Systematic review

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Overview

- Over 2,000,000 articles are published in over 20,000 journals, annually in the biomedical literature.
- No scientific study stands alone - it is one piece of a jigsaw.

Framework

- What precise questions drives the review?
  - What is the average effect?
  - Who benefits most?
  - Will the treatment work here?
- What studies should we include?
  - All studies?
  - Stratified by key characteristics?
  - Expert selection?
- Should findings be adjusted for publication bias?
  - Track down all studies
  - Statistical adjustment

What is evidence-based medicine (EBM)?

- The conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient' (Sackett, 1996).

Two types of knowledge

- Michael Polanyi (1964) made a theoretical/ philosophical distinction between two types of knowledge used not only by people in everyday life but also by healthcare professionals during practice.
  - Tacit knowledge
  - Explicit knowledge

Tacit knowledge

- Subconsciously understood or applied.
- Difficult to articulate.
- Developing from direct action and experience.
- Shared through conversation, story-telling etc.

Explicit Knowledge

- Can be precisely and formally articulated.
- Easy to codify, document, transfer, share, and communicate.

- Evidence-based medicine is calling for explicit knowledge.

Definition

- Systematic review
  - A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review.
- Meta-analysis
  - The use of statistical techniques in a systematic review to integrate the results of included studies.

Why carry out a systematic review?

- The volume of scientific knowledge relevant to health care is vast.
- A single study adds data to the knowledge base, but is rarely definitive.
- Studies use a variety of methods, are of variable quality, and may appear to have contradictory findings.
- A systematic review efficiently integrates valid information and provides a basis for rational decision making that is based on the totality of the available evidence.

Outcome

- Resolve conflicting evidence
- Explain variations in study results
- Answer questions where the answer is uncertain
- Confirm the appropriateness of current practice

- Primary aim of a systematic review is to summarise and help people understand the evidence.

Steps in a systematic review

- Formulate the review question
- Write the protocol
- Search for and select primary studies
- Assess study quality
- Abstract relevant data
- Analyse data
- Interpret results
- Write report

Contents of the protocol

- Background information and objectives
- Inclusion/exclusion criteria for studies
- Search strategy for identifying studies
- Methods for data abstraction
- Assessment of methodological quality
- Statistical methods to be used

PICO model

- Participants
- Interventions
- Comparisons
- Outcomes

Case I

- Investigate the effect of Estrogen Replacement Therapy on Osteoporosis and Breast or Endometrial Cancer in Post-Menopausal Women?

Case I

- **Participants**
- **Interventions**
- **Comparisons**
- **Outcomes**

Case II

- A 28 year old male presents with recurrent furunculosis for the past 8 months; these episodes have been treated with drainage and several courses of antibiotics, but they have kept recurring. He asks you if recurrences can be prevented?

- Among patients with recurrent furunculosis, does the use of prophylactic antibiotics, compared to no treatment, reduce the recurrence rate?

Case II

- **Participants**
- **Interventions**
- **Comparisons**
- **Outcomes**

Search strategy

- Search electronic databases
  - Use key words in title and abstract
  - Standardised subject terms particular to that database
- Hand search
  - Manual page-by-page search of the entire journal
- Conference proceedings
  - Abstracts and other grey literature

Search strategy

- Check reference lists of other review articles
- Print versions of electronic databases
  - For citations before the electronic ones if it is thought there may be relevant early studies
- Identify unpublished studies
  - May be important to minimise bias, but no easy way to obtain information about studies that have been completed but not published

Database

- Medline - world's largest general biomedical database, indexes ~ 1/3 of all biomedical articles
- CINAHL - for Nursing and allied health studies
- Psycinfo – psychology / psychiatry related
- Embase – medical and pharmacological
- Cochrane Library - for therapies and interventions, provides systematic reviews of trials of health care interventions and a registry of controlled trials

Cochrane Collaboration

- The Cochrane Collaboration is an international organisation that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of healthcare interventions.

The Cochrane Library

- This is the main output of the Collaboration, updated quarterly and distributed on an annual subscription basis on disk, CD-ROM and via the Internet. It currents includes several different databases:
- The Cochrane Database of Systematic Reviews
- The Database of Abstracts of Reviews of Effectiveness
- The Cochrane Controlled Trials Register
- The Cochrane Review Methodology Database
- The Cochrane Collaboration section

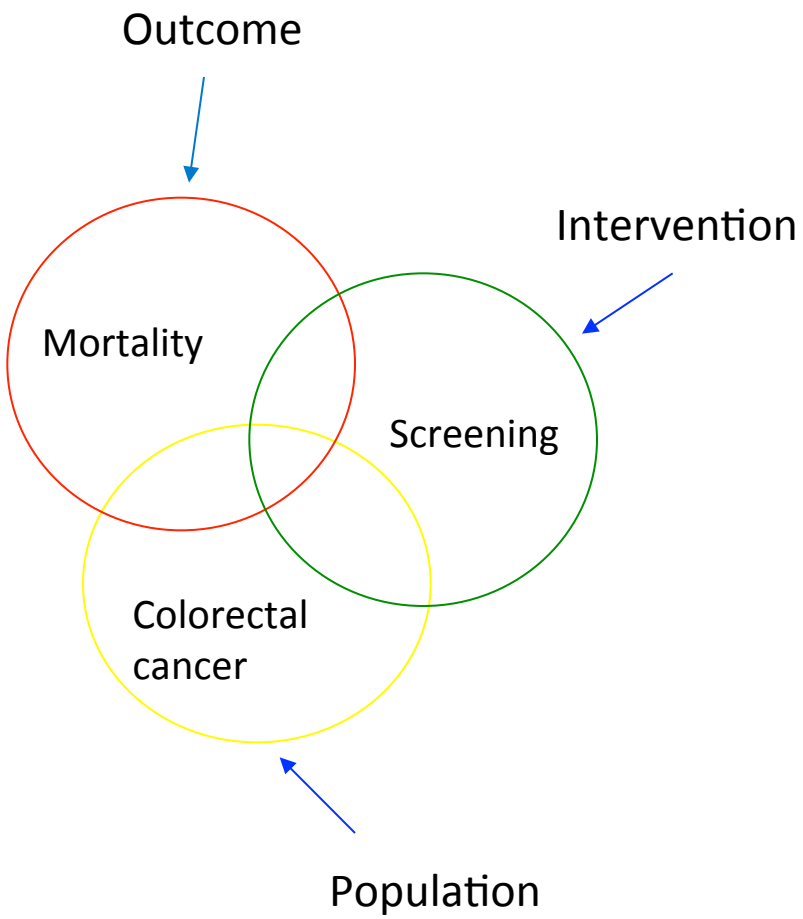
An effective search strategy

- Example:

  What is the mortality reduction in colorectal cancer as a result of performing haemoccult of the stool (faecal occult blood test) screening in well-appearing adults?

An effective search strategy

- Identify key words / concepts
- PICO format:
  - **P**opulation of interest
  - **I**ntervention
  - **C**omparison
  - **O**utcome of interest



Organising studies

- Keep track of all studies identified in the search in a reference management system such as ProCite, EndNote, Reference Manager.
- Check for duplicates
  - A study may only be included in an analysis once otherwise bias will be introduced, therefore important to only include each study (not report) once
- Search can be time consuming and challenging but it is very important, a systematic review can only be good if it includes all relevant studies

Assessment of study quality

- Quality of a systematic review largely depends on the quality of the primary studies included in the review
- Quality usually assessed during data abstraction
- Quality assessment of studies may limit bias

Assessment of study quality

- Factors to be assessed are those related to
  - Applicability of findings
  - Validity of individual studies (clear indications of bias: incomplete data, selective reporting)
  - Certain design characteristics that affect interpretation of results (no clear sample size, setting, randomisation)

Possible biases

- Selection bias
  - Systematic differences between the groups that are compared
  - Systematic differences between those selected for study and those that aren't
- Attrition bias
  - Systematic differences between comparison groups in withdrawals or exclusions of participants from the results of a study (most common: participant withdrawal)
- Detection bias
  - Systematic differences between comparison groups in how outcomes are ascertained, diagnosed or verified (different diagnostic criteria)

Possible biases

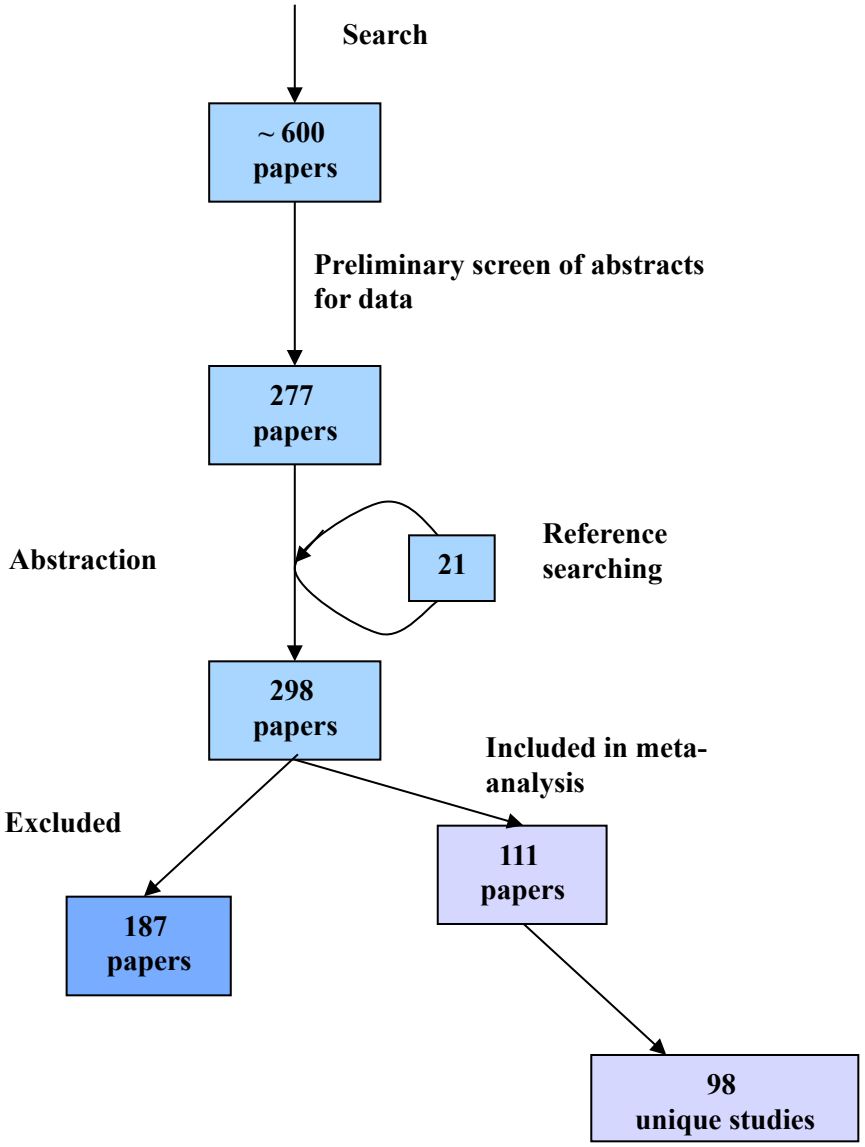
- Recall bias
  - Arises from mistakes in recollecting events both because of failures of memory, and looking at things “with hindsight” and possibly changed views (particularly cases and controls remembering things differently)
- Confounders
  - Which are important and are they measured and controlled for appropriately?
- Reporting bias
  - Caused by only a subset of the relevant data being available, either publication bias or subgroup analysis

Publication bias

- Publication bias is caused when only a subset of the relevant data is available
- Failure to include all relevant data may over (or under) estimate the effect of exposure/ intervention
- Null or non-significant findings (especially in small studies) are less likely to be reported/published than statistically significant findings

Data extraction and elimination

- Developed form to abstract relevant details from each study
- 2 reviewers independently abstracted and compared ~ 250 papers
- Duplicate studies identified and excluded by comparing
  - Authors
  - Time period
  - Country
  - Numbers of cases and controls
- Database of 98 studies for analysis



Meta-analysis

- When should we do a meta-analysis?
  - When more than one study has estimated a treatment effect.
  - When there are minimal differences in characteristics across studies.
  - When the outcome has been measured in the same way.
  - When the data in each study are available.

Methods

- Once the set of studies have been identified, for each study calculate summary statistics.
- Then, calculate a weighted average across the studies, using the inverse of the variance as weights [recall the variance is the standard error squared]
- This gives more weight to studies with small variance (ie the informative studies) and less weight to studies with high variance

What is Heterogeneity?

- Variability in estimates of treatment effects between studies
- Significant Heterogeneity suggests that trials (studies) are not estimating a single common effect – possibly due to differences in patients, intervention, setting and outcomes.

Types of Heterogeneity

- Clinical Heterogeneity
  - Variation in participants, interventions, outcomes, study designs
- Methodological
  - Variation in methods used in studies eg allocation concealment
- Statistical
  - Variation in treatment effects and results of studies

Assessment of Heterogeneity

- Fixed effects- assumes all studies are estimating the same true mean- all differences observed are due to sampling variation
- Random effects- assumes the studies them selves may differ. This introduces a 'between-studies' variance component. This needs to be incorporated into the calculations of the weighted mean and variance, and leads to wider confidence intervals.

Assessment of Heterogeneity

- There are two approaches to assessment of heterogeneity;
  1. Hypothesis testing- involves calculation of the Q statistic to test whether variation between studies is more than one would expect by chance.
  2. Estimation- the I^2 statistics provides a measure of the proportion of variation due to the between studies variation.

Assessment of study quality

- No “gold standard” for the “true” validity of a study
- Quality scale
  - Each item in a scale gets a score
  - Overall quality score by adding up scores of each item
  - Complex and not likely to be transparent to users of the review
- Simple approach – use certain “objective” criteria to decide whether a study is good, average or poor with respect to potential bias:

Scoring system

- Developed to assess relevance and quality of studies
- Simple scoring system minimised subjectivity of quality assessment
- Studies split into 3 groups
  - **Score 1** – study does not have good design (i.e. missing information too high; response rate low; no consideration given to age)
  - **Score 2** – study of good design, but insufficient control for confounding
  - **Score 3** – good design and adequate control for confounding

Dealing with heterogeneity

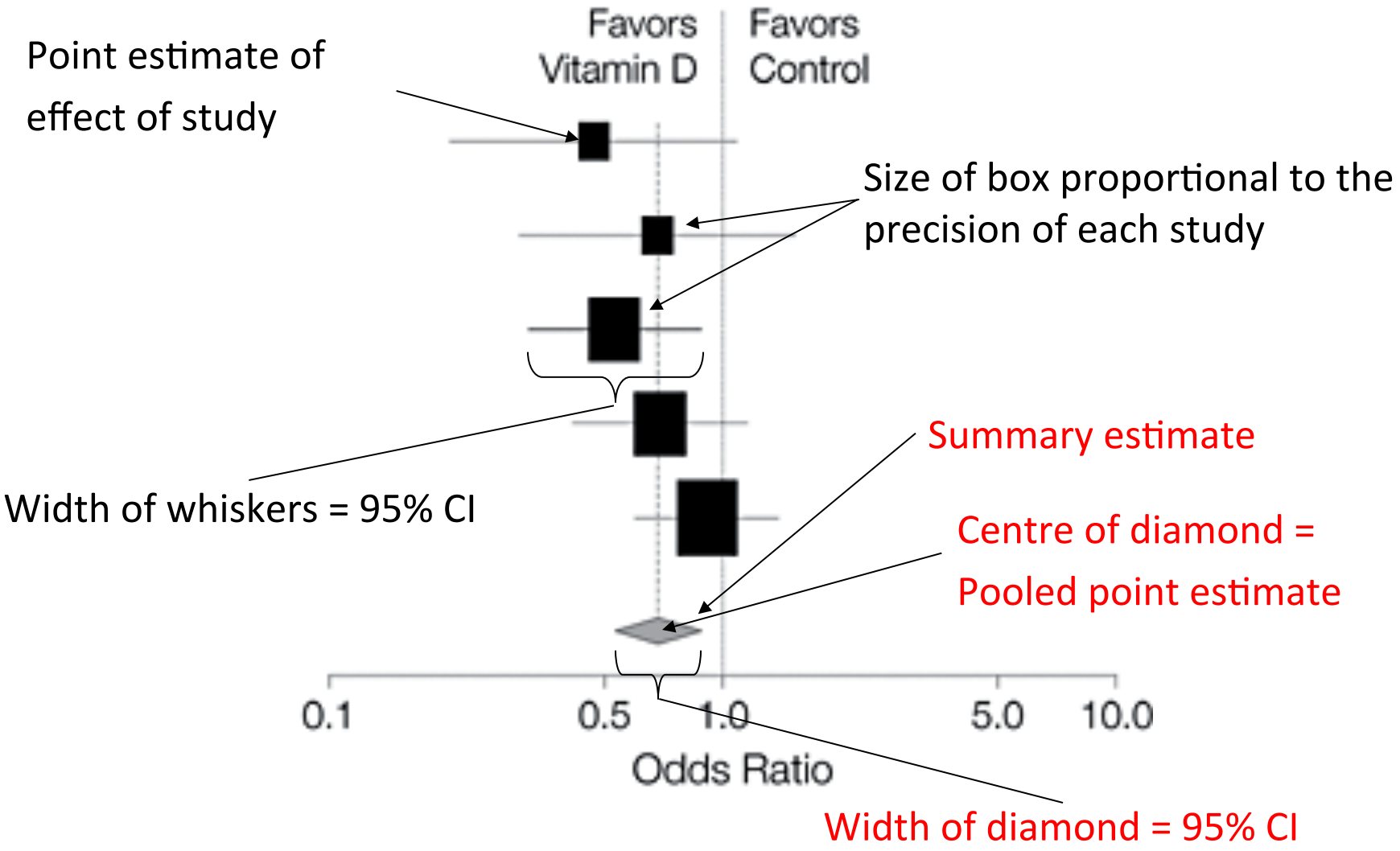
- If no heterogeneity exists, a fixed effects model can be used to pool the effect estimates
- If some heterogeneity exists, use a random effects model to pool the effect estimates
- If too much heterogeneity exists, it might not be appropriate to pool the studies
  - Use subgroup analysis or meta-regression to explore possible causes of heterogeneity
  - Be careful, subgroup analysis can be prone to reporting bias

Test for heterogeneity

- $Q = \sum w_i \left(y_i - \hat{y} \right)^2$
- *Q* has an approximate χ^2 distribution on *I*-1 degrees of freedom (*I* studies)
- Low power
- Combine this test with your own knowledge of the studies

Forest plot

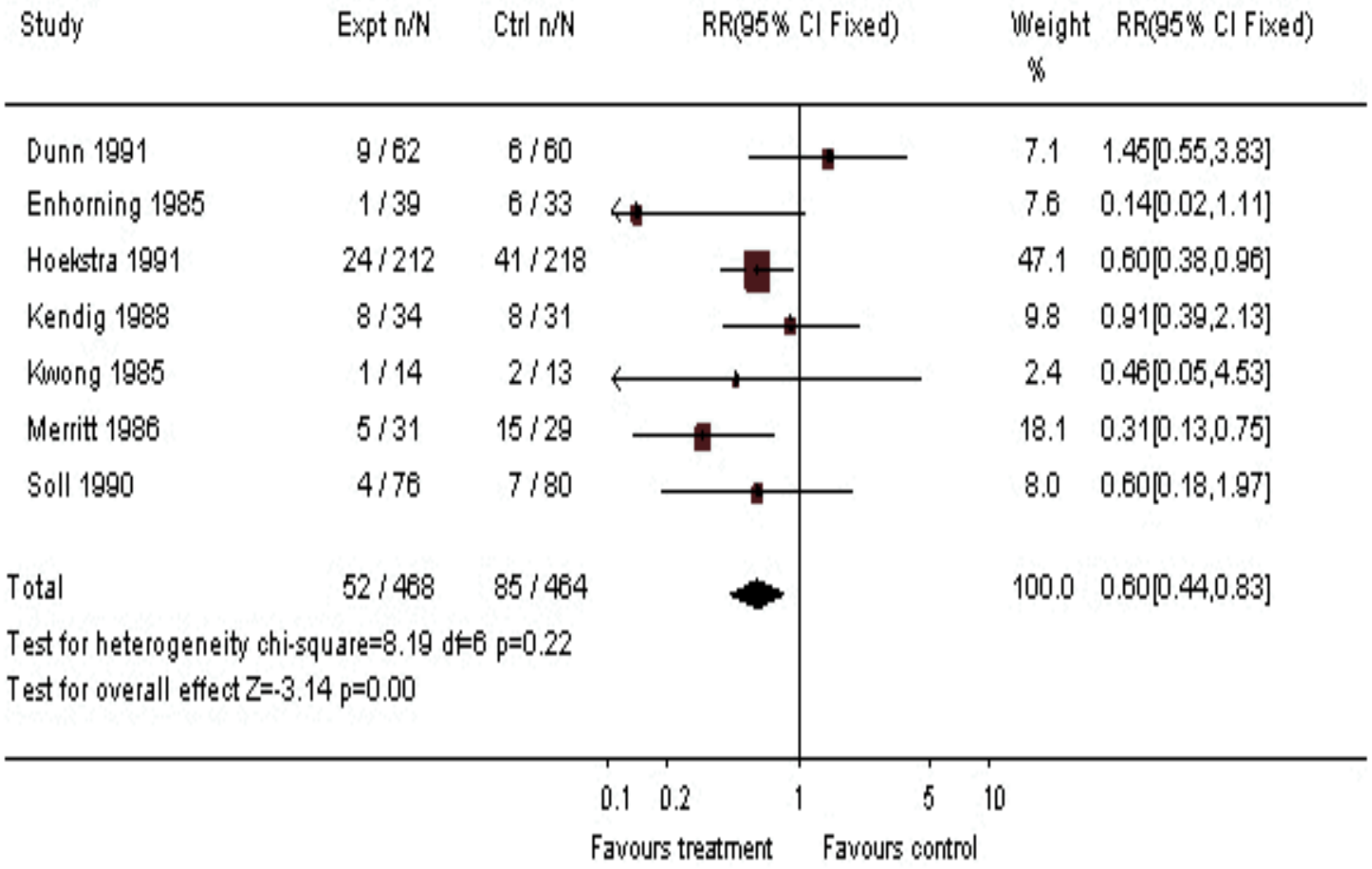
- Most common way of presenting the results
- Eye-ball examination of results
- Get idea of between study variability
- Plotting symbol to mark the point estimate for each study is proportional to it’s precision
- Most precise estimates have the largest plotting symbols


Point estimate of effect of study
Favors Vitamin D
Favors Control
Size of box proportional to the precision of each study
Summary estimate
Width of whiskers = 95% CI
Centre of diamond = Pooled point estimate
0.1
0.5
1.0
5.0
10.0
Odds Ratio
Width of diamond = 95% CI

Review: Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants

Comparison: Natural Surfactant Extract vs. Control

Outcome: Effect on neonatal mortality



Things to concern..

- Regressions are often non-linear, but treated as linear. (The danger of extrapolation).
- Effects may be multivariate rather than univariate (e.g effects of smoking on lung cancer, ignoring personality).
- Quality of studies. What is the effect of exclusions?
- Adding applies and oranges
- Inappropriate combination of studies due to reviewer ignorance (e.g effect of therapy on behaviour).
- The theory-directed approach; individual studies may be biased towards establishing their hypotheses.

Advantages of a systematic review

- Use of explicit, systematic methods limits bias (systematic errors) and reduces chance effects, therefore providing more reliable results
- Consistent research results can be applied across populations, settings and small differences in treatment (e.g. dose)
- Inconsistencies in results between studies can be identified and new hypotheses may be generated about particular subgroups
- Meta-analysis can provide more precise estimates than those derived from single studies
- Methods are explicit and are open to scrutiny, so that others can see what was done and question the results

Summary

- Managing unmanageable amounts of information.
- Synthesis/comparison of scientific evidence is important in its own right.
- Scientific efficiency: do we need yet another study?
- Generalisation from specific to broader populations.
- Assessment of consistency
- Assessment of inconsistency
- Increased power/ precision of estimates
- Increased accuracy due to systematic versus non-systematic review.