

Introduction to meta-analysis

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Trusted evidence.
Informed decisions.
Better health.



Steps of a Cochrane Review

1. define the question
2. plan eligibility criteria
3. plan methods
4. search for studies
5. apply eligibility criteria
6. collect data
7. assess studies for risk of bias
- 8. analyse and present results**
9. interpret results and draw conclusions
10. improve and update review

Session outline

- **principles of meta-analysis**
- steps in a meta-analysis
- presenting your results



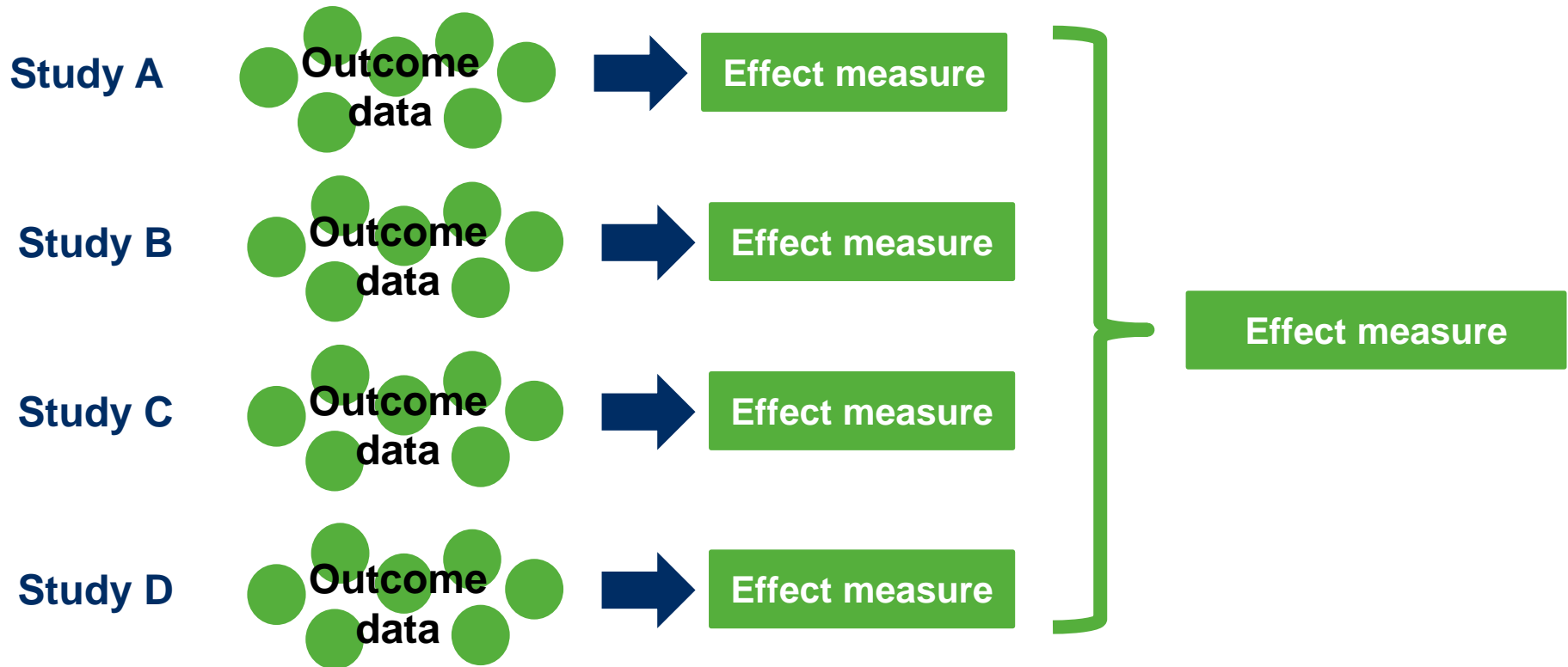
See Chapter 9 of the Handbook



Study level

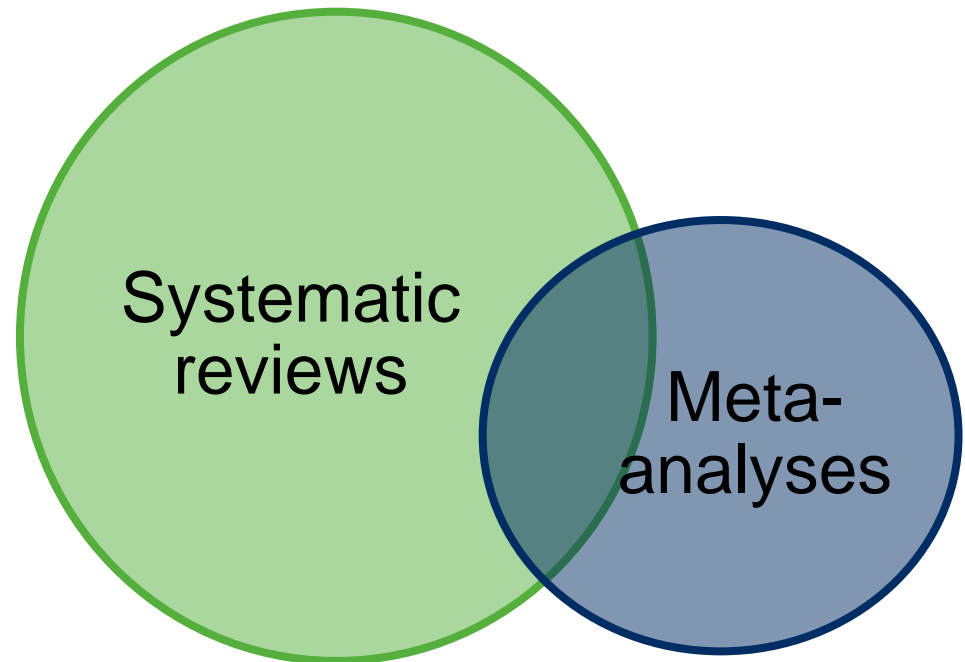


Review level



What is a meta-analysis?

- combines the results from two or more studies
- estimates an 'average' or 'common' effect
- optional part of a systematic review



Why perform a meta-analysis?

- quantify treatment effects and their uncertainty
- increase power
- increase precision
- explore differences between studies
- settle controversies from conflicting studies
- generate new hypotheses

When not to do a meta-analysis

- **mixing apples with oranges**
 - each included study must address same question
 - consider comparison and outcomes
 - requires your subjective judgement
 - combining a broad mix of studies answers broad questions
 - answer may be meaningless and genuine effects may be obscured if studies are too diverse

When not to do a meta-analysis

- **garbage in – garbage out**
 - a meta-analysis is only as good as the studies in it
 - if included studies are biased:
 - meta-analysis result will also be incorrect
 - will give more credibility and narrower confidence interval
 - if serious reporting biases present:
 - unrepresentative set of studies may give misleading result

When can you do a meta-analysis?

- more than one study has measured an effect
- the studies are sufficiently similar to produce a meaningful and useful result
- the outcome has been measured in similar ways
- data are available in a format we can use

Session outline

- principles of meta-analysis
- **steps in a meta-analysis**
- presenting your results



Steps in a meta-analysis

- identify comparisons to be made
- identify outcomes to be reported and statistics to be used
- collect data from each relevant study
- combine the results to obtain the summary of effect
- explore differences between the studies
- interpret the results

Selecting comparisons

Hypothetical review: Caffeine for daytime drowsiness

caffeinated coffee

vs

decaffeinated coffee

- break your topic down into pair-wise comparisons
- each review may have one or many
- use your judgement to decide what to group together, and what should be a separate comparison

Selecting outcomes & effect measures

Hypothetical review: Caffeine for daytime drowsiness

caffeinated coffee

vs

decaffeinated coffee

- asleep at end of trial (RR)
- irritability (MD/SMD)
- headaches (RR)

- for each comparison, select outcomes
- for each outcome, select an effect measure
 - may depend on the available data from included studies

Common types of outcome data

(1) Binary (or dichotomous) e.g. Survival status (Alive, Dead)

- For revman: Enter number of participants with events and total number of participants in experimental and control groups.

(2) Continuous e.g. blood pressure measurement

- For revman: Enter mean, standard deviation and number of participants in experimental and control groups

Types of effect measure

(1) Binary (or dichotomous) data

Risk Ratio (or Relative Risk)

Odds Ratio

Risk Difference

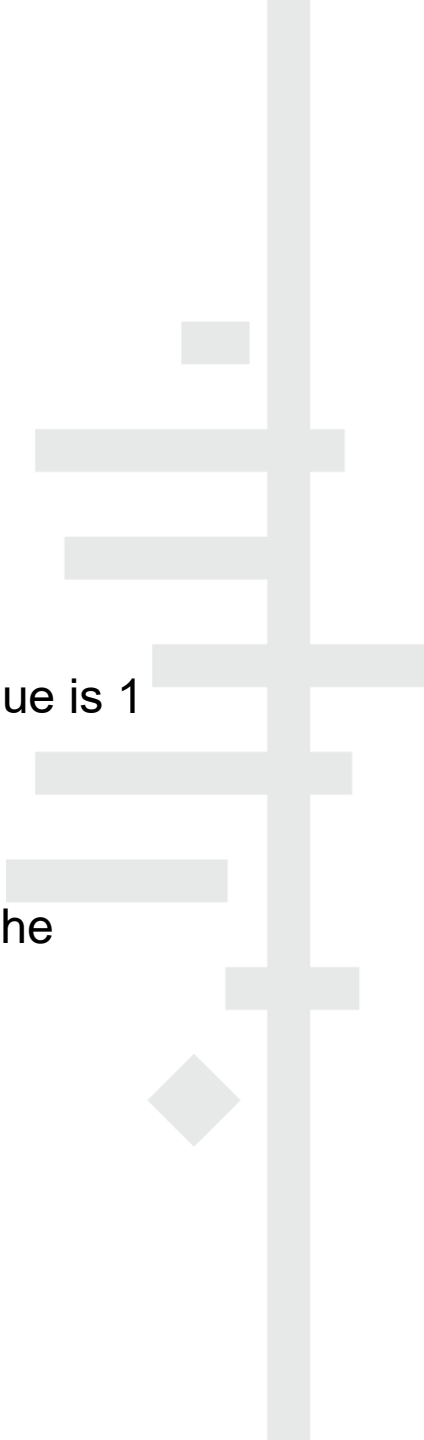
RR and OR are ratio measures - the 'null' value is 1

(2) Continuous data:

Mean Difference

Standardised Mean Difference

RD, MD and SMD are difference measures – the 'null' value is 0



Calculating the summary result

- collect a summary statistic from each contributing study
- how do we bring them together?
 - treat as one big study – add intervention & control data?
 - breaks randomisation, will give the wrong answer
 - simple average?
 - weights all studies equally – some studies closer to the truth
 - weighted average

Weighting studies

- more weight to the studies which give more information
 - more participants, more events, narrower confidence interval
 - calculated using the effect estimate and its variance
- inverse-variance method:

$$\text{weight} = \frac{1}{\text{variance of estimate}} = \frac{1}{SE^2}$$

$$\text{pooled estimate} = \frac{\text{sum of (estimate} \times \text{weight)}}{\text{sum of weights}}$$

For example

Headache	Caffeine	Decaf	Weight
Amore-Coffea 2000	2/31	10/34	
Deliciozza 2004	10/40	9/40	
Mama-Kaffa 1999	12/53	9/61	
Morrocona 1998	3/15	1/17	
Norscafe 1998	19/68	9/64	
Oohlahlazza 1998	4/35	2/37	
Piazza-Allerta 2003	8/35	6/37	

For example

Headache	Caffeine	Decaf	Weight
Amore-Coffea 2000	2/31	10/34	6.6%
Deliciozza 2004	10/40	9/40	21.9%
Mama-Kaffa 1999	12/53	9/61	22.2%
Morrocona 1998	3/15	1/17	2.9%
Norscafe 1998	19/68	9/64	26.4%
Oohlahlazza 1998	4/35	2/37	5.1%
Piazza-Allerta 2003	8/35	6/37	14.9%

Meta-analysis options

- for dichotomous or continuous data
 - inverse-variance
 - straightforward, general method
- for dichotomous data only
 - Mantel-Haenszel (default)
 - good with few events – common in Cochrane reviews
 - weighting system depends on effect measure
 - Peto
 - for odds ratios only
 - good with few events and small effect sizes (OR close to 1)

Meta-analysis options

New Outcome Wizard

Which analysis method do you want to use?

Statistical Method

- Peto
- Mantel-Haenszel
- Inverse Variance
- Exp[(O-E) / Var]

Analysis Model

- Fixed effect
- Random effects

Effect Measure

- Peto Odds Ratio
- Odds Ratio
- Risk Ratio
- Risk Difference
- Mean Difference
- Std. Mean Difference
- Name of Effect Measure:

Hazard Ratio

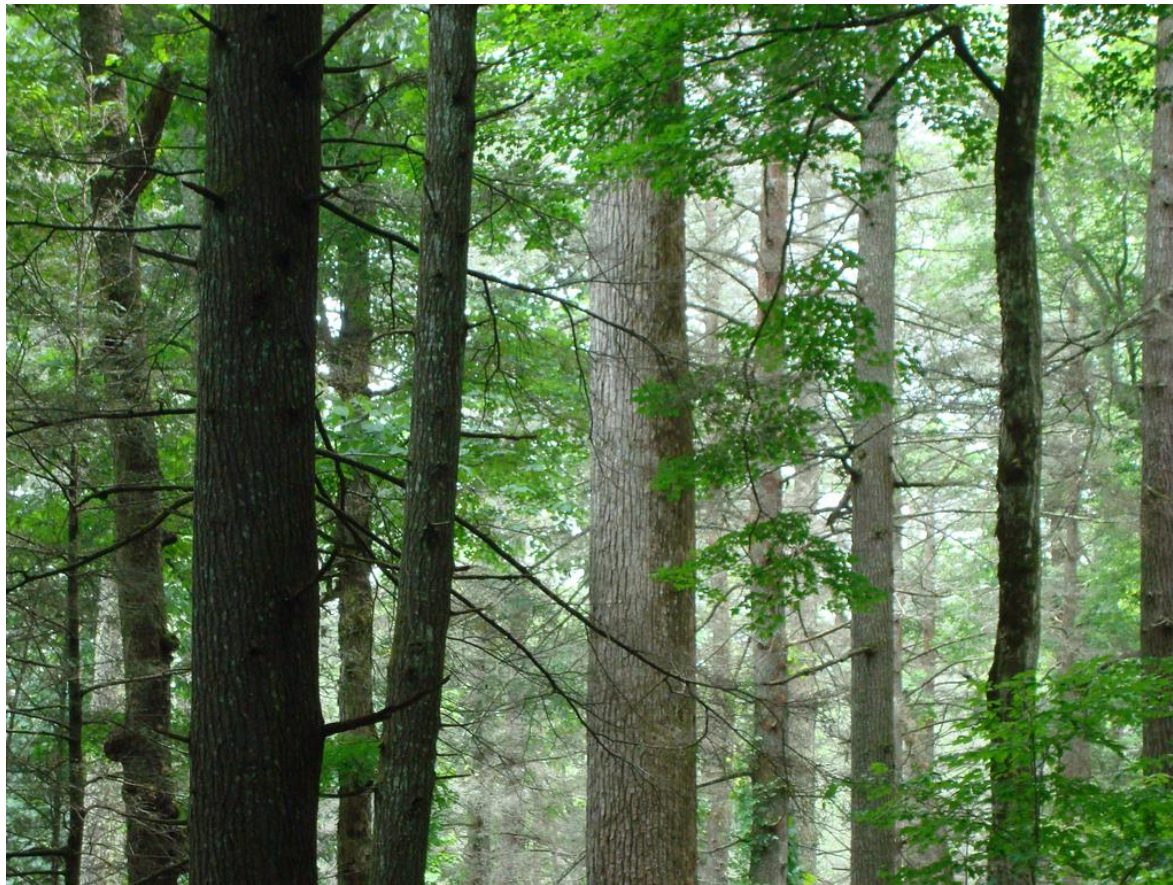
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Session outline

- principles of meta-analysis
- steps in a meta-analysis
- **presenting your results**

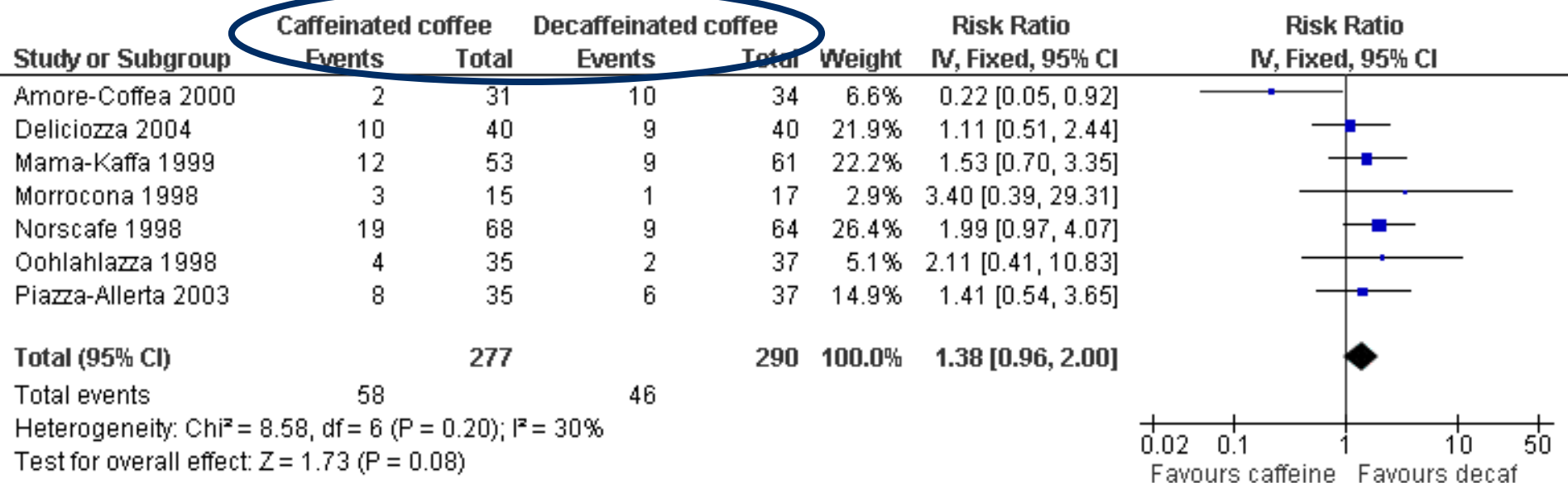


A forest of lines



Forest plots

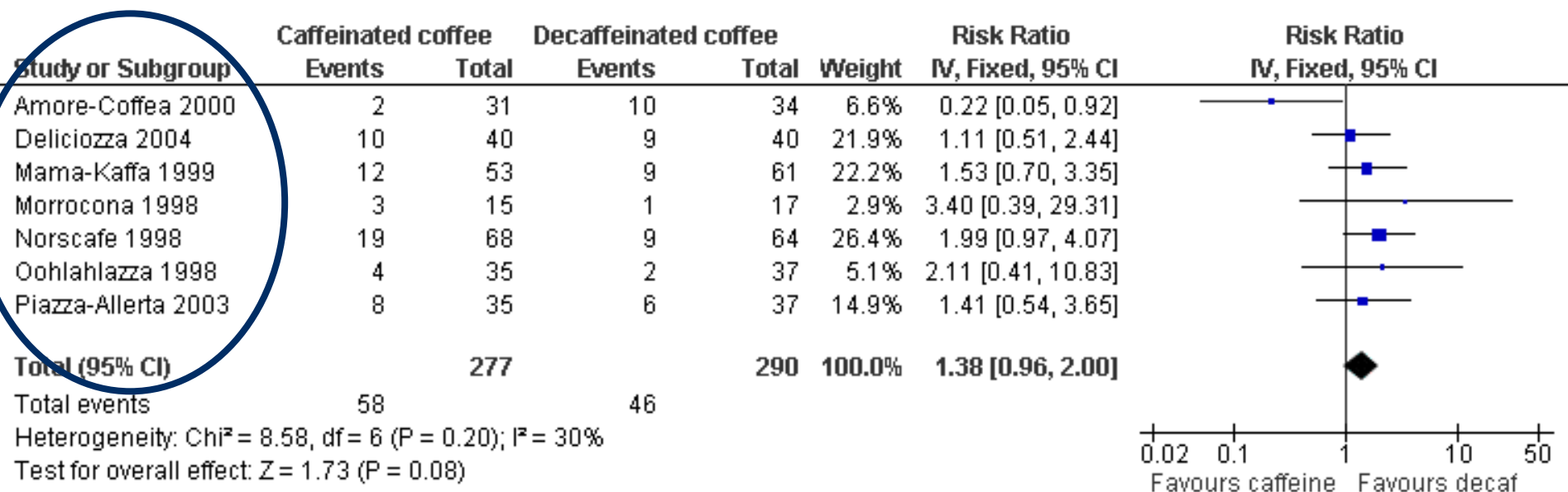
Headache at 24 hours



- headings explain the comparison

Forest plots

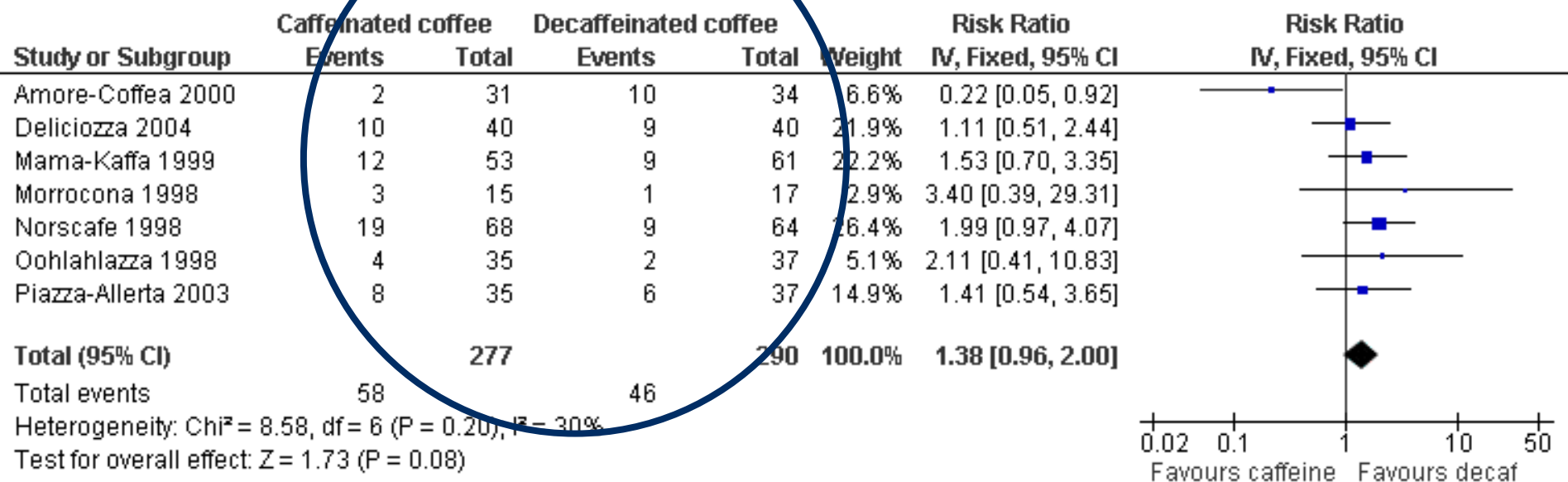
Headache at 24 hours



- list of included studies

Forest plots

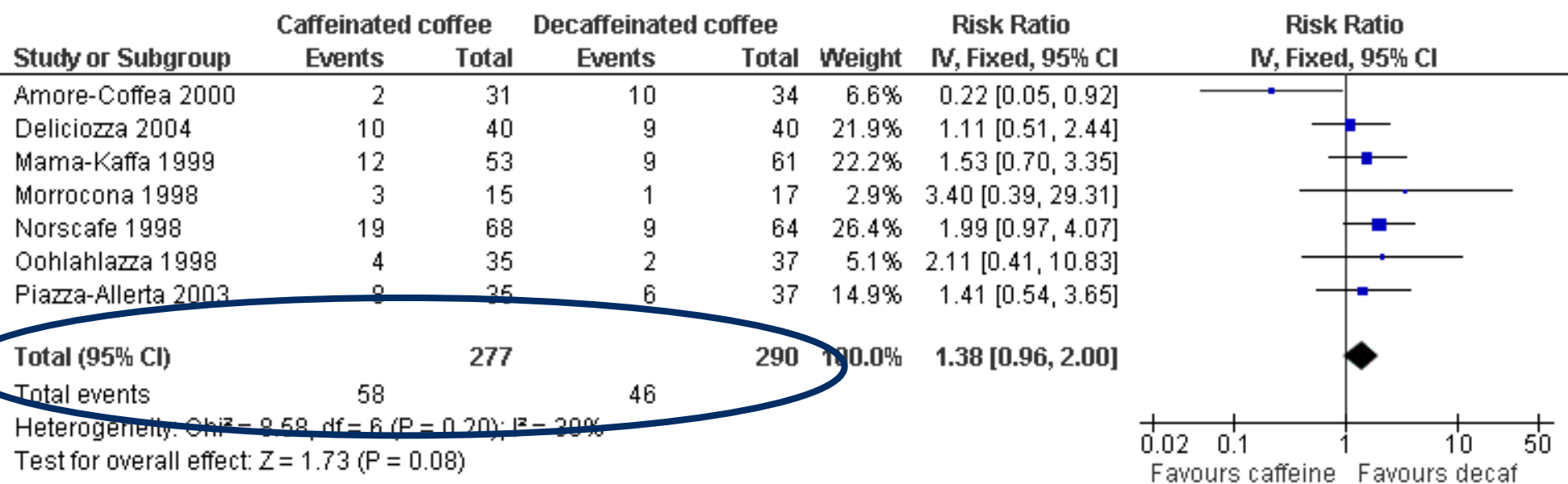
Headache at 24 hours



- raw data for each study

Forest plots

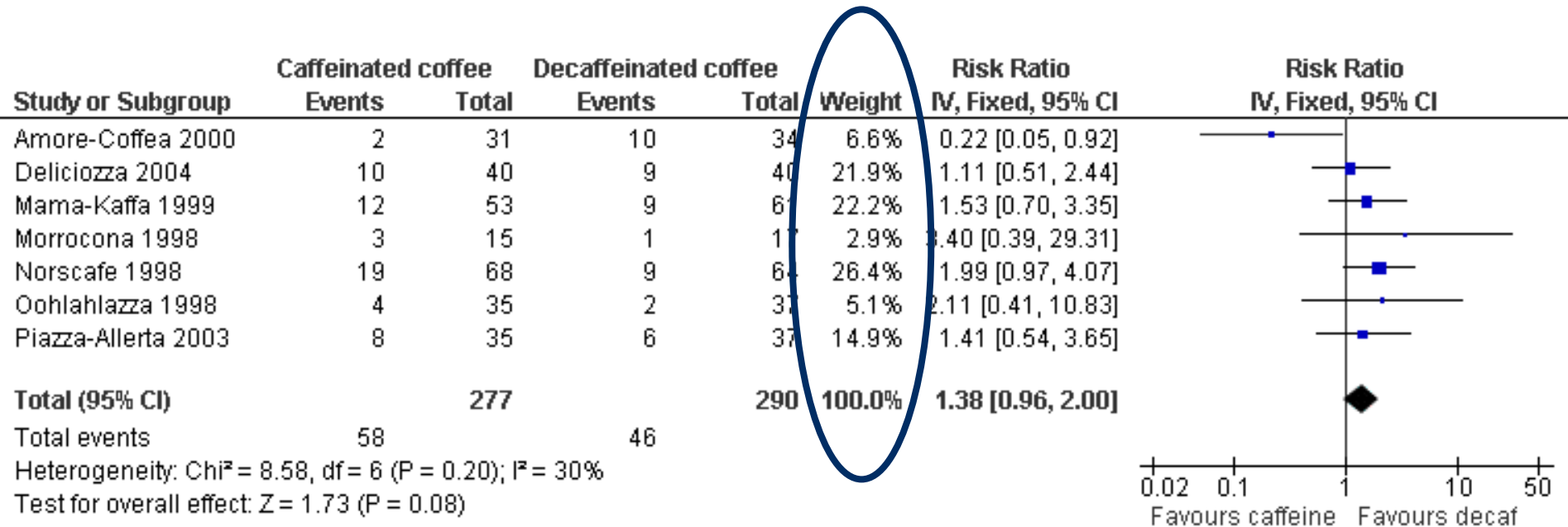
Headache at 24 hours



- total data for all studies

Forest plots

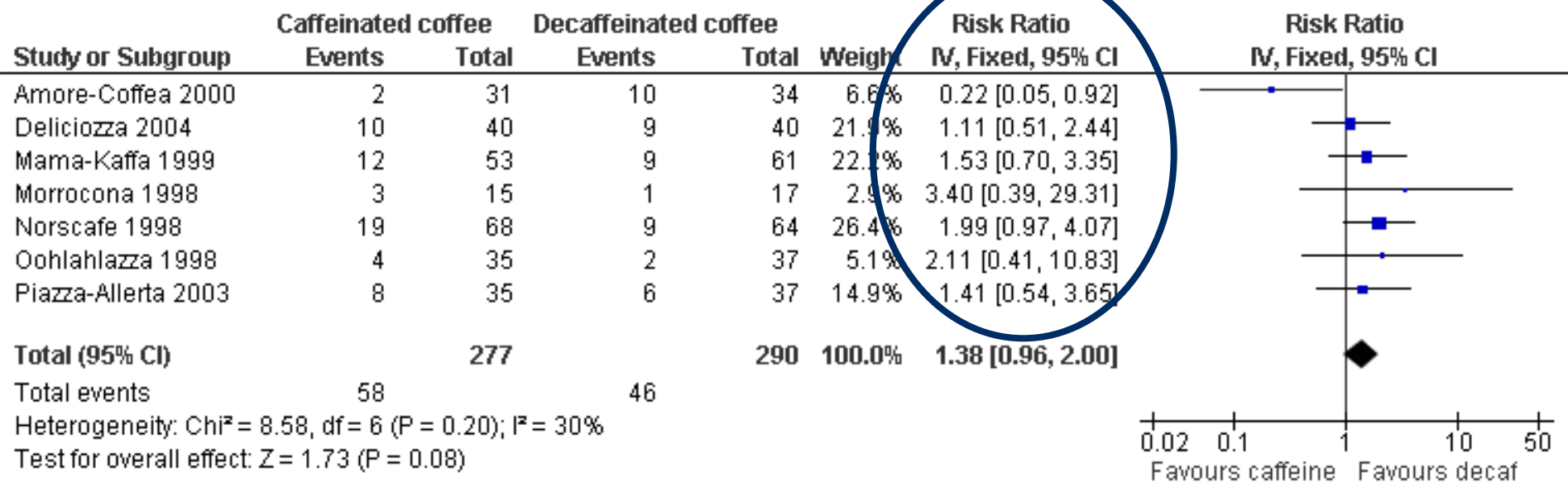
Headache at 24 hours



- weight given to each study

Forest plots

Headache at 24 hours



- effect estimate for each study, with CI

Forest plots

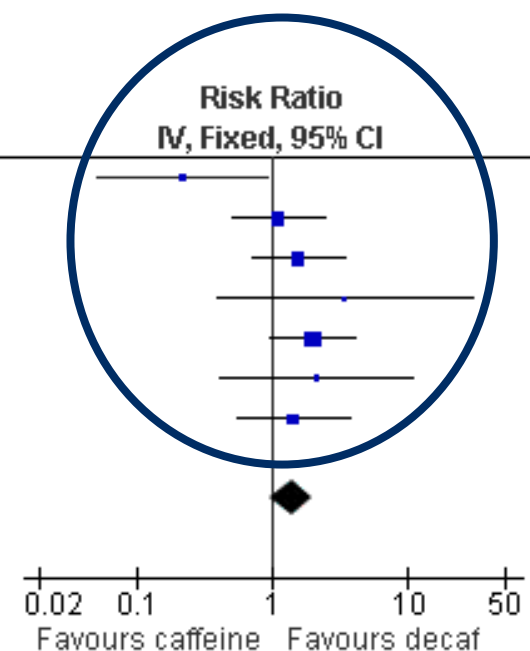
Headache at 24 hours

Study or Subgroup	Caffeinated coffee		Decaffeinated coffee		Weight	Risk Ratio
	Events	Total	Events	Total		IV, Fixed, 95% CI
Amore-Coffea 2000	2	31	10	34	6.6%	0.22 [0.05, 0.92]
Deliciozza 2004	10	40	9	40	21.9%	1.11 [0.51, 2.44]
Mama-Kaffa 1999	12	53	9	61	22.2%	1.53 [0.70, 3.35]
Morrocona 1998	3	15	1	17	2.9%	3.40 [0.39, 29.31]
Norscafe 1998	19	68	9	64	26.4%	1.99 [0.97, 4.07]
Oohlahlazza 1998	4	35	2	37	5.1%	2.11 [0.41, 10.83]
Piazza-Allerta 2003	8	35	6	37	14.9%	1.41 [0.54, 3.65]
Total (95% CI)		277		290	100.0%	1.38 [0.96, 2.00]

Total events 58 46

Heterogeneity: $\text{Chi}^2 = 8.58$, $\text{df} = 6$ ($P = 0.20$); $I^2 = 30\%$

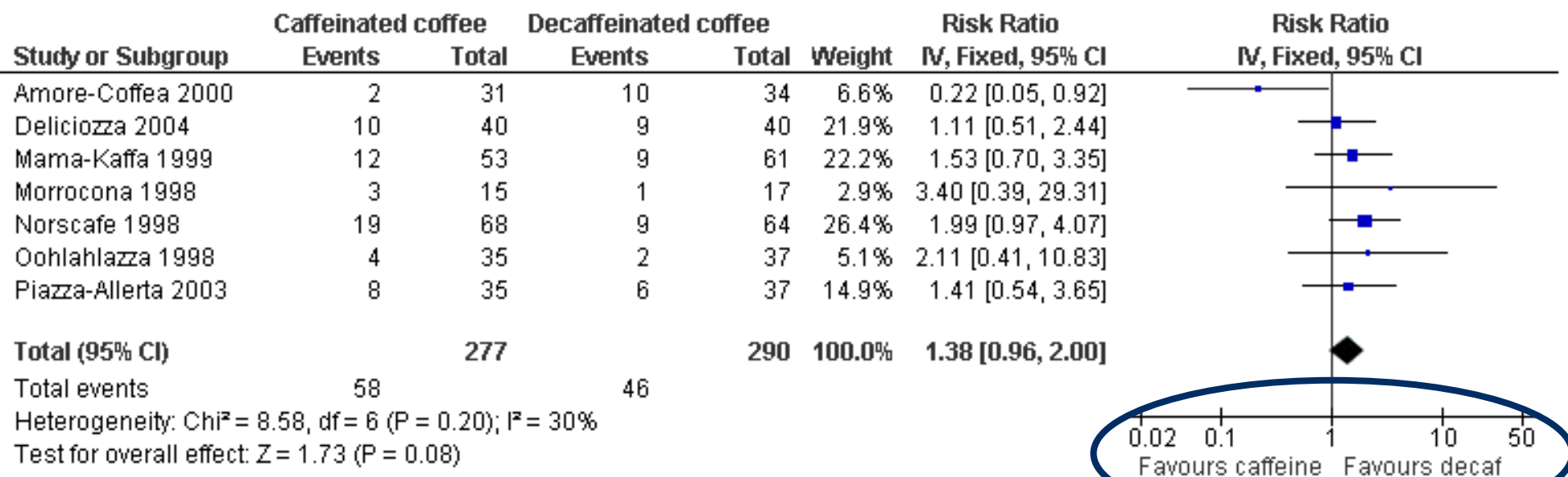
Test for overall effect: $Z = 1.73$ ($P = 0.08$)



- effect estimate for each study, with CI

Forest plots

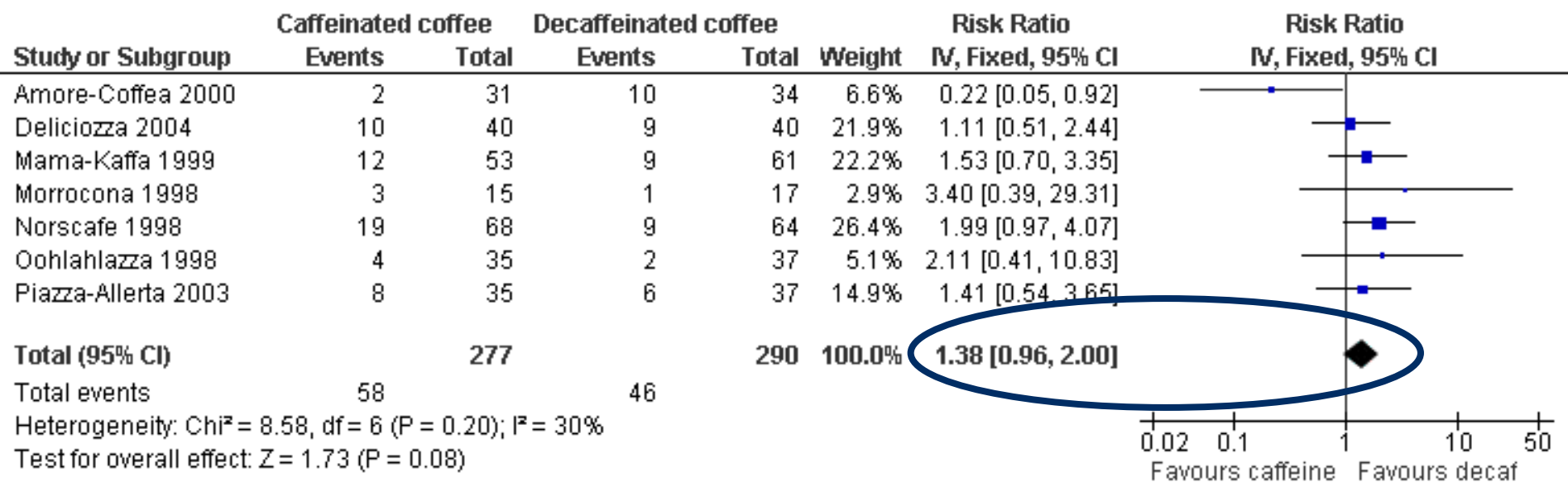
Headache at 24 hours



- scale and direction of benefit

Forest plots

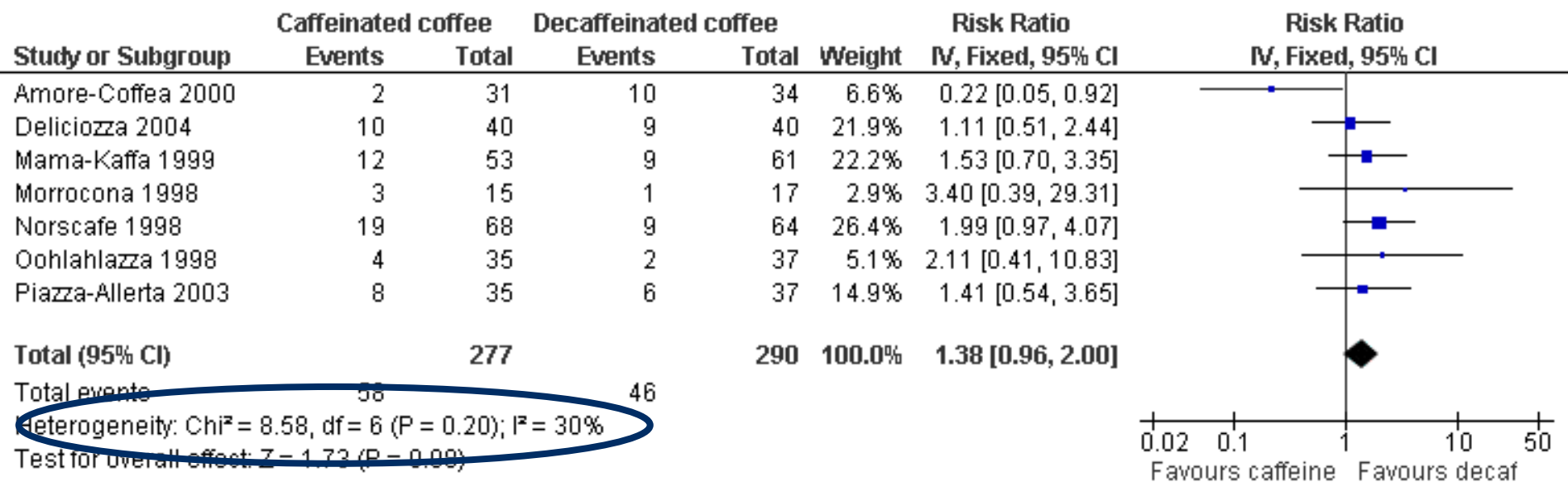
Headache at 24 hours



- pooled effect estimate for all studies, with CI

Forest plots

Headache at 24 hours



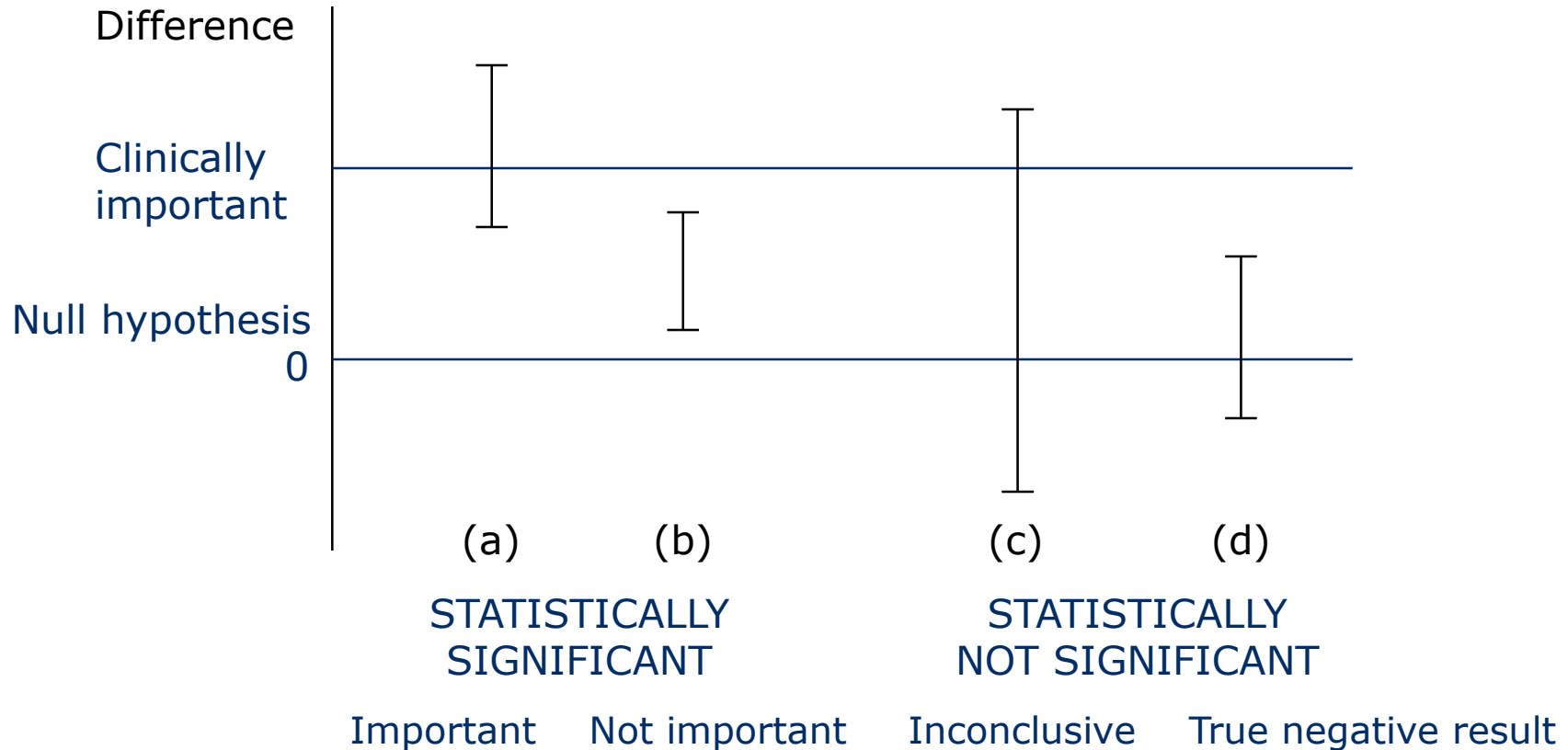
- Heterogeneity

Interpreting confidence intervals

- always present estimate with a confidence interval
- precision
 - point estimate is the best guess of the effect
 - CI expresses uncertainty – range of values we can be reasonably sure includes the true effect
- significance
 - if the CI includes the null value
 - rarely means evidence of no effect
 - effect cannot be confirmed or refuted by the available evidence
 - consider what level of change is clinically important

Statistical and clinical significance

(from Berry G. (1986), *Med. J. Aust*, 144: 618-619)



Presenting data in your review

- present outcomes in consistent order throughout
 - Abstract, Methods, Results, data
- forest plots
 - key forest plots linked as figures
 - usually primary outcomes
 - all forest plots will be published as supplementary data
 - avoid forest plots with only one study
- may also add other data tables
 - results of single studies
 - summary data for each group, effect estimates, confidence intervals
 - non-standard data

What to include in the protocol

- how will you decide whether a meta-analysis is appropriate?
- meta-analysis model to be used

Take home message

- there are several advantages to performing a meta-analysis but it is not always possible (or appropriate)
- plan your analysis carefully, including comparisons, outcomes and meta-analysis methods
- forest plots display the results of meta-analyses graphically
- interpret your results with caution

References

- Deeks JJ, Higgins JPT, Altman DG (editors). **Chapter 9: Analysing data and undertaking meta-analyses.** In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from <http://community.cochrane.org/handbook>
- Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. **Chapter 11: Presenting results and 'Summary of findings' tables.** In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from <http://community.cochrane.org/handbook>

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