

Heterogeneity

Tabriz University of Medical
Sciences
Standard Workshop on Systematic
Reviews _ October 2012
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Outline

- what is heterogeneity?
- causes of heterogeneity
- identifying heterogeneity
- dealing with heterogeneity
- fixed and random effects meta-analysis



What is heterogeneity?

- Heterogeneity is variation between the results of a set of studies



Causes of heterogeneity: clinical

Differences between studies with respect to:

- participants
 - conditions under investigation, eligibility criteria for trials, geographical variation
- interventions
 - e.g. type of drug, intensity, dose, duration, mode of administration, experience of practitioners, nature of control (placebo, none, standard care)
- outcomes
 - e.g. type, follow-up duration, ways of measuring outcomes, definition of an event



Causes of heterogeneity: methodological

Differences between studies with respect to:

- design
 - e.g. randomised vs non-randomised, parallel group vs crossover vs cluster randomised, length
- conduct
 - e.g. allocation concealment, blinding, approach to analysis, imputation methods for missing data



Statistical heterogeneity

- excessive variation in the results of studies above that expected by chance



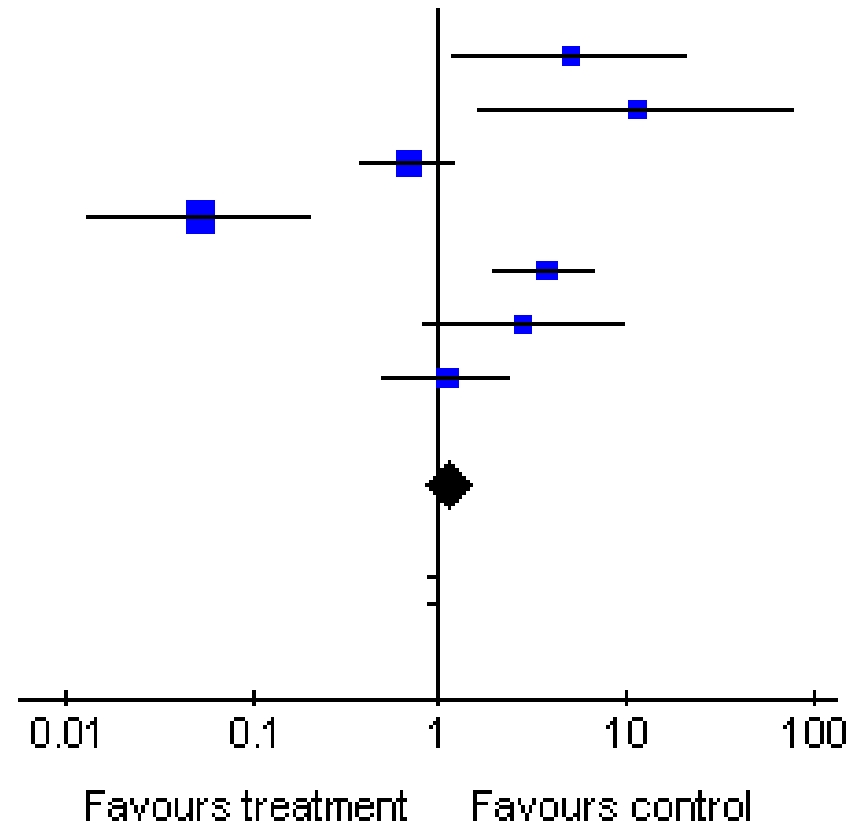
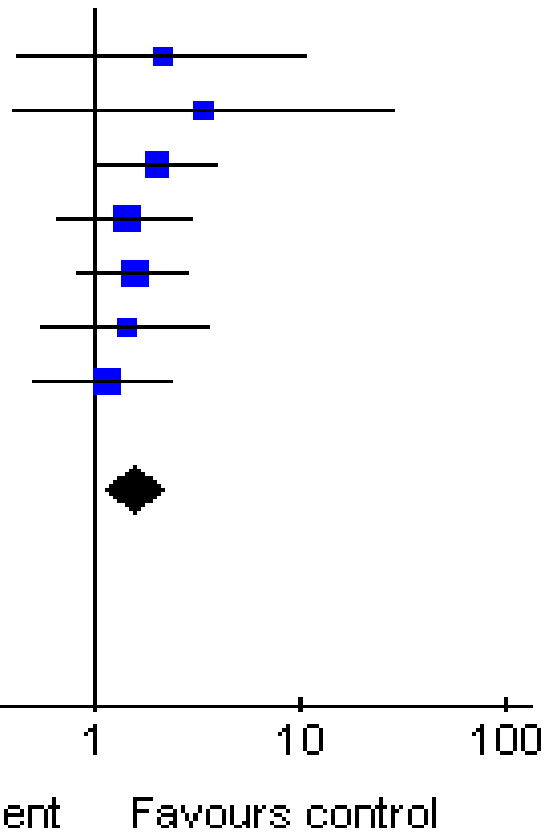
Identifying heterogeneity

1. graphically – the eyeball test
2. numerically – the I^2 test



Forest plot A

Forest plot B



Quantifying heterogeneity

- I^2 describes the proportion of total variation across studies that is due to heterogeneity rather than chance
- based on Cochran Q test and its degrees of freedom
- $I^2 = \frac{(Q - df)}{Q} \times 100\%$ (df = the number of studies minus 1)

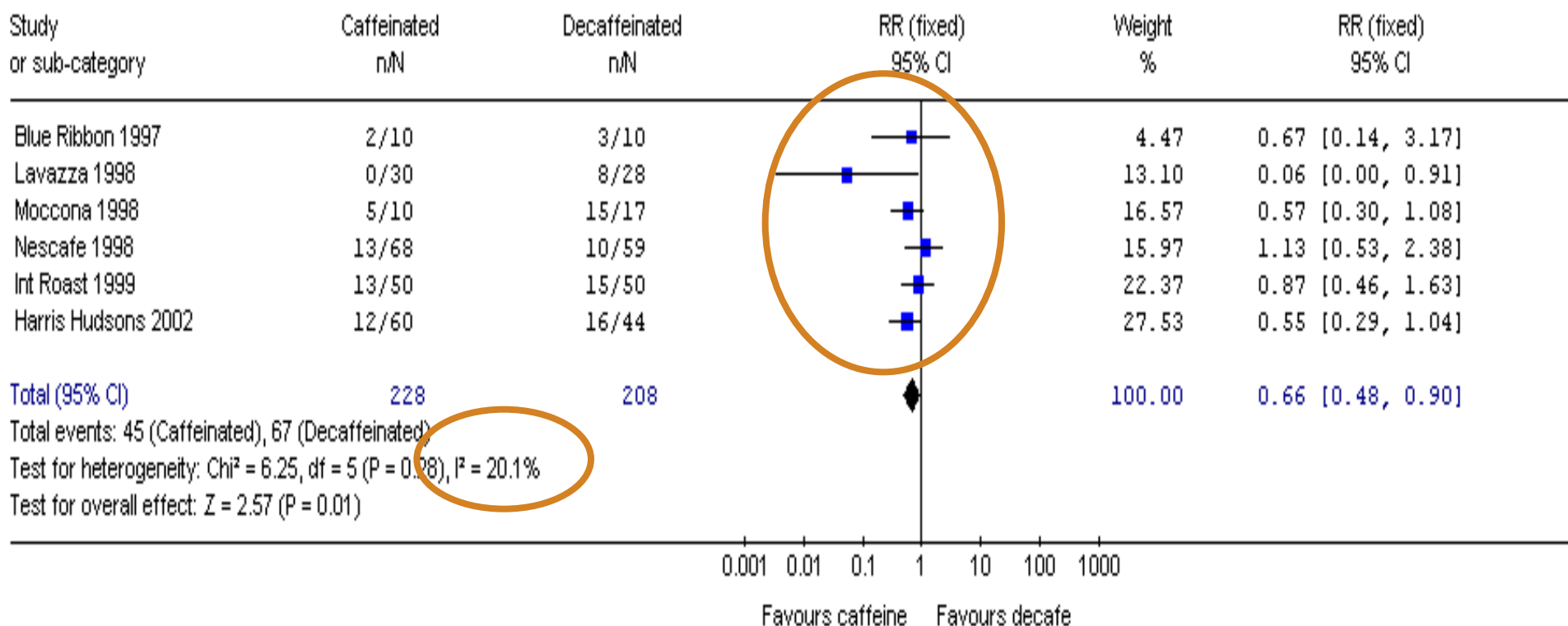


Quantifying heterogeneity

- low (and negative) values of I^2 indicate no, or little, heterogeneity
- larger values of I^2 show increasing heterogeneity
- roughly, values of 25%, 50% and 75% correspond to low, moderate and high levels of heterogeneity (Higgins et al 2003, BMJ)



Review: Caffeine for daytime 'sluggishness'. (version with data)
 Comparison: 01 Caffeinated Coffee versus Decaffeinated Coffee
 Outcome: 09 Asleep at the end of the lecture



Dealing with heterogeneity

Options available to you:

1. check the data
2. don't pool studies
3. ignore heterogeneity: use fixed effect model
4. investigate reasons for heterogeneity
5. incorporate heterogeneity: use random effects model



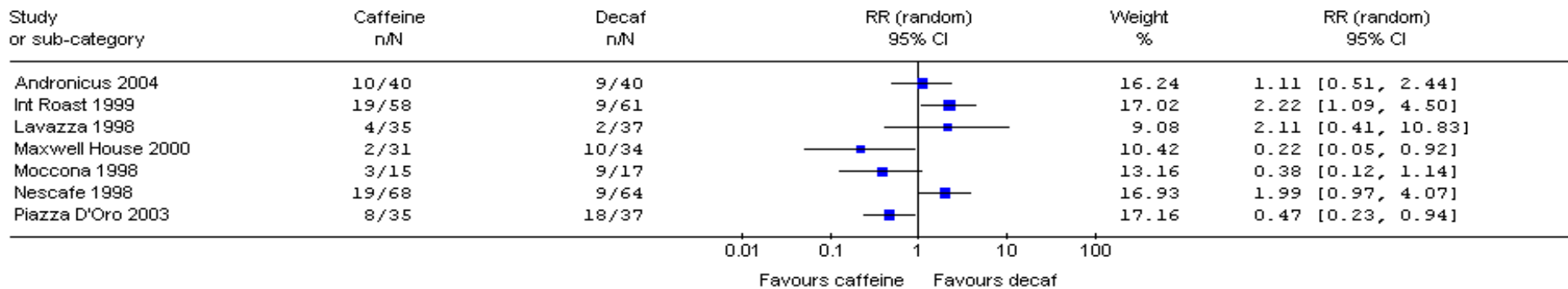
Option 1: Check the data

- Check extracted data
- Check analyses of individual studies



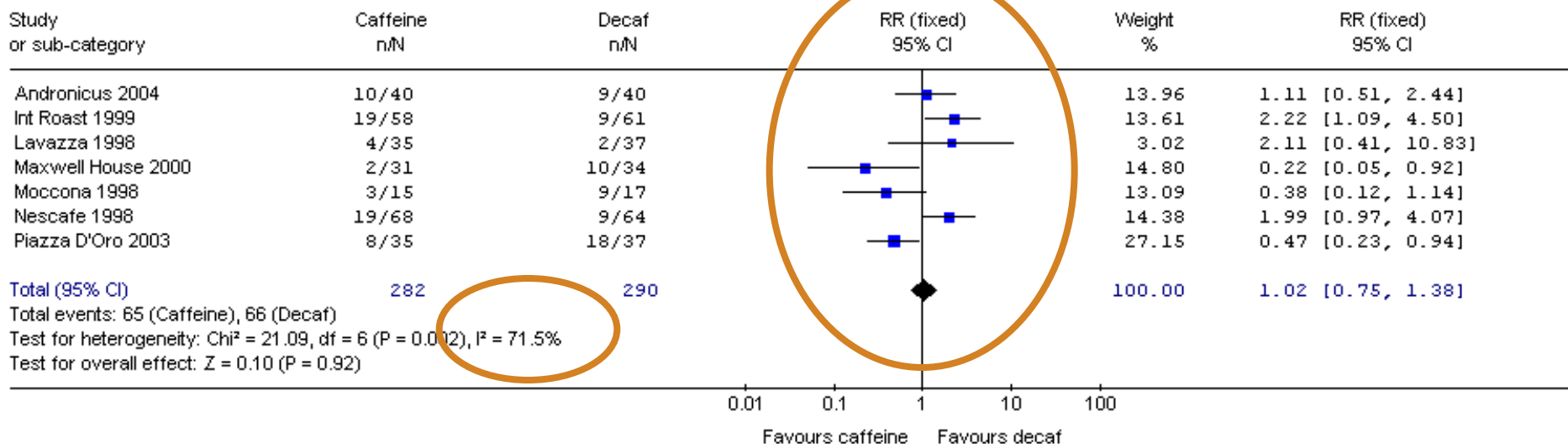
Option 2: Don't pool studies

Review: Caffeine for daytime 'sluggishness'. (Version 251105)
 Comparison: 01 Caffeinated Coffee versus Decaffeinated Coffee
 Outcome: 02 Headache



Option 3: Ignore heterogeneity

Review: Caffeine for daytime 'sluggishness'. (Version 251105)
 Comparison: 01 Caffeinated Coffee versus Decaffeinated Coffee
 Outcome: 02 Headache



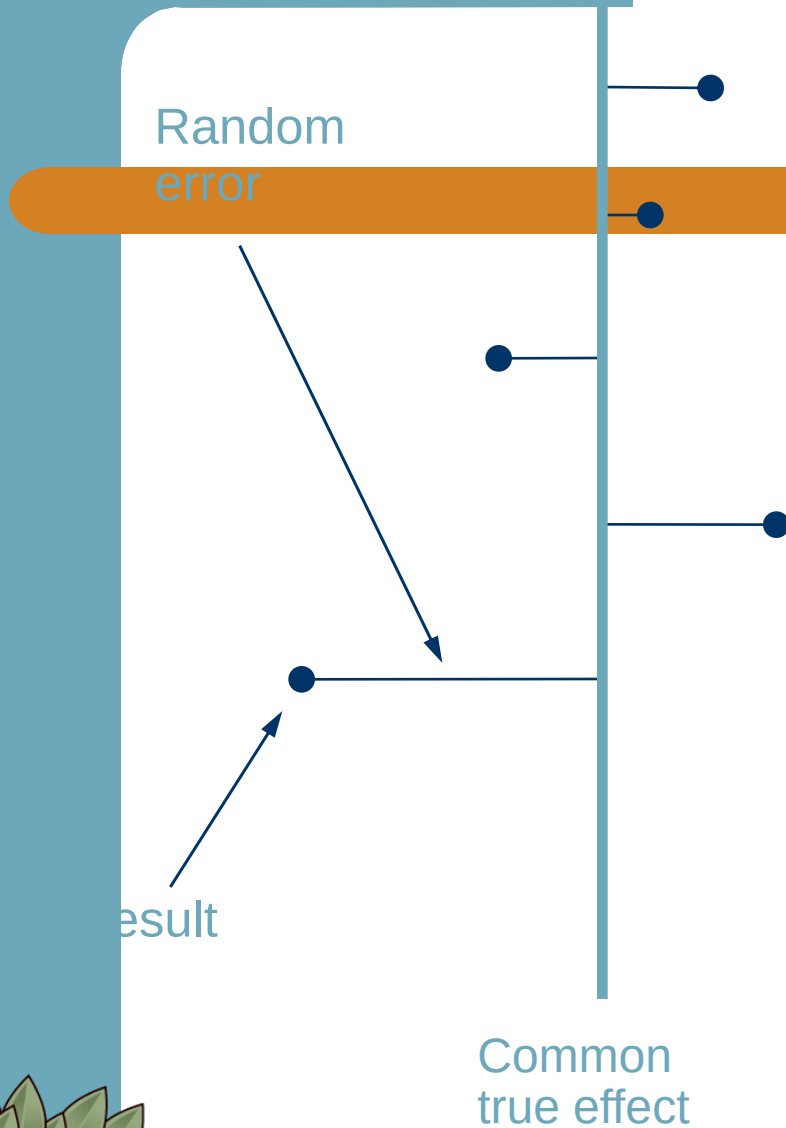
Fixed effect model

Philosophy behind model:

- there is one real value for the treatment effect
- all trials are estimating this common treatment effect



Fixed effect model



- assumes that all studies are evaluating the same treatment effect
- *i.e.* if they were all infinitely large they'd produce an identical result

Option 4: Investigating heterogeneity

- as an objective of your review
(should be pre-specified in your protocol)
- to determine causes of unexpected statistical heterogeneity
 - note. post hoc investigations should be reported as such and are hypothesis-generating at best

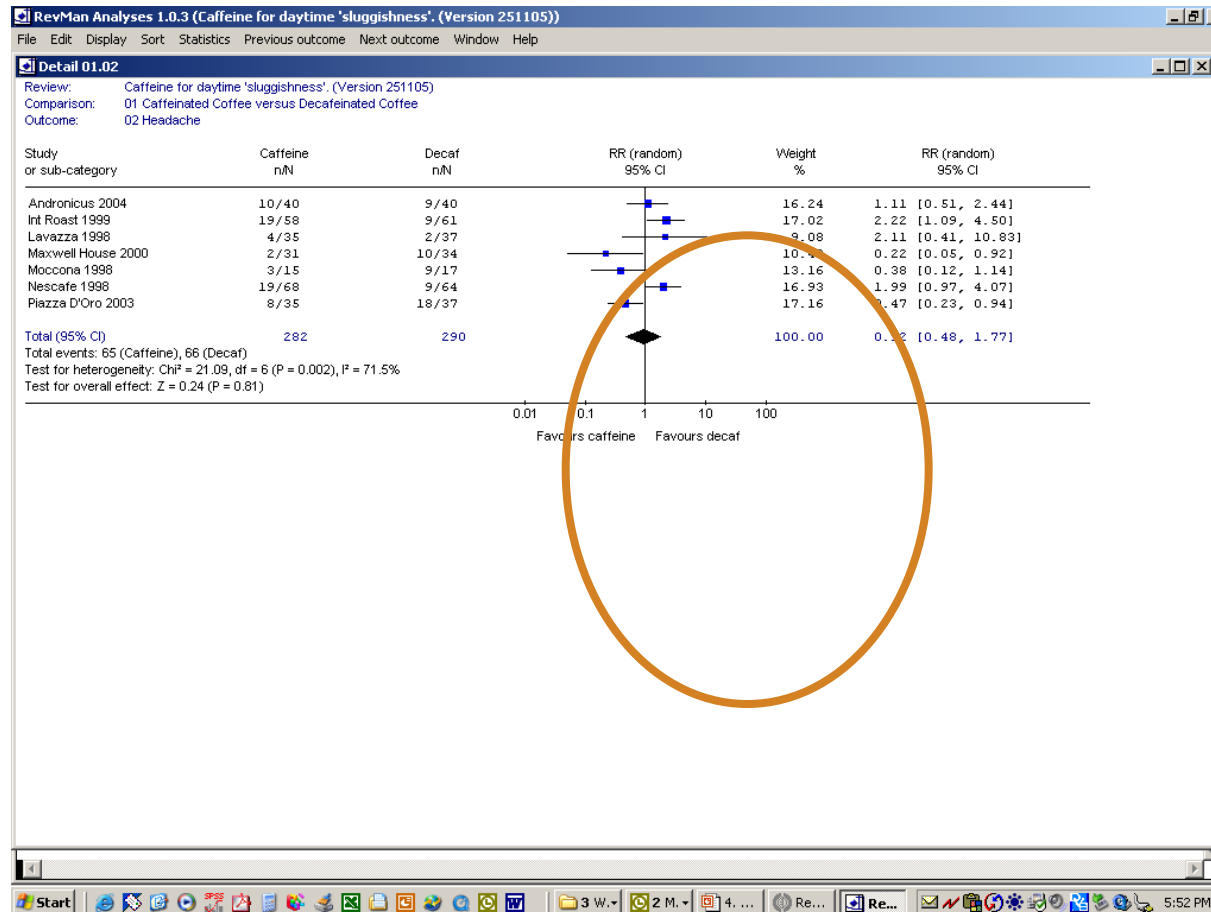


Investigating heterogeneity: tools

- subgroup analysis
 - get answers to secondary questions concerning subsets of participants or interventions
 - can yield spurious findings if not used carefully
- meta-regression
 - examine relationship between treatment effect and a particular characteristic of the study (not patients)
 - not available in RevMan
- individual patient data (IPD) meta-analysis
 - investigate patient-level characteristics
 - time consuming and expensive



Option 5: Incorporate heterogeneity

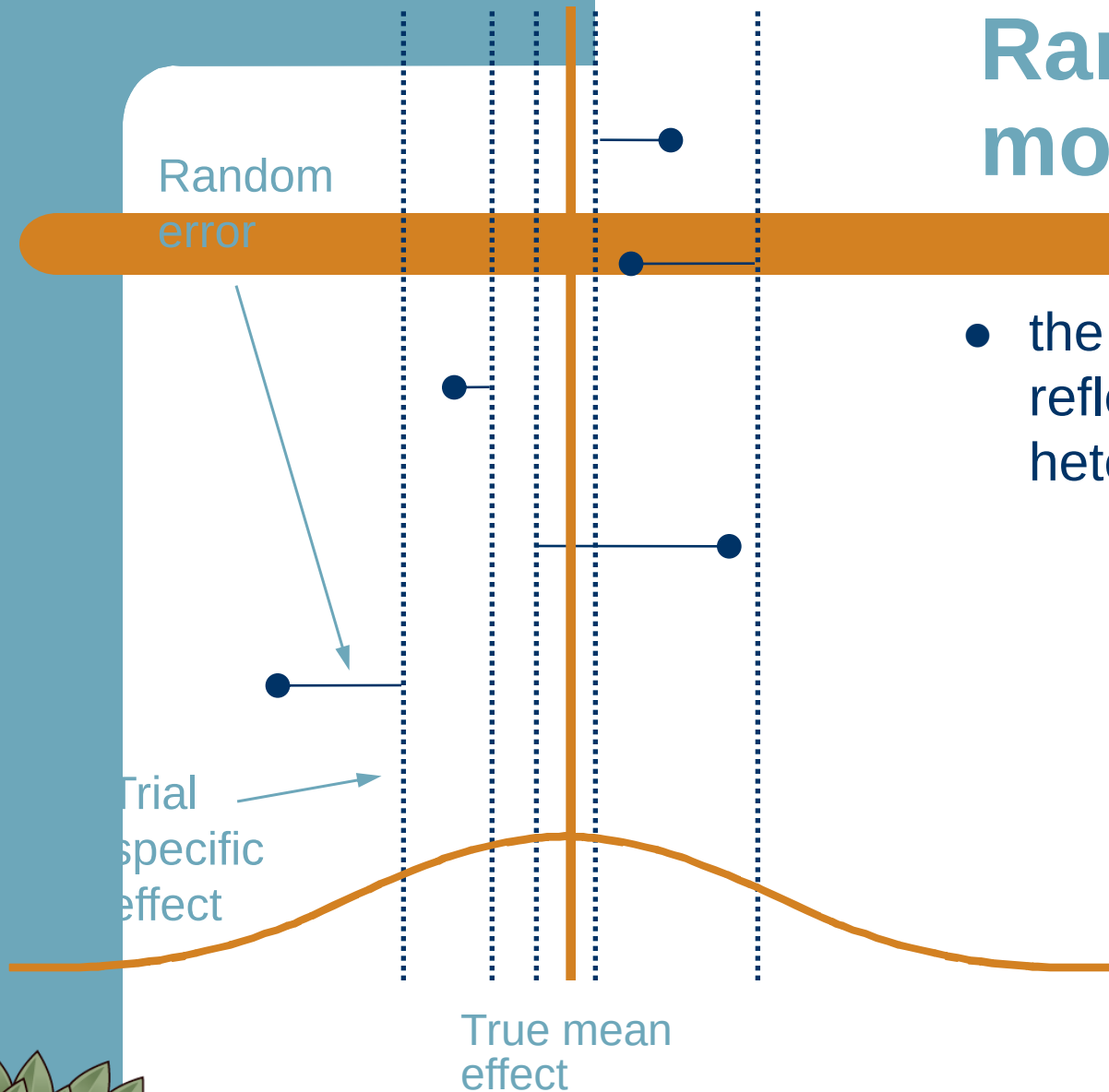


Random effects model

- if heterogeneity cannot be explained by characteristics of the studies, it may be incorporated into the meta-analysis using the random-effects model
- the true treatment effects underlying the studies are allowed to differ and are assumed to be distributed around a central (mean) value
- weights are adjusted to account for both within-study and between-study variation



Random effects model



- the width of the bell shape reflects the amount of heterogeneity

Interpreting random effects meta-analyses

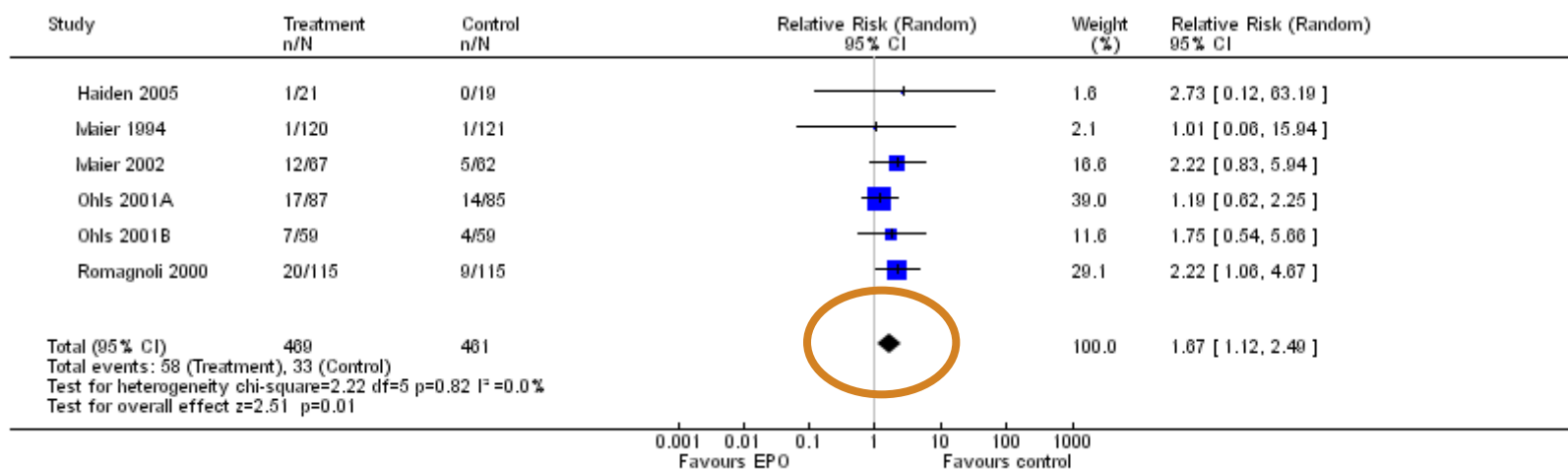
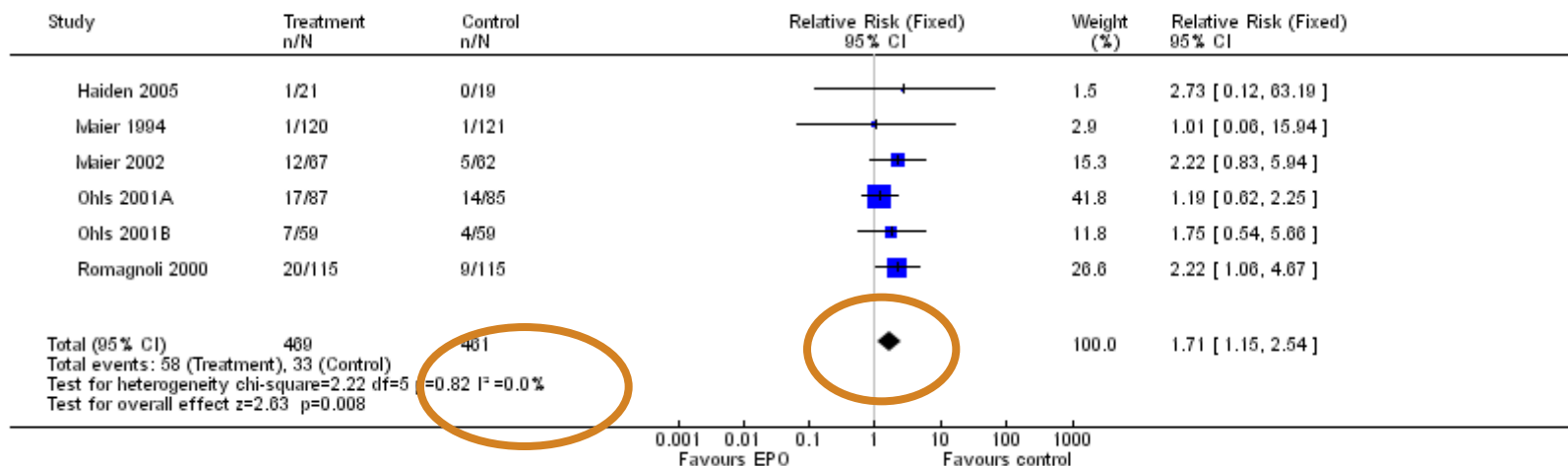
Random effects meta-analyses are...

- **identical** to fixed effect analyses when there is no clear heterogeneity
- **similar** to fixed effect meta-analyses but *with wider confidence intervals* when there is heterogeneity
- **different** from fixed effect meta-analyses when there is publication bias (or funnel plot asymmetry)
 - random effects analyses give relatively more weight to smaller studies

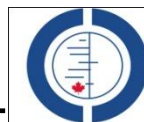


Fixed versus random effects

Review: Early erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants
 Comparison: 01 Erythropoietin vs. placebo or no treatment
 Outcome: 09 Retinopathy of prematurity (stage ≥ 3)

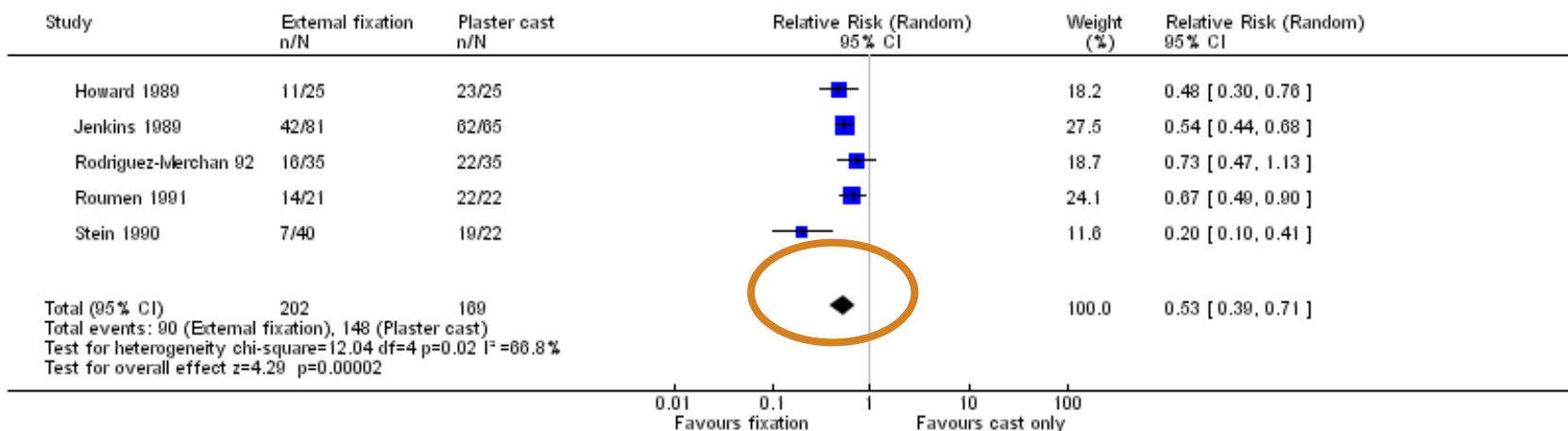
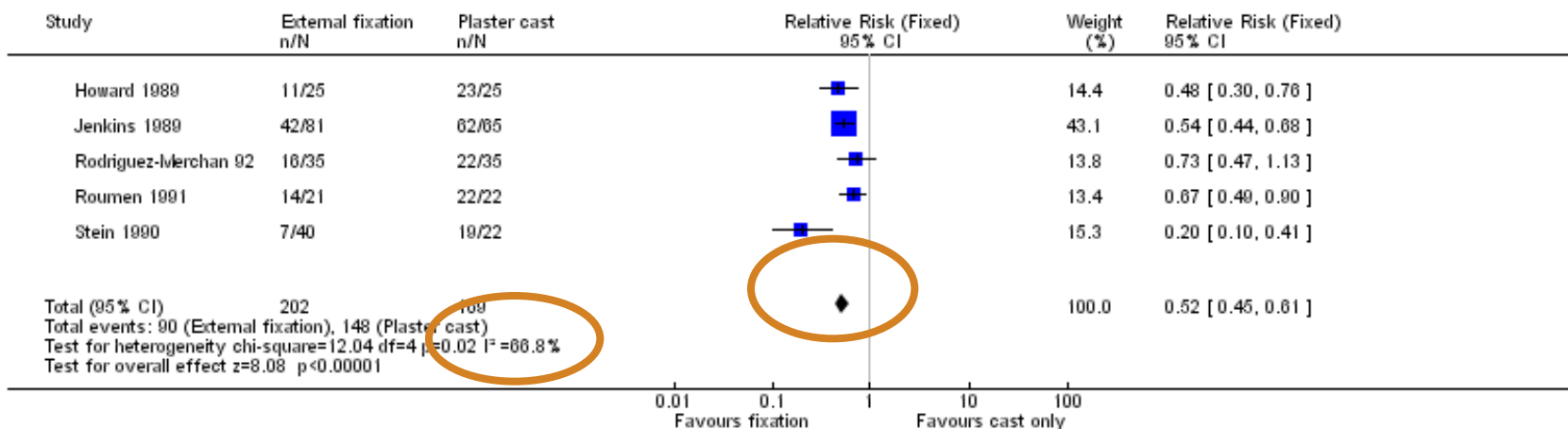


almost identical



Fixed versus random effects

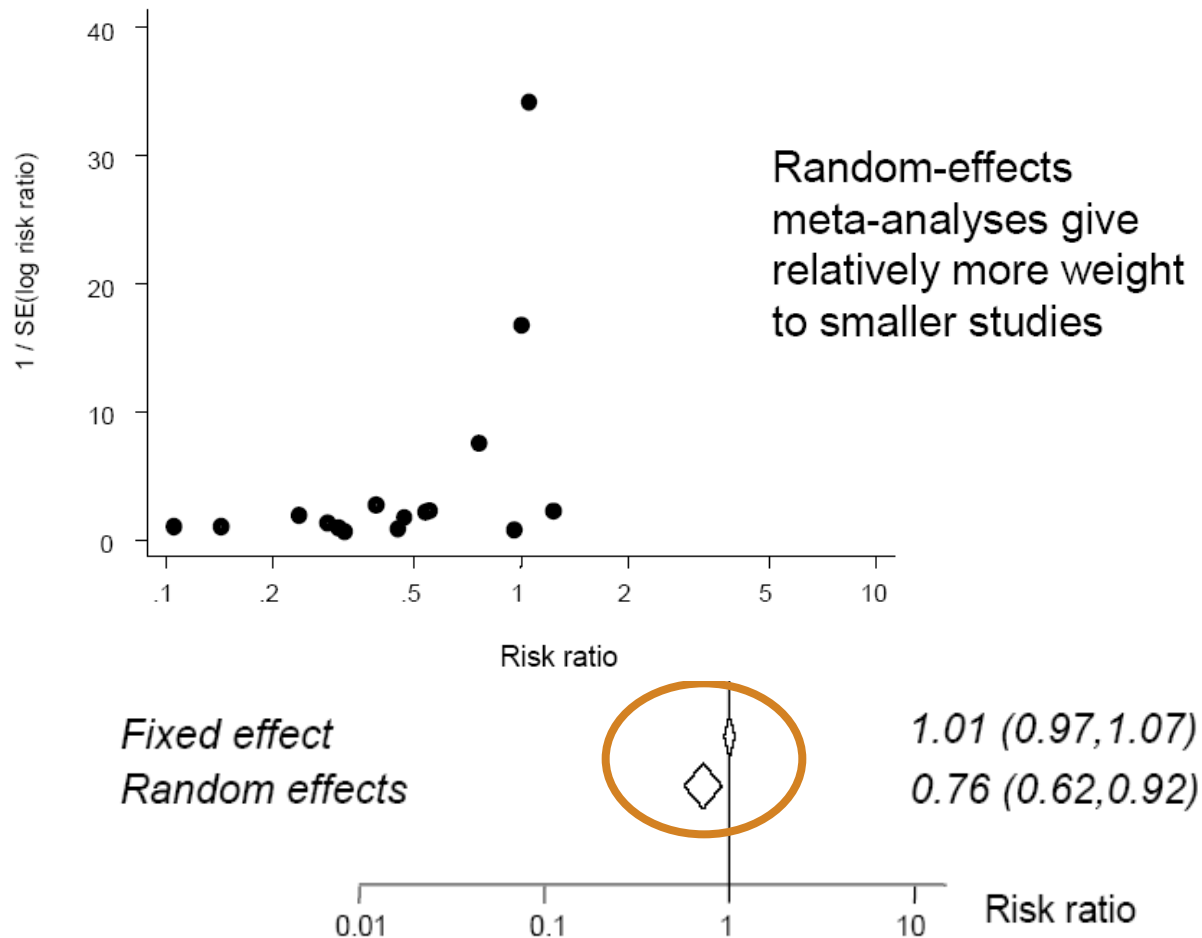
Review: Surgical interventions for treating distal radial fractures in adults
 Comparison: 01 External fixation versus plaster cast
 Outcome: 03 Anatomical grading: not excellent



similar, but wider CIs



Fixed versus random effects



very different results



Take home messages

- heterogeneity should be assessed and addressed
- statistical heterogeneity occurs when studies are not all evaluating the same treatment effect
- looking at overlap of confidence intervals on forest plot is a good way to identify statistical heterogeneity
- I^2 can quantify the degree of inconsistency across studies
- there are several options for dealing with heterogeneity
- methods to investigate heterogeneity should be pre-specified in the protocol
- random effects meta-analyses are useful for incorporating unexplained variability into a summary
- but random effects meta-analyses are not a panacea

