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Bias in meta-analysis and funnel plot asymmetry

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Abstract. International experiences reveal the important role played by scientific research and systematic study a problems, in effectively tackling change in the health sector. Meta-analysis was introduced to address the problem of synthesizing the large quanty of information on a particular subject. It is viewed, only as a step in the process of developing better tools to quantify information across studies.
The selection of trials for inclusion in a meta-analysis may be biased if selection is restricted to published trials, to trials published in English language journals, to trials published in prestigious journals or to trials cited by other authors.
Funnel plot is graphical display of sample size plotted against effect size for the studies included in a meta-analysis, which can be used to investigate bias. When all the studies have been located, the distribution of points should resemble a funnel. If there are gaps in the funnel shape it indicates that some studies may have not been published or located.
In evaluating bias, we use meta-analysis studies about radiotherapy alone versus combined radiotherapy and chemotherapy in stages IIIa and IIIb non-small cell lung cancer.
A simple analysis of funnel plots provides useful test for the likely presence of bias in meta-analyses, but as the capacity to detect bias will be limited when meta-analyses are based on a limited number of small trials the results from such analyses should be treated with considerable caution.

1. Introduction

Evidence Based Medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical experts with the best available external clinical evidence from systematic research.

When a doctor is pondering what is the best cours of treatment for an uncommon disease or a biomedical researcher is launching a new project this person would review current literature for relevant citation on the subject of interest. The search of literature database is an efficient way to begin the assembly of relevant information from vast volume of biomedical publication.

Papers that summarise other papers are systematic reviews and meta-analyses. Systematic rewiev is an overview of primary studies that used explicit and reproduciable methods. Meta-analysis in clinical research is based on simple principles: systematically searching and when possible quantitavely combining results of all studies that addressed a

similar research question. A good meta-analysis is often easier for the non-statistician to understand then the stack of primary research papers from which it was derived [1].

The selection of trials for inclusion in a meta-analysis may be biased if selection is restricted to published trials (publication bias), to trials published in English language journals (language bias), to trials published in prestigious journals or to trials cited by other authors such as in review articles (reference bias). Furthermore, even if all relevant trials are eventually published, the selection of trials may still be biased if it is restricted to trials that are published early [2]. The findings of some meta-analyses have letter been contradicted by large randomised controlled trials.

Although several ways of examing the potential impact of publication bias on the results of systematic review have been described, all of them are problematic. There is growing concesus that the only satisfactory way to address this bias is through prospective registration of trials. Nonetheless, reviewers may want to consider using a "funnel plot" to look for publication bias if there is a sufficient number of studies. This can be done by plotting the study weight (one divided by variance of the odds ratio) or sample size (on the "y" axis) against the odds ratios (on the "x" axis). Typically this will give the appearance of a funnel with larger studies (with greater weights) at the top in the middle and smaller studies spread out at the bottom. A gap at the bottom of the funnel on the right side (assuming smaller odds ratios (less than one) represent beneficial effects) indicates that small "positive studies" were identified wheras equal numbers of small studies in the opposite direction were not. In the absence of bias the plot will resemble a symetrical inverted funnel. If there is bias, funnel plots will often be skewed and asymetrical.

Through visual examination funnel plots have been interpreted differently by different observes. We want systematically examined symmetry or asymmetry of funnel plot because that we measured funnel plot asymmetry numerically [3].

2. Material and methods

We used a linear regression approach to measure funnel plot asymmetry on the natural logaritham scale of the odds ratio. The standard normal deviate (SND; the odds ratio divided by its standard error) is regressed against the estimates precision (the inverse of the standard error). Regression equation:

$$SND=a+bxprecison$$

Small trials will be close to zero on both axis. First, precision depends largely on simple size and because that small trials will be close to zero on the x axis. In other hand small trials may produce an odds ratio that differs from unity, but because the standard error will be large, the resulting standard normal deviate will again be close to zero. Large studies will produce precise estimates and, if the treatment is effective, standard normal deviates is also large. Situation corresponds to a symmetrical funnel plot will be when the points from homogeneous set of trials not distorted by selection bias will thus scatter about a line that runs through the origin at standard normal deviate zero (a=0), with the slope b indicating the size and direction of effect.

If there is asymmetry, the regression line will not run through the origin. The intercept a provides a measure of asymmetry. When the larger its deviation from zero the more pronounced the asymmetry. If the smaller studies show big protective effects, they will force regression line below the origin on the logarithmic scale. Smaller studies show more pronounced beneficial effects than larger studies when we have negative value of intercept a.

Power of study including in meta-analysis, in some situations is gained by weighting the analysis by the inverse of variance of the effect estimate.

The test for funnel plot asymmetry in contrast to the overall test of heterogeneity, provides a more powerful test in this situation. However any analysis any analysis of heterogeneity depends on the number of trials included in meta-analysis which is generally small, and this limits the statistical power of test. Because that, we based evidence of asymmetry on $p<0.1$ and we present intercept with 90% confidence interval [3].

We use meta-analysis studies about radiotherapy alone versus combined radiotherapy and chemotherapy in stages IIIa and IIIb non-small cell lung cancer and single agent chemotherapy versus combination chemotherapy in advanced non-small lung cancer. The bibliographic search for published reports meta-analysis was made using MEDLINE database in all languages, covering period from 1993 to 1998.

3. Results

We examined bias in three meta-analysis about therapy in stages IIIa and IIIb non-small cell lung cancer. In that study an adaption of method Mantel and Haenszel was applied to estimate and pool odds ratios (ORs) of death. Values of OR less than unity indicated beter overall survival with chemotherapy/radiotherapy than with radiotherapy alone. Tabele 1 show results of analysis of funnel plot asymmetry. One out of three meta-analyses showed significant ($p<0.1$) funnel plot asymmetry. In two meta-analyses funnel plot don't show statistical significant.

Tabela 1 Analysis of funnel plot asymmetry

Meta-analysis	No of trials	Linear regresion analysis	
		Intercept (90% CI)	P value
Milicic B. [4]	8	2.769 (-1.233-6.770)	0.141
Marino P. [5]	12	2.741 (-1.287-6.769)	0.126
Marino P. [6]	9	-9.650 (-17.779-(-1.521))	0.026

Pooled OR in one of them was 1.05 (CI=0.7-1.5), while other gave pooled OR value about 0.84 (CI=0.68-1.04). Study with significant funnel plot asymmetry gave value of poolrd OR 0.8 and its 95% confidence interval 0.6-1.0 thus favoring combination chemotherapy. In that meta-analysis larger study had OR less or equal unity, while smaller show OR larger than unity. OR discordance between small and large study include in this meta-analysis was consequence of a large study showing more beneficial effects of use combination, rather than single agent chemotherapy in advanced non-small cell lung cancer than small study.

4. Discussion

International experiences reveal the important role played by scientific research and systematic study a problems, in effectively tackling change in the health sector. Meta-analysis was introduced to address the problem of synthesizing the large quanty of information on a particular subject [7]. It is viewed, only as a step in the process of developing better tools to quantify information across studies. It has been suggested that investigators should combine quantitative and qualitative review data to enable practioners to apply results to individual patients or program problems. In this way researches can investigate issues that are important, but difficult to quantify. Non-quantitative information, such as expert opinion and anecdotal evidence, does have a significant impact on policy.

Finally, one must be concerned that although, even the best meta-analysis may represent all available trials and relevant studies, it may not represent clinical practice because, of the nature of how and where research is conducted.

The validity of meta-analysis depends on complete sampling of all the studies performed on a particular topic. Validity can be preserved if representative sampling of studies is obtained, but any incomplete sampling is a potentially biased one [8].

Sources of bias and funnel plots asymmetry

Selection bias

- Publication bias
- Location biases:
  -English language bias
  -Citation bias
  -Multiple publication bias

True heterogeneity

- Size of effect differs according to study size:
  -Intensity of intervention
  -Differences in underlying risk

Data irregularities

- Poor methodological design of small studies
- Inadequate analysis
- Fraud

Artefactual

- Choice of effect measure

Chance

The selection of trials for inclusion in a meta-analysis may be biased if selection is restricted to published trials, to trials published in English language journals, to trials published in prestigious journals or to trials cited by other authors. It is the tendency of studies which report statisticly significant results to be published. Publication bias is a form of selection bias. This will lead to a biased review but can be minimised by using a comprehensive search and unbiased processes for choosing studies for inclusion [9]. Multiple publications bias occurs when studies whose results are published in series of articles are more likely to be sampled than those published only once [10]. There is systematic differences between studies included in meta-analysis and the studies which were missed which relating to the study results.

In the language of meta-analysis, homogeneity means that the results of each individual trial are mathematically compatible with the results of any of the others. Statistical heterogeneity is a mathematical exercise and is the job of the statistician, but explaining this heterogeneity (looking for, and accounting for, clinical heterogeneity) is an interpretive exercise and requires imagination, common sense, and hands-on clinical or research experience. Critical examination for the presence of publication and related biases must therefore become an essential part of meta-analytic studies and systematic reviews. The findings presented here indicate that a simple graphical and statistical method is useful for this purpose.

Another source of funnel plot asymmetry arises from differences in methodological quality. If study results are weighted for quality in the analysis a bias in scoring study quality may have real impact on meta-analysis results. Smaller studies are on average conducted and analysed with less methodological rigour then larger studies. Trials of lower quality also tend to show larger effects [11]. The degree of symmetry found in a funnel plot may depend on the statistic used to measure effect. Odds ratios overestimate the relative reduction, or increase, in risk if the event rate is high [12]. This can lead to funnel plot

asymmetry if the smaller trials were consistently conducted in patients at higher risk. Similarly, if events accrue at a constant rate, relative risks will move towards unity with increasing length of follow up. In large trials, follow up is often longer than in small studies.

The trials included in meta-analysis may not estimate the same underlying effect of the intervention, and such heterogeneity between results may lead to asymmetry in funnel plots.

Some interventions may have been implemented less thoroughly in larger trials, thus explaining the more positive results in smaller trials. Small trials are generally conducted before larger trials are established. In the intervening years, control treatments may have improved or changed in a way that could reduce the efficacy of the experimental treatment [13].

Finally, an asymmetrical funnel plot may arise by chance.

5. Conclusions

Meta-analysis has made and continues to make major contributions to medical research, clinical decision making, and standards of research reportage. Aggregation of data from multiple trials should enhance the precision and accuracy of any pooled result. But combining data requires a leap of faith: it presumes that the differences among studies are primarly due to chance. In fact, differences in the direction or size of treatment effects may be caused by other factors including subtle differences in treatments, populations outcome measures, study design and study quality. Thus meta-analysis may generate misleading results by ignoring meaningful heterogeneity among studies entrenching the biases in individual studies, and introducing further biases through the process of finding studies and selecting results to be pooled.

If the sensitivity analysis that are done do not materially change the results, it strengt hens the confidence that can be placed in them. If the results change in a way that might lead to different conclusions, this indicates a need for greater caution in interpreting the results and drawing conclusions. It might also enable reviewers to clarify the source of exsiting contraversis about the effectiveness of an intervention, or lead reviewers to hypothesise potentially important factors that might be related to the effectiveness of the intervention and warrant further investigation.

The possibility that the study selection was affected by publication bias can be investigated in the data analysis. Funnel plots show the distribution of effect sizes according to sample size: it is to be expected that the points will full a funnels shape, there being more variability in reported affect sizes for smaller studies. Large gaps in the funnel indicate a group of possibly "missing" publications. These omissions are usually small studies showing no effect and are unilikely to be missing at random. Statistical methods are available to investigate how serios publication bias would have to be to change the review's overall conclusion. The technique discussed here should contribute to this goal, providing reproducible measure for the likely presence, or apparent absence of such biases.

Meta-analysis cannot tell clinicians how to treat an individual patient but it can provide information that helps decision making.

References

[1] Greenhalgh T. Papers that summarise other papers (systematic reviews and meta-analyses). BMJ 1997:315, pp 672-675.
[2] Stern J.M., Simes J.R. Publication bias: evidence of delayed publication ina a cohort study of clinical research projects. BMJ 1997:315, pp 640-645.
[3] Egger M., Smith G.D., Schneider M., Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997:315, pp 629-634.
[4] Milicic B., Mrainkovic J., Jeremic B., Radotiv M., Arsenijevic N. Radiotherapy alone versus combined radiotherapy and chemotherapy in stages IIIA and IIIb non-small cell lung cancer: meta-analysis study. 9 th World Congress on Medical Informatics. Medinf' 98. IOS Press, 1998 Amsterdam; pp: 885.
[5] Marino P., Preatoni A., Cantoni A. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in stages IIIa and IIIb nonsmall cell lung cancer. A meta-analysis. Cancer 1995: 76, pp: 593-60.
[6] Marino P., Preatoni A., Cantoni A., Buccheri G. Single agent chemotherapy versus combination chemotherapy in advanced non-small cell lung cancer: a quality and meta-analysis study. Lung Cancer 1995: 13, pp: 1-12.
[7] Stephan B., Tacher M.D. Meta-analysis. A quantitative approach to research integration. JAMA 1988: 259, pp: 1685-9.
[8] Framer M.R., Reynolds J.M., Moor R.A., McQuay H.J. Impact of covert duplicate publication on meta-analysis: a case study. BMJ 1997:315, pp 635-640.
[9] Gotzche P.C. Reference bias in reports of drug trials. BMJ 1987: 295, 654-6.
[10] Felson D.T. Bias in meta-analytic research. J Clin Epidemiol 1992:vol 45 No8, pp: 885-892.
[11] Villar J., Piaggio G., Carroli G., Donner A. Factors affecting the comparability of meta-analysis and largest trials results in perinatology. J Clin Epidemiol 1997: 50, pp: 997-1002.
[12] Schulz K.F., Chalmers I., Hayes R.J., Altman D.G., Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995: 273, pp: 408-12.
[13] Altman D.G. The scandal of poor medical research. BMJ 1994:308, pp:283-4.