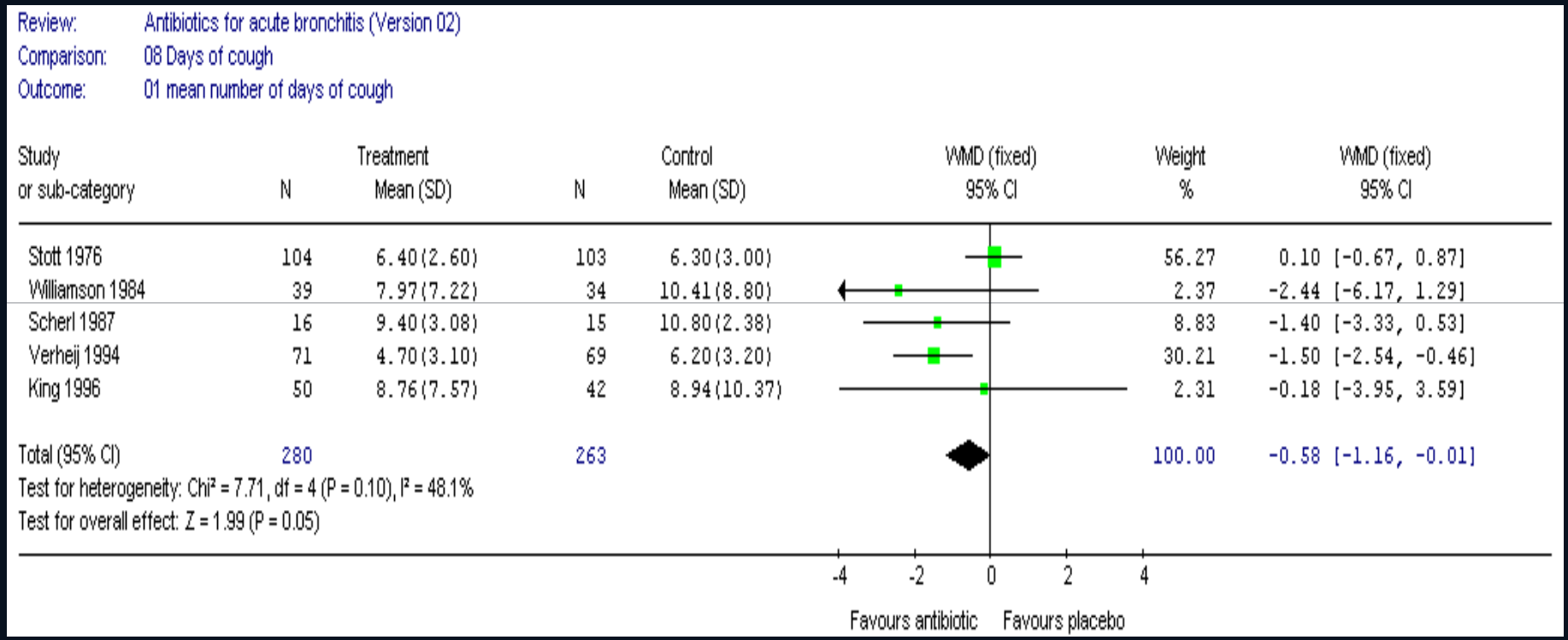
(Weighted) Mean Difference

- When studies have comparable outcome measures (i.e. Same scale, probably same length of follow-up etc)

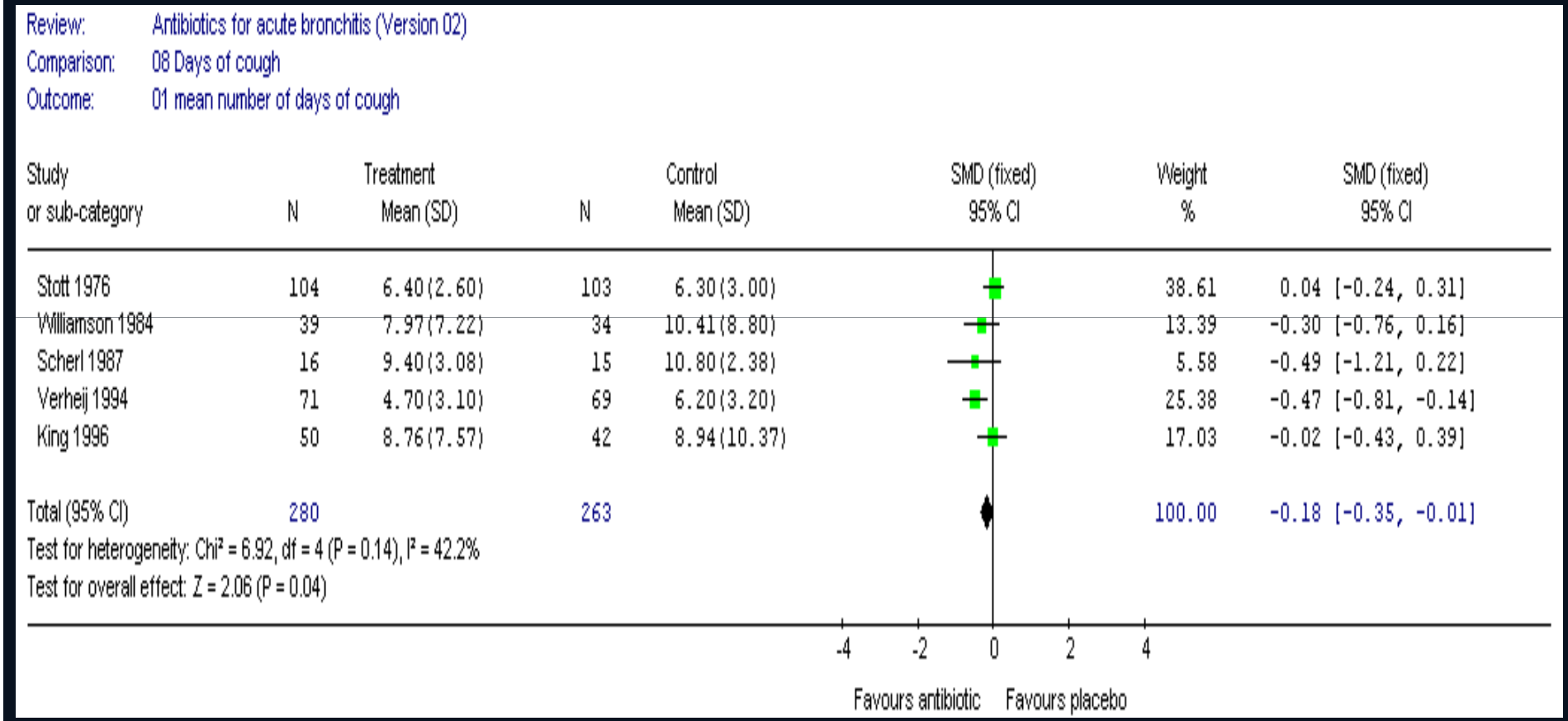
Standardized Mean Difference

- When studies use different outcome measurements to address the same clinical outcome (e.g. different scales)

Continuous data –Weighted Mean Difference



Continuous data –Standardised Mean Difference



Heterogeneity

- Indicates that effect varies a lot across studies
- If heterogeneity is present, a common, summary measure is hard to interpret

Types of heterogeneity

- **Statistical**

  - Excessive variation in the results of studies

  - Variation in treatment effects above that expected by chance

    – Some degree of statistical heterogeneity is inevitable?

Types of heterogeneity

- **Clinical**
  - Can be due to differences in:
    - Patient populations studied
    - Interventions used
    - Co-interventions
    - Outcomes measured

Types of heterogeneity

- **Methodological**
  - Variation in methods used in studies e.g. quality of allocation concealment

Identifying heterogeneity graphically

- If studies are estimating the same thing we would expect confidence intervals to overlap to a large extent
- Statistical heterogeneity may appear in a forest plot as poor overlap of confidence intervals
- Look for outliers

Analysis 01.01. Comparison 01 All nursing intervention vs control trials, grouped by intensity of intervention, Outcome 01 Smoking cessation at longest follow-up

Review: Nursing interventions for smoking cessation

Comparison: 01 All nursing intervention vs control trials, grouped by intensity of intervention

Outcome: 01 Smoking cessation at longest follow-up

Study	Treatment n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 High intensity intervention					
Allen 1996	9/14	6/11		0.7	1.48 [0.30, 7.16]
Bolman 2002	103/334	110/401		16.6	1.18 [0.86, 1.62]
Canga 2000	25/147	3/133		2.8	5.12 [2.35, 11.17]
Carlsson 1997	16/32	9/35		1.8	2.78 [1.04, 7.44]
Curry 2003	4/156	3/147		0.8	1.26 [0.28, 5.63]
DeBusk 1994	92/131	64/121		6.6	2.08 [1.25, 3.46]
Hollis 1993	79/1997	15/710		7.8	1.73 [1.09, 2.77]
Lancaster 1999	8/249	10/248		1.9	0.79 [0.31, 2.03]
Lewis 1998	4/62	3/61		0.7	1.33 [0.29, 6.07]
Miller 1997	245/1000	191/942		37.3	1.27 [1.03, 1.58]
Rice 1994	24/207	16/48		2.3	0.19 [0.08, 0.46]
Rigotti 1994	22/44	22/43		2.4	0.96 [0.41, 2.20]
Taylor 1990	47/84	20/82		4.4	3.68 [1.98, 6.83]
Terazawa 2001	8/117	1/111		1.0	4.75 [1.26, 17.99]
Subtotal (95% CI)	4574	3093		87.0	1.43 [1.24, 1.64]
Total events: 686 (Treatment), 473 (Control)					
Test for heterogeneity chi-square=52.42 df=13 p=<0.0001 I? =75.2%					
Test for overall effect z=4.98 p<0.00001					

0.1 0.2 0.5 1 2 5 10

Favours Control Favours Treatment

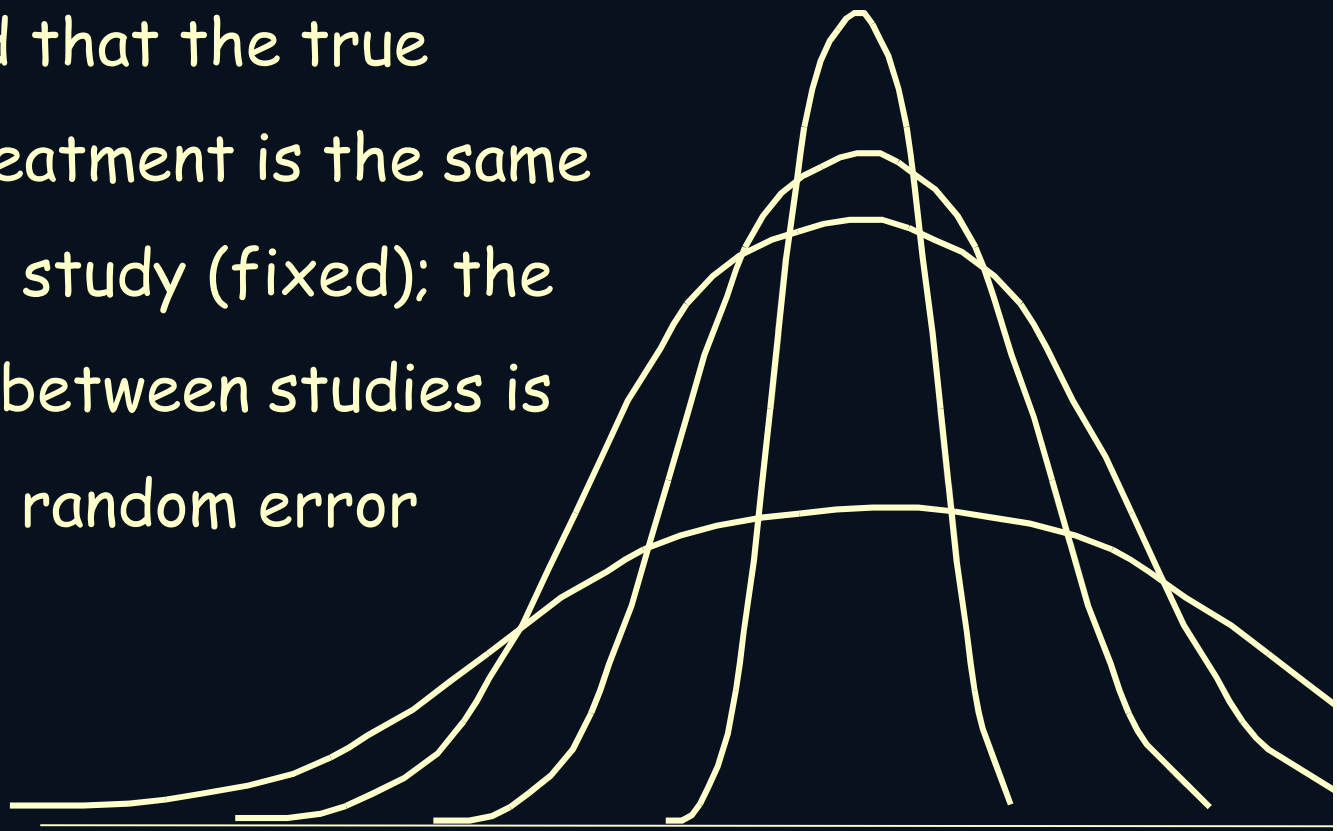
(Continued . . .)

Rice VH, Stead LF. Nursing interventions for smoking cessation (Cochrane Review). In: *The Cochrane Library*, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

If heterogeneity is found

Statistical models for combining data:

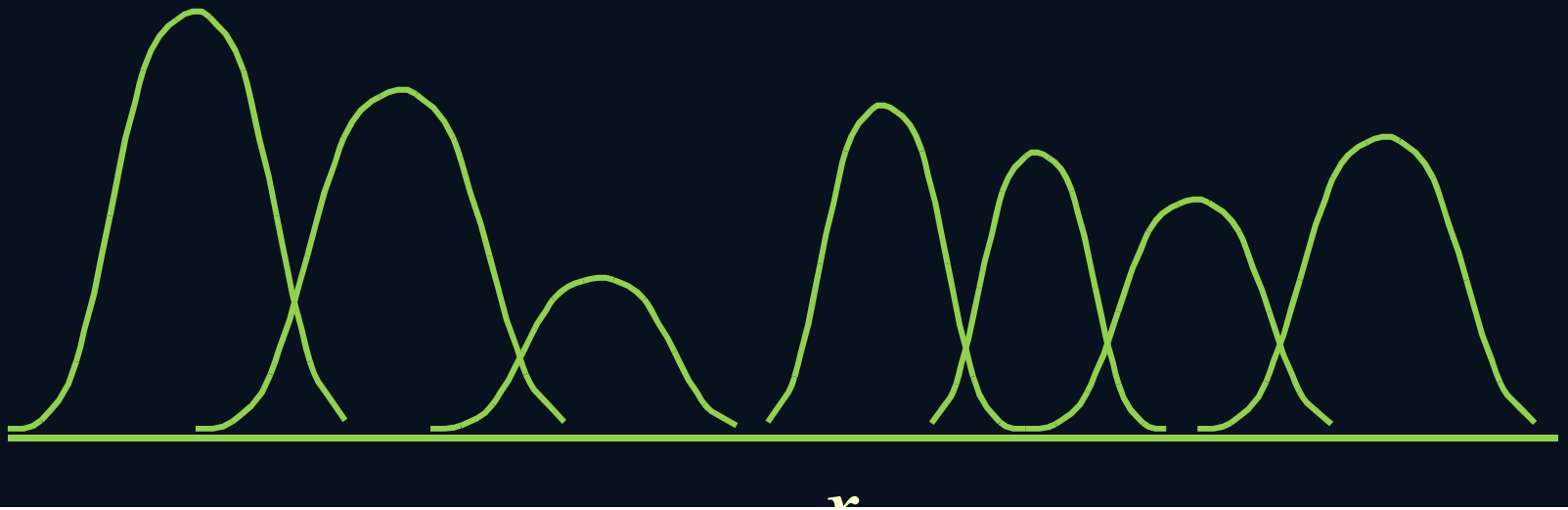
- Fixed effects model
  - it is assumed that the true effect of treatment is the same value in each study (fixed); the differences between studies is solely due to random error



If heterogeneity is found

Statistical models for combining data:

- Random effects model
  - the treatment effects for the individual studies are assumed to vary around some overall average treatment effect
  - Studies tend to be weighted more equally



Identifying factors that can explain heterogeneity

- Sensitivity analysis
- Subgroup analysis
- Meta-regression

When can meta-analyses mislead?

- When a meta-analysis is done outside of a systematic review
- When quality issues are ignored
- When inadequate attention is given to heterogeneity
- When reporting biases are a problem
  - Publication bias
  - Time lag bias
  - Duplicate publication bias
  - Language bias
  - Outcome reporting bias
  - Citation bias

Egger M et al. Uses and abuses of meta-analysis. Clinical Medicine 2001;1:478-84

Meta-analysis software

- Free
  - RevMan [Review Manager]
  - Meta-Analyst
  - Epi Meta
  - Easy MA
  - Meta-Test
  - Meta-Stat
- Commercial
  - Comprehensive Meta-analy
  - Meta-Win
  - WEasy MA
- General stats package
  - Stata
  - SAS
  - S-Plus

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http://www.cochrane.org/

Thank you

REVMAN is a data entry, word processing and statistical package produced by the Cochrane Collaboration