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Meta-analysisTutorial in Medical Statistics: A systematic approach

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ABSTRACT *Medical data analysis are used by data software's but knowledge about the methods far from the result, In many I nstances, the results of these multiple small studies of an issue are diverse and conflicting, which makes the clinical decision-making difficult. The need to arrive at decisions affecting clinical practice fostered the momentum toward "evidence-based medicine.Systematic review is the entire process ofcollecting, reviewing and presenting all available evidence .Meta-analysis is the statistical technique involved in extracting and combining data to produce a summary result. A meta-analysis is also possible without doing a systematic review. With no attempt to be systematic about the particular studies were chosen.*

KEYWORDS : Hyseroscope, Endometrial sampling, Abnormal uterine bleeding.

Introduction

• A meta-analysis is a two-stage process

– Stage 1. Extraction of data from individual study, Calculation of a result for that study (point estimate) and Estimation of chance variation (confidence interval)

– Stage 2. Deciding if it is appropriate to calculate and pool average results across studies.If so, calculate and present the results. What are the main comparisons in your view?How will you summarise the results of the outcomes for each study?How will you decide whether to combine the results of the separate studies?Do you plan any subgroup or sensitivity analyses?

• Dichotomous data (e.g. dead or live)
• Counts of events (e.g. no. of pregnancies)
• Short ordinal scales (e.g. pain score)
• Long ordinal scales (e.g. quality of life)
• Continuous data (e.g. cholesterol con.)
• Censored data or survival data (e.g. time to 1st service)

Inclusion or Exclusion Criteria and Potential for Bias.

Studies are chosen for meta-analysis based on inclusion criteria. If there is more than one hypothesis to be tested, separate selection criteria should be defined for each hypothesis. Inclusion criteria are ideally defined at the stage of initial development of the study protocol. The rationale for the criteria for study selection used should be clearly stated.

One important potential source of bias in meta-analysis is the loss of trials and subjects. Ideally, all randomized subjects in all studies satisfy all of the trial selection criteria, comply with all the trial procedures, and provide complete data. Under these conditions, an "intention-to treat" analysis is straightforward to implement; that is, statistical analysis is conducted on all subjects that are enrolled in a study rather than those that complete all stages of study considered desirable.

Efforts to minimize this potential bias include working from the references in published studies, searching computerized databases of unpublished material, and investigating other sources of information including conference proceedings, graduate dissertations and clinical trial registers.

Aim and Objectives:

- To increase power
- To improve precision
- To answer questions not posed by the individual studies
- To settle controversies arising from apparently conflicting studies or
- To generate new hypothesis
- Assessment of strength of evidence
- To determine whether an effect exists in a particular direction
- Statistical pooling of results
- To obtain a single summary result
- Investigation of heterogeneity
- To examine reasons for different results

Statistical analysis

Methods of calculating summary measures of association or effect

- Continuous data
  – Calculation of overall effect size (standardised mean difference)
  – Rate data
  – Measures of effect (difference between incidence in the population of exposed *vs* not exposed)
- Relative risk
- Odds ratio

Statistical models

- Risk difference **Fixed effect models**

– Mantel-Hansel (MH)

- Has optimal statistical power
- Software's are available for the analysis

– Peto test (modified MH method)

- Recommended for non-experimental studies

- **Random effect models**

– DerSimonian & Laird method
– Bayesian method

- **Regression models (Mixed model)**
- This model is based on a mathematical assumption that every study is evaluating a common treatment effect.In this model, the true treatment difference is considered to be the same for all trials.The SE of each trial estimate is based on sampling variation within the trial.The summary results are specific to the trials included.The summary results can not be generalised to the population

- **Fixed effects assumption**
- "did the treatment produce benefit on average in the studies in hand"?
- "what is the best estimate of the treatment effect"?

- **Random effects assumption**
- "will the treatment produce benefit on average"?
- "what is the average treatment effect"?
- **Choice between fixed and random effects may be decided**
- By a formal chi-square test of homogeneity,That is whether the between study variance component is zero or not

- **Odds Ratio (OR)**
- The odds of the event occurring in one group divided by the odds of the event occurring in the other group

- **Relative risk or Risk Ratio (RR)**

• The risk of the events in one group divided by the risk of the event in the other group

- **Risk difference (RD; -1 to +1)**
- Risk in the experimental group minus risk in the control group
- **Confidence interval (CI)**
- The level of uncertainty in the estimate of treatment effect
- An estimate of the range in which the estimate would fall a fixed percentage of times if the study repeated many times
- Odds ratio (OR) will always be further from the point of no effect than a risk ratio (RR)
- If event rate in the treatment group
- OR & RR > 1, but
- OR > RR
- If event rate in the treatment group
- OR & RR < 1, but
- OR < RR

- **Relative Risk (Fixed and Random effect model)**
- **Fixedi= Fixed effect RR with inverse variance method**
- **Fixed= M-H RR method**

Meta-analysis features in Stata1. metan2. labbe3. Metacum4.Metap5.metareg
6. metafunnel7. Confunnel8.Metabias9.metatrim 10. metandi&metandiplot
11. glst12. Metamiss13.mvmeta&mvmeta_make14. metannt
15. metaninf16. Midas17.meta_lr18.Metaparm
Softwar programming Example

metanevtrtnon_evtrtevctrlnon_evctrl, rr fixed second(random)
favours(reduces pregnancy rate # increases pregnancy rate)
lcols(names outcome dose) by(status) sortby(outcome) force
astext(70) textsize(200) boxsca(80) xsize(10) ysize(6)
pointopt(msymbol(triangle) mcolor(gold) msize(tiny)
mlabel() mlabsize(vsmall) mlabcolor(forest_green)
mlabposition(1))
ciopt(lcolor(sienna) lwidth(medium)) rfdistrflevel(95) counts

- **Saving the graph in different formats**

graph export "D:\Forest plot.gph", replace
graph export "D:\Forest plot.gph".png", replace
graph export "D:\Forest plot.gph".eps", replace

The most common measures of effect used for dichotomous data are the risk ratio (also called relative risk) and the odds ratio. The dominant method used for continuous data are standardized mean difference (SMD) estimation. Methods used in meta-analysis for post hoc analysis of findings are relatively specific to meta-analysis and include heterogeneity analysis, sensitivity analysis, and evaluation of publication bias.

One of the foremost decisions to be made when conducting a meta-analysis is whether to use a fixed-effects or a random-effects model. A fixed-effects model is based on the assumption that the sole source of variation in observed outcomes is that occurring within the study; that is, the effect expected from each study is the same. Consequently, it is assumed that the models are homogeneous; there are no differences in the underlying study population, no differences in subject selection criteria, and treatments are applied the same way Fixed-effect methods used for dichotomous data include most often the Mantel-Haenzelmethodand the Peto method (only for odds ratios).

Homogeneity

- Meta-analysis should only be considered when a group of trials is sufficiently homogeneous in terms of participations, interventions and outcomes to provide a meaningful summary Examination for "heterogeneity" involves determination of whether individual differences between study outcomes are greater than could be expected by chance alone.

- Analysis of "heterogeneity" is the most important function of MA, often more important than computing an "average" effect.

Three basic base differ studies

- **Clinical diversity:** Variability in the participants, interventions and outcomes studied
- **Methodological diversity**: Variability in the trial design and quality
- **Statistical heterogeneity:** Variability in the treatment effects being evaluated in the different trials. This is a consequence of clinical and/or methodological diversity among the studies

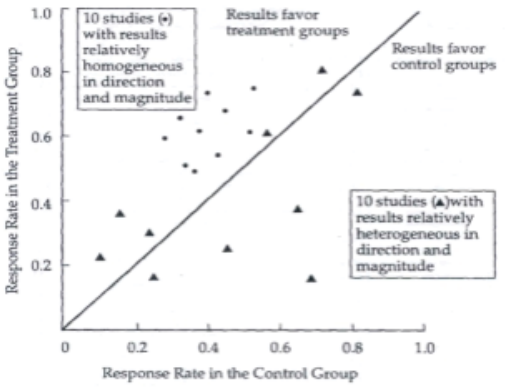
Methods for estimation of heterogeneity

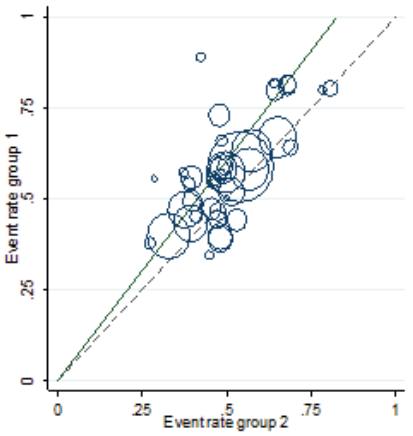
- Conventional chi-square (χ^2) analysis (P>0.10)
- I^2= **[(Q-df)/Q x 100% (Higgins et al. 2003),** where

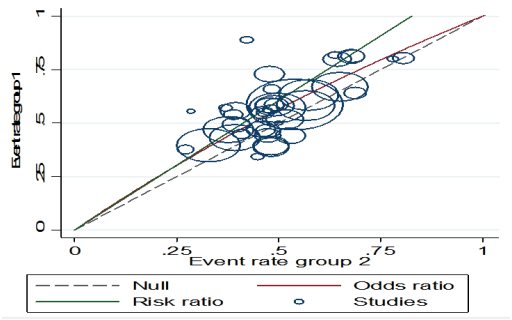
Q is the chi-squared statistic; df is its degrees of freedom

- **Graphical** test-forest plots (OR or RR and confidence intervals)
- **L'Abbe**plots (outcome rates in treatment and control groups are plotted on the vertical and horizontal axes)
- **Galbraith plot**
- Regression analysis

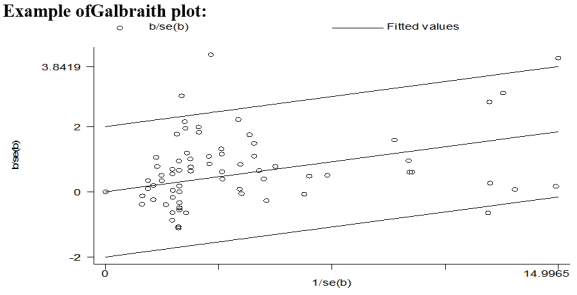
Example of L'Abbe plot:

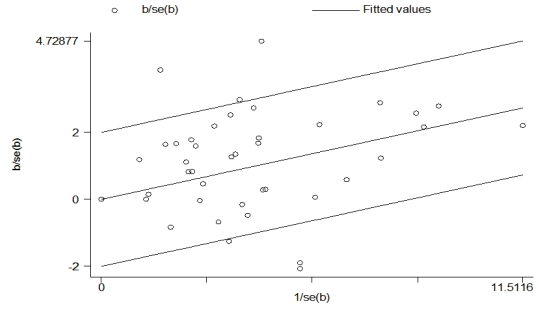






Example ofGalbraith plot:





Meta-regression

- To investigate whether heterogeneity among results of multiple studies is related to specific characteristics of the studies (e.g. dose rate)
- To investigate whether particular covariate (potential 'effect modifier') explain any of the heterogeneity of treatment effect between studies.Can find out if there is evidence of different effects in different subgroups of trials
- It is appropriate to use meta-regression to explore sources of heterogeneity even if an initial overall test for heterogeneity is non-significant

Meta-regression is potentially a very useful technique.If used inappropriately, its interpretation can be misleading. This is again because differences between studies, even if they are well-performed randomized trials, are entirely observational in nature and are prone to "bias" and "confounding". If you summarize case characteristics at a trial level, you run the risk of completely failing to detect genuine relationships between these characteristics and the size of treatment effect. Further, the risk of obtaining a spurious explanation for variable treatment effects is high when you have a small number of studies and may characteristics that differ.

Biases in meta-analysis

Although the intent of a meta-analysis is to find and assess all studies meeting the inclusion criteria, it is not always possible to obtain these. A critical concern is the papers that may have been missed. There is good reason to be concerned about this potential loss because studies with significant, positive results (positive studies) are more likely to be published and, in the case of interventions with a commercial value, to be promoted, than studies with non-significant or "negative" results (negative studies). Studies that produce a positive result, especially large studies, are more likely to have been published and, conversely, there has been a reluctance to publish small studies that have non-significant results. Further, publication bias is not solely the responsibility of editorial policy as there is reluctance among researchers to publish results that were either uninteresting or are not randomized48. There are, however, problems with simply including all studies that have failed to meet peer-review standards. All methods of retrospectively dealing with bias in studies are imperfect.

Evolution of meta-analyses

The classical meta-analysis compares two treatments while network meta-analysis (or multiple treatment metaanalysis) can provide estimates of treatment efficacy of multiple treatment regimens, even when direct comparisons are unavailable by indirect comparisons[60]. An example of a network analysis would be the following. An initial trial compares drug A to drug B. A different trial studying the same patient population compares drug B to drug C. Assume that drug A is found to be superior to drug B in the first trial. Assume drug B is found to be equivalent to drug C in a second trial. Network analysis then, allows one to potentially say statistically that drug A is also superior to drug C for this particular patient population. (Since drug A is better than drug B, and drug B is equivalent to drug C, then drug A is also better to drug C even though it was not directly tested against drug C.)

Meta-analysis can also be used to summarize the performance of diagnostic and prognostic tests. However, studies that evaluate the accuracy of tests have a unique design requiring different criteria to appropriately assess the quality of studies and the potential for bias. Additionally, each study reports a pair of related summary statistics (for example, sensitivity and specificity) rather than a single statistic (such as a risk ratio) and hence requires different statistical methods to pool the results of the studies.Various techniques to summarize results from diagnostic and prognostic test results have been proposed.

Conclusions

The traditional basis of medical practice has been changed by the use of randomized, blinded, multicenter clinical trials and meta-analysis, leading to the widely used term "evidence-based medicine". Leaders in initiating this change have been the Cochrane Collaboration who have produced guidelines for conducting systematic reviews and meta-analyses.Meta-analysis of randomized clinical trials is not an infallible tool, however, and several examples exist of meta-analyses which were later contradicted by single large randomized controlled trials, and of meta-analyses. However, the reason for this controversy was explained by the numerous methodological flaws found both in the meta-analysis and the large clinical trial.

No single study, whether meta-analytic or not, will provide the definitive understanding of responses to treatment, diagnostic tests, or risk factors influencing disease. Despite this limitation, meta-analytic approaches have demonstrable benefits in addressing the limitations of study size, can include diverse populations, provide the opportunity to evaluate new hypotheses, and are more valuable than any single study contributing to the analysis. The conduct of the studies is critical to the value of a meta-analysis and the methods used need to be as rigorous as any other study conducted.

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