Planning analysis in a systematic review

Writing analysis section of the protocol

- Which study designs are appropriate to combine?
- What treatment effect measures?
- How to identify and investigate heterogeneity?
- Fixed or random effects or both?
- How to impute missing data?
- How to address publication bias?

Planning the analysis

- Effect or Rx effect: The contrast between the outcomes of two groups treated differently.
- What is the direction of effect?
- What is the size of effect?
- Is the effect consistent across studies?
- What is the strength of evidence for the effect?

Reasons for meta-analysis

- To increase power
- To improve precision
- To check consistency or reasons for inconsistency across studies
- To settle controversies
- To generate new hypotheses.

When not to do meta-analysis in a review?

- Poor quality studies
- Different populations
- Different interventions
- Different comparisons
- Different outcomes

Planning analyses : ITT issue

What is ITT?

Includes all trial participants in the assigned groups regardless of what happened subsequently.

Issues:

1. Compliance to the protocol by patients/physicians
2. Losses to follow-up
3. Ineligibility

Available case Analysis

- Includes those with known outcome
- Three types of exclusions
  - Pre-specified, based on

    pre randomization information
  - Immediate post-randomization before Rx
  - Drop outs: assess potential impact

ITT analysis using imputation

- Dichotomous:
  Worst-case/best-case scenario analysis
- Continuous:
  last observation carried forward
- Imputing 'Zero' QOL for deaths
- (Consider hierarchy of outcomes)

Synthesis: combining

- Taking out average

- A question

Question

- A class has 200 boys and 100 girls
- Average weight: boys (70 kg), girls (40 kg)
- What is the average weight of the class?

Two studies: weight reduction prevents heart attack

- How many years follow up is required?
- Where is it easy to follow up?
- One smart proposal (2000 subjects)
- One conventional proposal

Results of the two studies

- Smart study:
  - weight reduction arm: 1/1000 events
  - Control arm: 2/1000 events
- Conventional study
  - Weight reduction arm: 75/1000 events
  - Control arm: 150/1000 events

  Should both studies get equal weight?

  Which study should get more weight?

Assigning weight to studies

- Based on quality (less the systematic error, more the weight)
- Based on sample size
- Based on number of outcome events

Dealing with students’ complaint

Students' union writes to the Dean

- There has been a problem with the examination results
- Some students who failed were actually good
- Some students who passed were not good at all.

Dean appoints a committee

- To examine whether there is really a need to investigate this?
- If so, then investigate the problem.

Overview of the examination

- Written exam: Full marks 100
- Practical: Full marks 100
- Oral (Viva-voce): Full marks 100
- Pass marks: 50% of total overall

FOUR PATTERNS

Parts of exam	Pattern 1	Pattern 2	Pattern 3	Pattern 4
Written (100)	55	15	40	90
Practical (100)	60	70	45	20
Oral (viva-voce) (100)	65	80	35	15
Total (300)	180 (60%) Pass	165 (55%) Pass	120 (40%) Fail	135 (45%) Fail

Patterns to investigate

- Patterns 2 and 4
- Why?

- Unacceptable because the marks are dissimilar across the various evaluations.
- Acceptable when the marks are similar.
- Any scientific word (synonym) for similarity?

Acceptability depends on

- similarity across evaluations
- Similarity = homogeneity
- Dissimilarity = heterogeneity

How does it fit with meta-analysis?

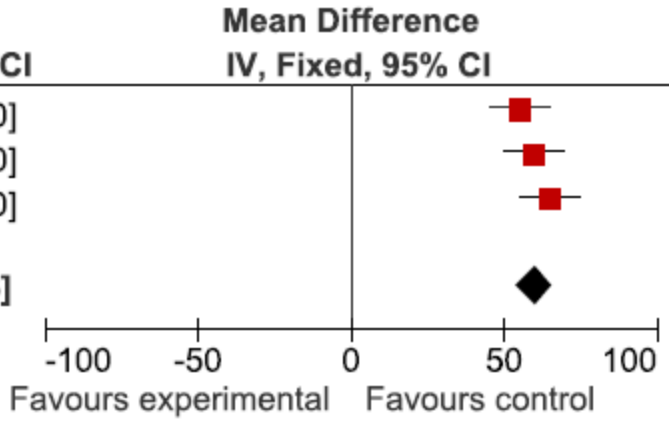
- Meta-analysis is a study of studies.
- Nothing but taking out an average from two or more measurements.
- Each study evaluates and measures the effect.
- Summary effect measure is the average.
- Acceptable if there is homogeneity across the studies
- If there is heterogeneity, investigate.

PATTERN 1

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Oral_a	55	5	33.3%	55.00 [45.20, 64.80]
Practical_a	60	5	33.3%	60.00 [50.20, 69.80]
Written 1010a	65	5	33.3%	65.00 [55.20, 74.80]
Total (95% CI)			**100.0%**	**60.00 [54.34, 65.66]**

Heterogeneity: $Chi^2 = 2.00$, $df = 2$ ($P = 0.37$); $I^2 = 0\%$

Test for overall effect: $Z = 20.78$ ($P < 0.00001$)

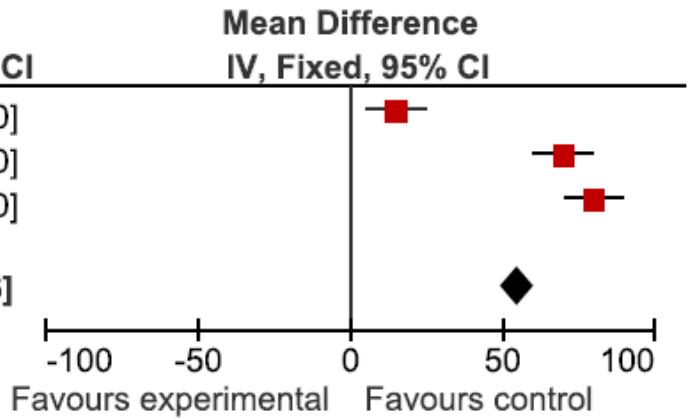


PATTERN 2

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Oral_a	15	5	33.3%	15.00 [5.20, 24.80]
Practical_a	70	5	33.3%	70.00 [60.20, 79.80]
Written 1010a	80	5	33.3%	80.00 [70.20, 89.80]
Total (95% CI)			**100.0%**	**55.00 [49.34, 60.66]**

Heterogeneity: Chi² = 98.00, df = 2 (P < 0.00001); I² = 98%

Test for overall effect: Z = 19.05 (P < 0.00001)

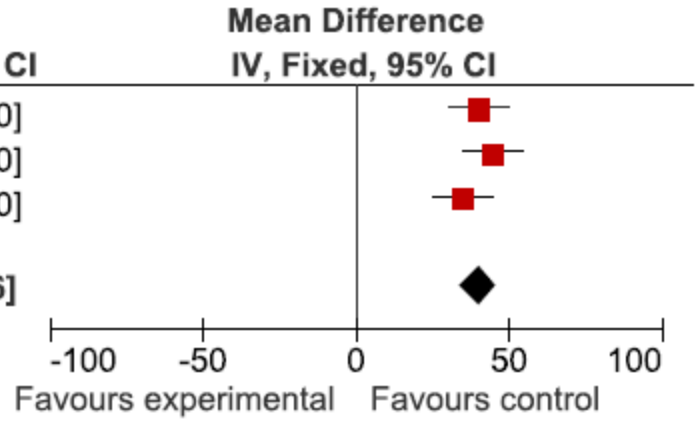


PATTERN 3

Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Oral_a	40	5	33.3%	40.00 [30.20, 49.80]
Practical_a	45	5	33.3%	45.00 [35.20, 54.80]
Written 1010a	35	5	33.3%	35.00 [25.20, 44.80]
Total (95% CI)			**100.0%**	**40.00 [34.34, 45.66]**

Heterogeneity: Chi² = 2.00, df = 2 (P = 0.37); I² = 0%

Test for overall effect: Z = 13.86 (P < 0.00001)

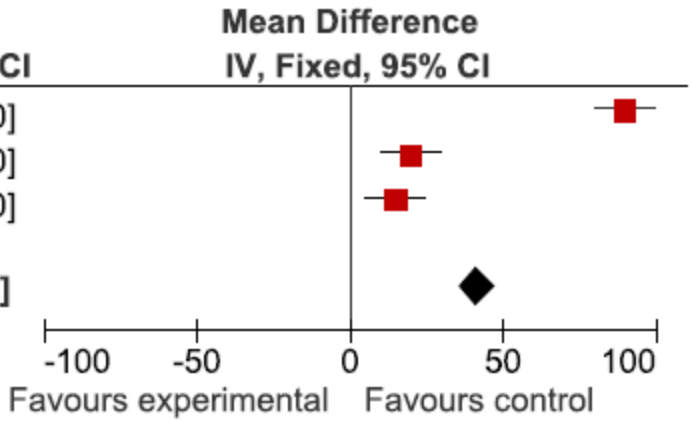


PATTERN 4

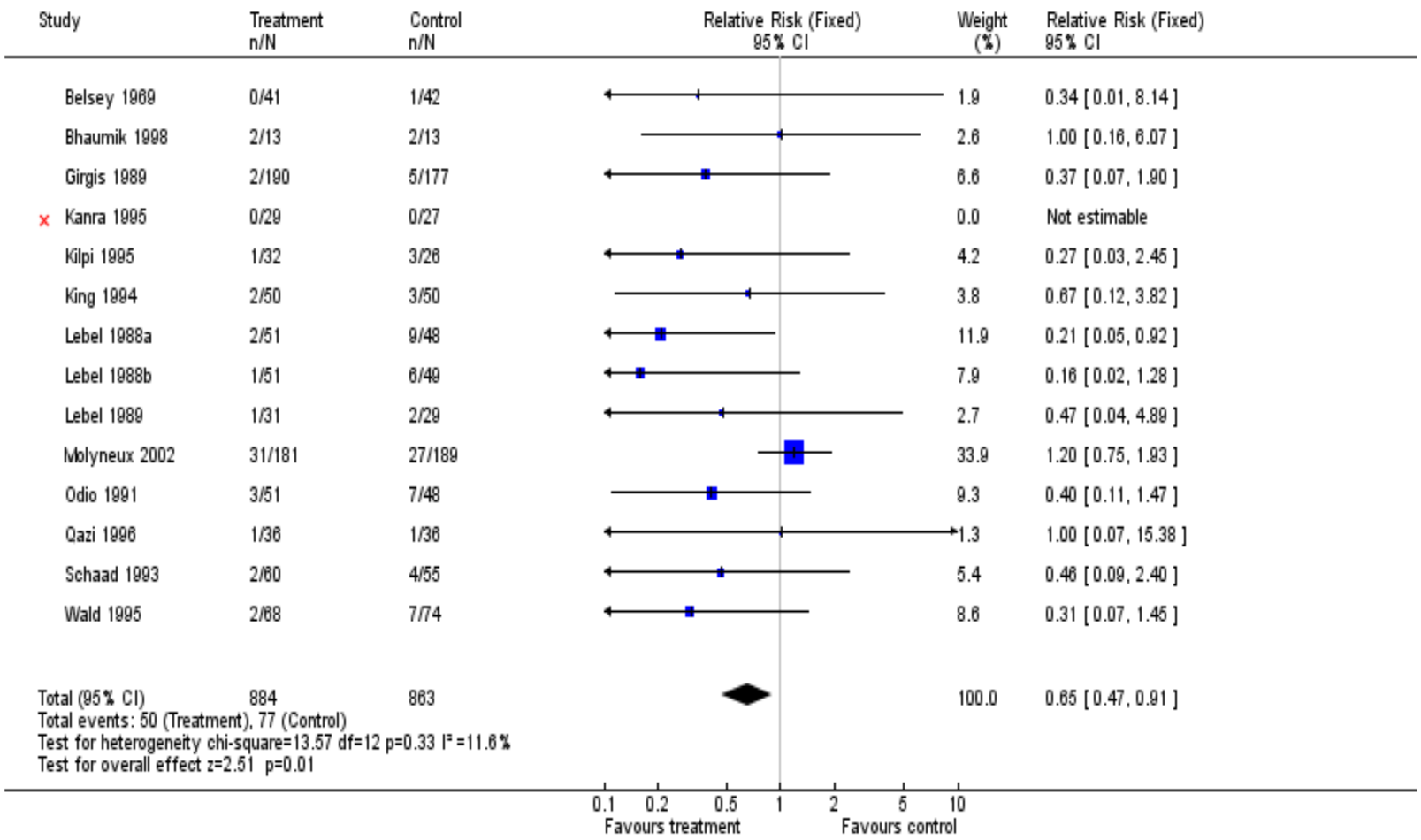
Study or Subgroup	Mean Difference	SE	Weight	Mean Difference IV, Fixed, 95% CI
Oral_a	90	5	33.3%	90.00 [80.20, 99.80]
Practical_a	20	5	33.3%	20.00 [10.20, 29.80]
Written 1010a	15	5	33.3%	15.00 [5.20, 24.80]
Total (95% CI)			**100.0%**	**41.67 [36.01, 47.32]**

Heterogeneity: Chi² = 140.67, df = 2 (P < 0.00001); I² = 99%

Test for overall effect: Z = 14.43 (P < 0.00001)



Review: Corticosteroids for acute bacterial meningitis
Comparison: 01 All patients
Outcome: 02 Severe hearing loss



Review: Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis
Comparison: 01 Third generation cephalosporins versus conventional therapy
Outcome: 01 Death

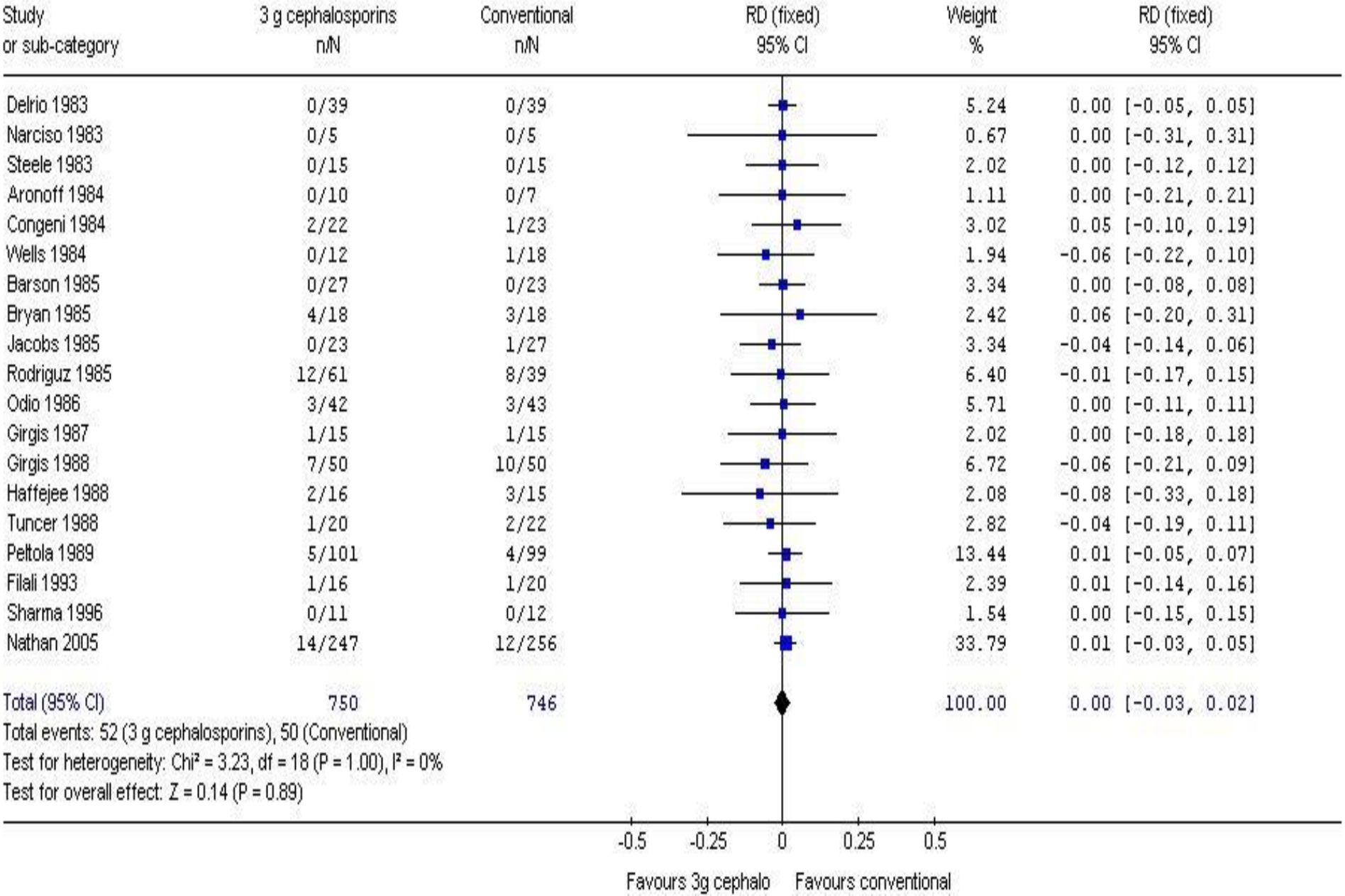
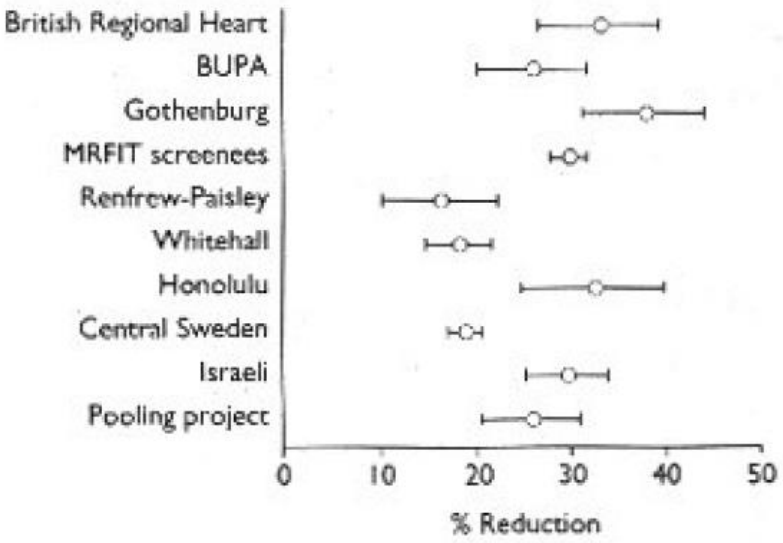


Figure 2. Percentage reduction in risk of ischaemic heart disease (and 95% confidence intervals) associated with 0.6 mmol/l serum cholesterol reduction in 10 prospective studies of men (Thompson 1994)



Take home message

- In a meta-analysis
- Results are acceptable if there is homogeneity
- Need to investigate if there is heterogeneity
- Heterogeneity lowers the level of evidence

Heterogeneity

- Variability among studies
- Three types
  - clinical (different Rx effect)
  - Methodological (different degree of bias)
  - statistical (due to above)
- Apples and oranges are all fruits

Identifying heterogeneity

- Closeness of point estimates
- Overlap of CIs
- Chi-squared test (false negative, false positive)
- I^2 = quantifies inconsistency.
- I^2 = percent of variability in effect estimates that is due to heterogeneity.

Addressing heterogeneity

- Check data
- Do not meta-analyse
- Explore heterogeneity (meta-regression)
- Ignore heterogeneity
- Incorporate heterogeneity
- Exclude studies or do sensitivity analysis

WHICH FORMULA TO USE FOR COMBINING?

Fixed vs Random effects model

- Fixed : differences solely due to chance
- Random : do not know why the effects are different (consider as if they were random)
- Normal distribution of effect
- Both co-incide if no heterogeneity
- Random : more weight to small studies and exacerbates publication bias.
- Few small trials – M- H method but ignores heterogeneity.

Sensitivity analyses

- Do results change by different ways of doing the meta-analysis?
- Do not change –'robust' results
- Do Change – 'sensitive'
- What if change inclusion criteria
- Include / exclude borderline studies
- Change outcomes
- Impute 'missing data' differently
- Random vs fixed effects.

Publication bias

- Positive results are favored for publication
- Investigate using 'funnel plot'
- Scatter plot of Rx effects of individual studies(x-axis) against a measure of sample size (y-axis)
- Symmetrical = no publication bias
- Asymmetry = has many causes.

Summary

- Quantitative/mathematical process of combining results from more than one study is meta-analysis.
- Sometimes, not advisable to do meta-analysis
- To do it select measure of effect (association), model for combining.
- Deal with missing data
- Investigate heterogeneity, do sensitivity analysis.

Thank You

RR vs OR

Death

- EGR/CGR
- 20%/60%
- RR=1/3
- Odds ratio = ¼*2/3
- RRR=0.66
- OR= 1/6

Survival

- EGR/CGR
- 80%/40%
- RR=80/40=2
- RBI = 100%
- OR =4*(3/2)= 6