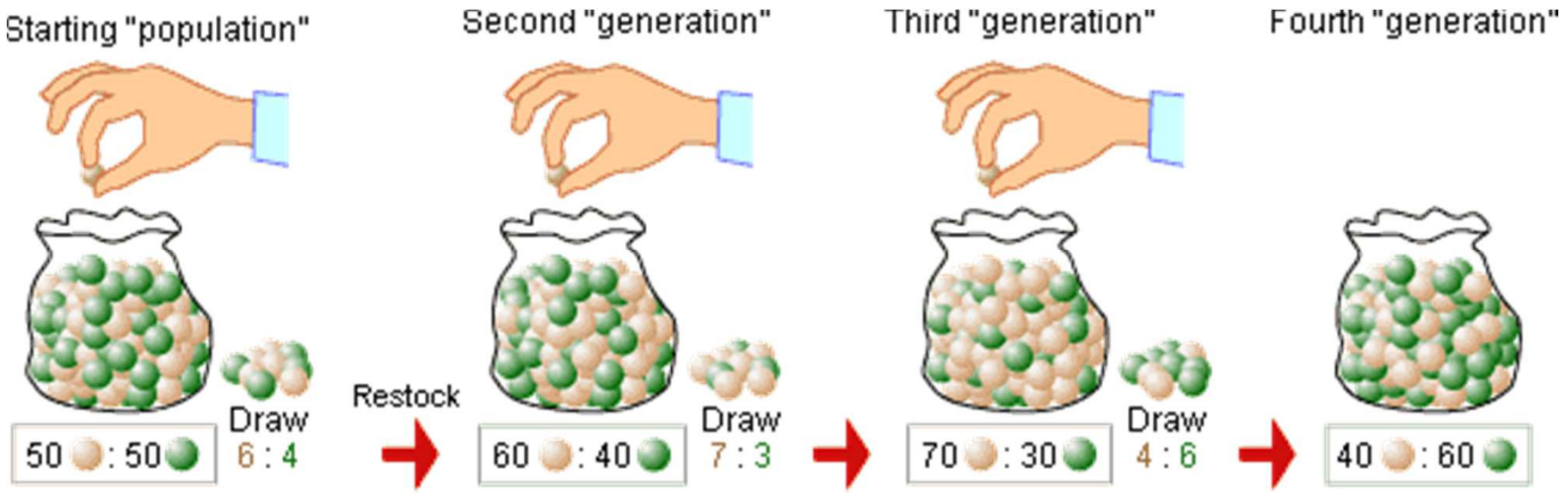
Systemic Reviews and Meta analysis

Dr Pooja Sharma
Senior Scientist
Medanta Institute of Education and Research


Starting "population"
Second "generation"
Third "generation"
Fourth "generation"
Restock
Draw
Draw
Draw
50 : 50
6 : 4
60 : 40
7 : 3
70 : 30
4 : 6
40 : 60

Reality?

- **Levels of evidence: U.S. Preventive Services Task Force (USPSTF)**

- Level I: Evidence obtained from at least one properly designed RCT
- Level II-1: Evidence obtained from well-designed controlled trials without randomization
- Level II-2: Evidence obtained from well-designed cohort or case control analytic studies, preferably from more than one center or research group.
- Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
- Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Evidence based medicine

- **Categories of recommendation:**
- **Level A**: Good scientific evidence suggests that the benefits of the clinical service substantially outweigh the potential risks. Clinicians should discuss the service with eligible patients.
- **Level B**: At least fair scientific evidence suggests that the benefits of the clinical service outweighs the potential risks. Clinicians should discuss the service with eligible patients.
- **Level C**: At least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks are too close for making general recommendations. Clinicians need not offer it unless there are individual considerations.
- **Level D**: At least fair scientific evidence suggests that the risks of the clinical service outweighs potential benefits. Clinicians should not routinely offer the service to asymptomatic patients.
- **Level I**: Scientific evidence is lacking, of poor quality, or conflicting, such that the risk versus benefit balance cannot be assessed. Clinicians should help patients understand the uncertainty surrounding the clinical service.

Evidence based medicine

http://summaries.cochrane.org/CD003934/mothers-position-during-the-first-stage-of-labour

http://summaries.cochrane.org/CD003930/eating-and-drinking-in-labour

http://summaries.cochrane.org/CD004816/statins-for-the-primary-prevention-of-cardiovascular-disease

- Systematic review
- Meta analysis
- Heterogeneity
- Bias in the study
- Methodology, inclusion and exclusion

Interesting terms

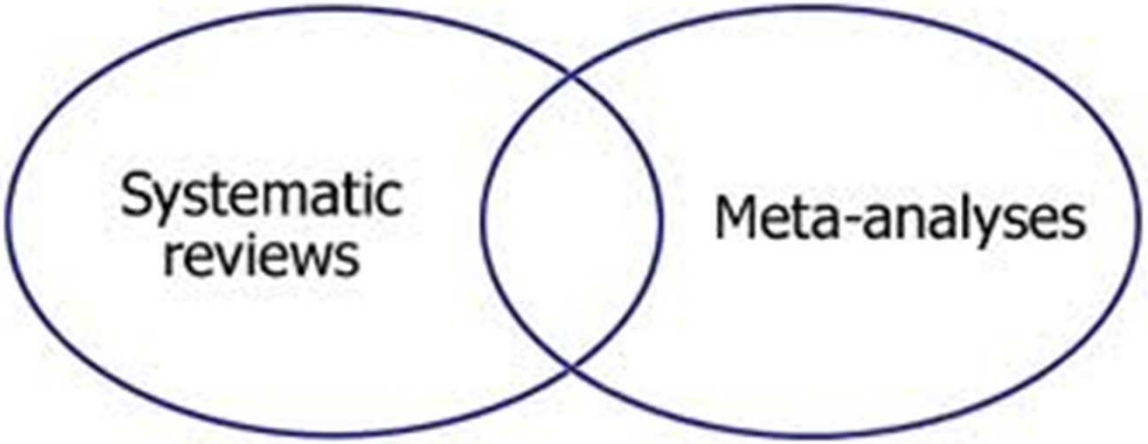
Non-metastatic head and neck squamous cell carcinoma

- loco-regional treatment ?
- loco-regional treatment + chemotherapy ?

- A review of a clearly formulated Question that uses a systematic and explicit methods to identify select and critically appraise relevant research, and to collect and analyze data from the studies included in the review.

- If statistical methods are applied to analyze and summarize the results of the included studies this meta analysis

Systematic Review and Meta analysis


Systematic reviews
Meta-analyses

- Attempt to summarize all past research to address a specific question-useful for the busy clinician!
- RCTs?
- Narrative or Literature review by expert?
- Quality and reproducibility are key
- Access not only care providers but patients and families too

- Summary statistics combining homogenous studies
- Binary outcomes
- Odds ratio
- Rarely risk ratios, risk difference and continuous outcome measures

Meta analysis

- Treated and control of same study must be compared as there may be different inclusion/exclusion, definitions etc in studies.
- Relative sizes of the studies must be accounted-most extreme results will be from small studies

Imp to remember

Do the pieces fit together?

Heterogeneity

Simon SD. Statistical evidence in medical trials: What do the data really tell us?
Oxford University Press, Oxford, 1st edition, 2006

- **Fixed effect meta analysis**: if the assumption that the underlying treatment effect is the same in all studies holds and that the observed variation is entirely due to sampling variation
- **A random effects meta analysis** allows for the heterogeneity
- *X2* test of heterogeneity (Q) to confirm the above assumption.

Test of heterogeneity

- If heterogeneity exists than we use a model to allow for the same between studies
- Because of the addition of the estimated between study variance the random effect weights are
  - Smaller
  - Wider CI
  - Larger P value
  - More conservative estimate than the fixed effect analysis
  - Variation due not only to sampling variation but also true effect being different

Random effects metanalysis

- **Fixed effect**: assumption is that the true effect is the same in all studies and that the only reason for the variation is sampling error and therefore meta analysis provides the best estimate of it
- **Random effects:** the estimate is of the mean effect about which it is assumed that the true study effects vary

Interpretation

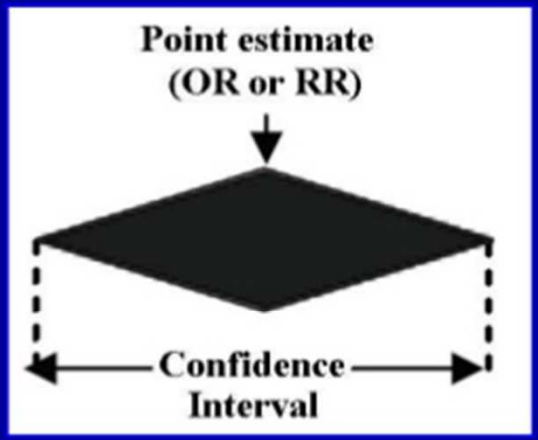
- The name refers to the forest of lines produced.
- The plot was named after a breast cancer researcher called Pat Forrest and as a result the name has sometimes been spelt "**forrest plot**"

Forest or Forrest plots?: Trying to see the woods and the trees

- Horizontal lines along box (CI)
- Box area is proportional to the weight for the individual study in the meta analysis.
- Diamond is the summary estimate and the CI for the summary corresponds to the width of the diamond.
- Unbroken vertical line is the null value (1) of the OR
- The horizontal axis is on log scale to make the CI symmetrical

Forest plots

The diamond



Shows combined point estimate (OR or RR)

& CI for the meta-analysis

Perera R, Heneghan C, Badenoch D. Statistics Toolkit.
Blackwell Publishing Ltd, Oxford, 1st edition, 2008.

Diamond in meta-analysis

Diamond on Left of the line of no effect

Less episodes of outcome of interest in treatment group

Diamond on Right of the line of no effect

MoRe episodes of outcome in treatment group

Diamond touches the line of no effect

No statistically significant difference between groups

Diamond does not touch the line of no effect

Difference between two groups statistically significant

Cochrane collaboration

http://summaries.cochrane.org/

Conducts systematic reviews and publishes in the Cochrane library

Archie Cochranes call for up-to-date, systematic reviews was taken up by the Research and Development Programme, initiated to support the United Kingdom‘s NHS.

The logo shows the results of a systematic review and meta analysis on inexpensive course of corticostseroids given to women in preterm labour– the evidence on effectiveness that would have been revealed had the available RCTs been reviewed systematically a decade earlier.

- Defining the review question and developing criteria for including studies
- Searching for studies
- Selecting studies and collecting data
- Assessing risk of bias in included studies
- Analysing data and undertaking meta-analyses
- Addressing reporting biases
- Presenting results and "summary of findings" tables
- Interpreting results and drawing conclusions

Cochrane Handbook

- Preferred Reporting Items for Systematic Reviews and Meta-Analyses

- http://www.prisma-statement.org/statement.htm

PRISMA

- http://www.sciencedirect.com/science/article/pii/S0167814009001881

Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

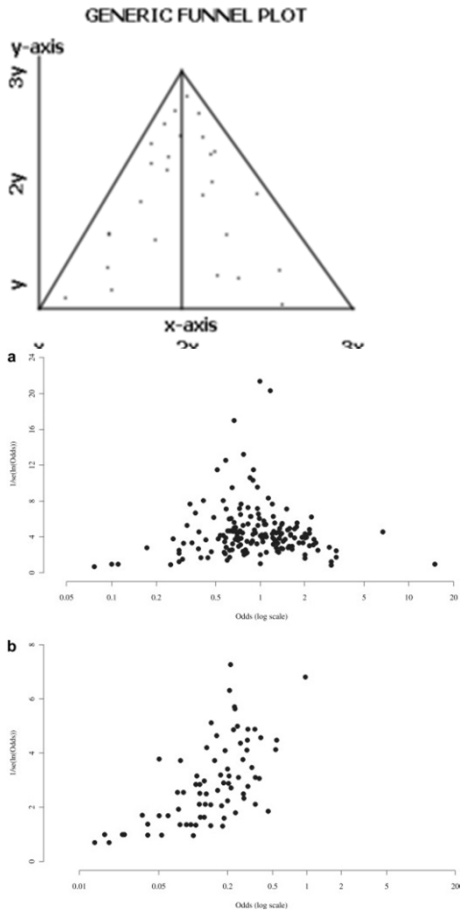
- Important for the studies that are a part of the review to have a sound methodology especially Randomization, allocation concealment
- CONSORT statement
- Publication bias
- Emphasis on ‘significant’results

Bias in meta analysis

Symmetrical plot-absence of publication bias

Asymmetrical plot- studies that show no beneficial effects may be missing

Asymmetrical plot- bias due to poor methodological quality –smaller studies may be biased towards larger beneficial effects-small study effect



Funnel plots to examine bias

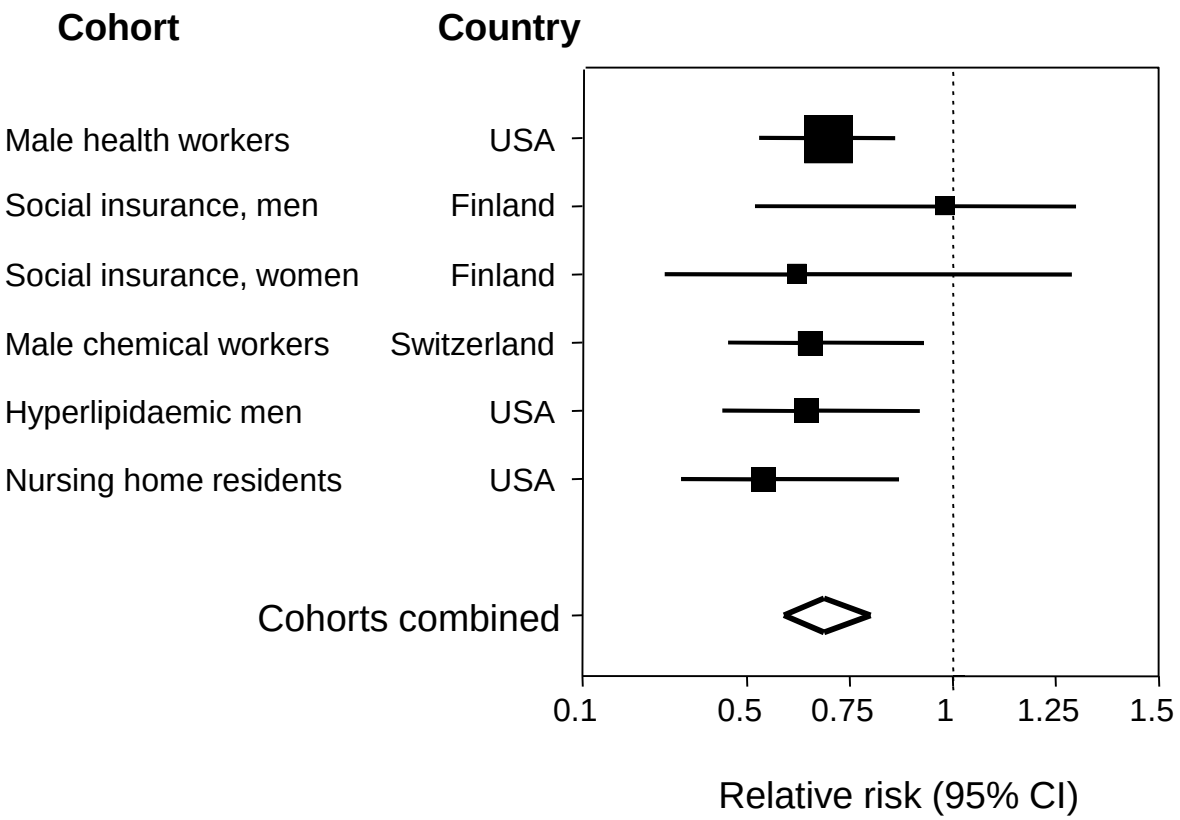
- For studies evaluating etiology
- Effectiveness of interventions that are already introduced (vaccines)
- Effectiveness of interventions on rare Aes
- Effectiveness of mass media campaigns
- Effectiveness in populations other than those in which they were initially assessed

Meta analysis of Observational studies

- Control of confounding factors (not so much in RCT as randomization takes care of confounders)
- Recall bias in observational studies

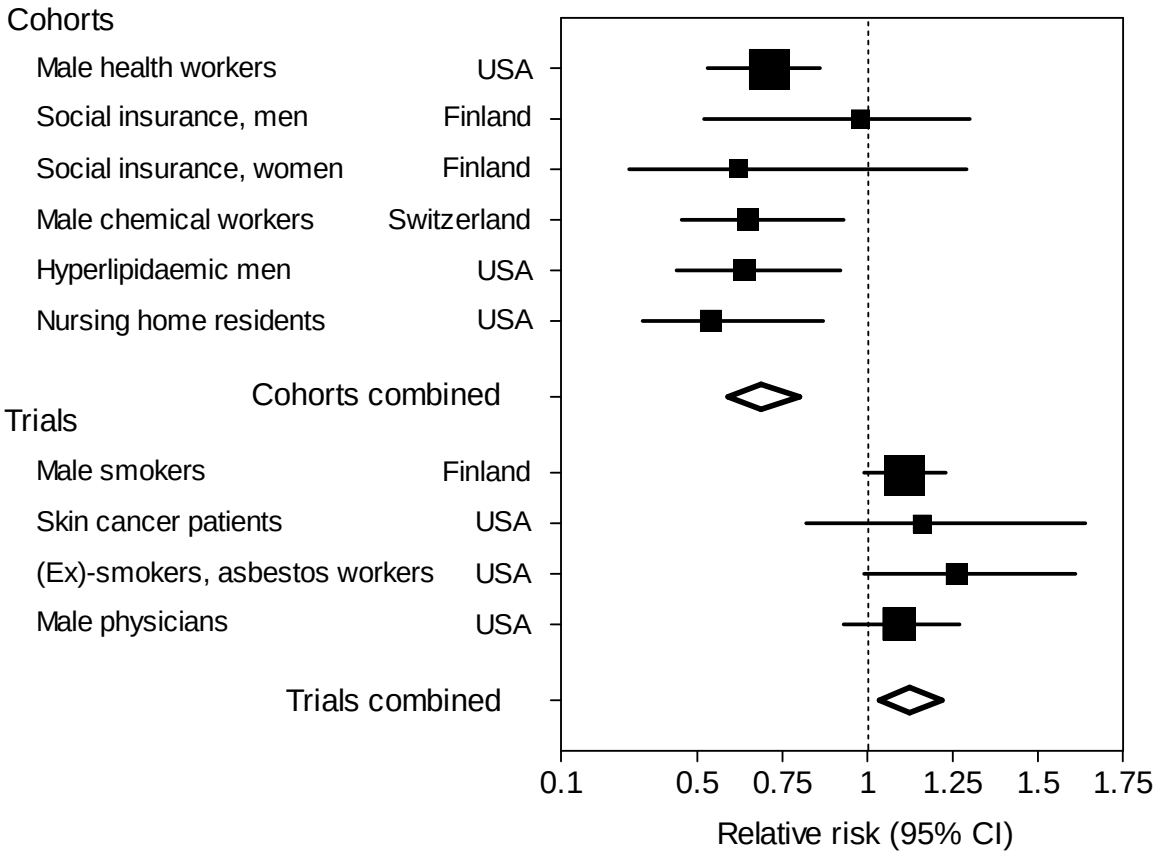
Observational meta analysis: issues

Beta-carotene and cardiovascular mortality



Jah et al *Ann Intern Med* 1995

Beta carotene and cardiovascular disease



Egger et al. BMJ 1998;316:140-4

- While reading or writing a systematic review
  - Be systematic (PRISMA)
  - Note the heterogeneity
  - Minimize the same
  - Qualitative systematic reviews have limitations
  - Registration of research and results may help minimize the same

Take home message

Useful links

- http://summaries.cochrane.org/CD003934/mothers-position-during-the-first-stage-of-labour
- http://summaries.cochrane.org/CD003930/eating-and-drinking-in-labour
- http://summaries.cochrane.org/CD004816/statins-for-the-primary-prevention-of-cardiovascular-disease
- http://www.cochrane-net.org/openlearning/html/mod3-2.htm
- www.systematicreviews.com
- http://www.cochrane-net.org/openlearning/Other/Forest_plot.pdf


Thank You!