INTRODUCTION OF META-ANALYSIS: WHAT, WHY AND WHO

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ABSTRACT: **Meta-analysis is a method of review that summarises the results of previous research of the same particular issue in a systematic and quantitative way. A meta-analysis that properly combines results from different studies will average out differences caused by random variation and produce a more precise estimate of the true effect. It may also detect and investigate heterogeneity among studies thus providing a deeper understanding of clinical dilemmas and guidance on resolving them, in this way a meta-analysis will be a better guide to practice than an individual study. Meta-analysis also has its limitations as it is largely dependent on the quality of published data and requires careful planning and execution of a valid protocol, together with cautious interpretation of the results.** *(JUMMEC 2000; 2:78-84)*

KEYWORDS: **Quantitative Review, Critical Appraisal, Overall Effect, Publication Bias.**

Introduction

Huque defined meta-analysis as "a statistical analysis that combines or integrates the results of several independent clinical trials considered by the analyst to be 'combinable'" (1). A properly conducted meta-analysis will have a written protocol that clearly specifies the techniques for searching, selecting, appraising, combining, and finally presenting quantitative data of two or more independent studies. Data from several different comparable studies are reviewed quantitatively to explore relations between study characteristics and findings. If judged combinable the study results are then pooled to produce an overall estimate (Figure 1). An advantage of this approach is it provides more statistical power than that of the separate studies to detect treatment effects. Many clinicals can be subjected to meta-analysis. The technique has been applied to trials on the effectiveness of treatment, preventive or therapeutic interventions, to diagnostic procedures, to epidemiological risk-factor studies and to relationships in etiological research (2).

Reviews incorporating meta-analyses have appeared in medical journals in increasing numbers. The National Library of Medicine has included Medical Subject Heading (MeSH) "META-ANALYSIS" (1989), and publication type "meta-analysis" (1993) within the Medline indexing system (3). A search of MEDLINE database using the subject heading META-ANALYSIS (1985-1999) revealed a remarkable increase of papers published on meta-analyses in medical research in the past decade (Figure 2).

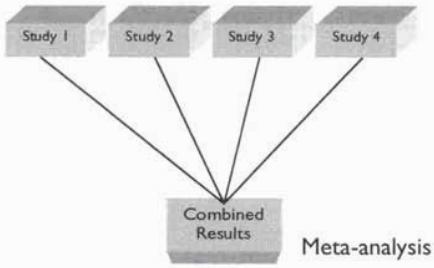

Fig 1. Meta-Analysis: Data from several different studies are combined, translated to a common metric, and produce a single estimate.

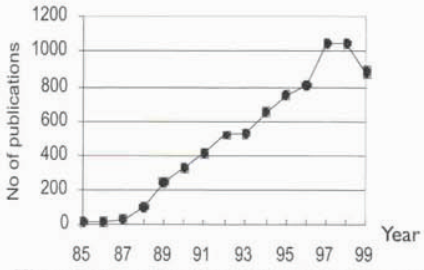

Fig 2. The number of publications about meta-analysis, 1985-1999, results from Medline search using text word and medical subject heading 'META-ANALYSIS'.

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History of Meta-Analysis

Efforts to pool results from separate studies are not new. The statistician Karl Pearson, was probably the first researcher who reported the use of formal techniques to combine data from different samples in 1904 (4). The first meta-analysis assessing the effect of a therapeutic intervention was published in 1955 (5). The development of more sophisticated statistical techniques, took place in the social sciences, particularly in education research, in the 1970s. Light and Smith were among the first to propose pooling original data from previously published research studies (6). In 1976, the psychologist Gene Glass was the first to use the term "meta-analysis" when referring to the statistical approach of pooling data from similar but disparate experiments (7). The prefix "meta" implying an analysis that is similar but more comprehensive, than the original ones. Other terms that are often used synonymously are overview, data pooling, literature synthesis, data synthesis, quantitative synthesis, and systematic review.

One of the earliest uses of meta-analysis in clinical trials was the study by Chalmers *et al* (8). The purpose of the study was to clarify the role of warfarin in patients. Chalmers reasoned that studies that showed statistically non-significant results, owing to inadequate sample size, could be pooled providing that they were of similar design. Such an expanded data set might overcome the lack of statistical power that precluded many of the individual studies from showing statistically significant results. The analysis showed that warfarin was superior to placebo in reducing long-term postinfarction outcome (8).

The Cochrane Collaboration (named after Archie Cochrane, a pioneer in the field of evaluation of medical interventions) is an international network of clinicians, epidemiologists, and other health professionals that aims to prepare, maintain and disseminate comprehensive and systematic reviews (meta-analyses) of the effects of health care (9,10). Since its establishment in Oxford in October 1992, the network has been growing rapidly, with the foundation of 15 other centres in Europe, North and Latin America, Africa, and Australia involving hundreds of individuals from all over the globe collaborating in review groups. Figure 3 is the Cochrane Collaboration logo (11).

The rationale of meta-analysis

The rationale of meta-analysis are summarized as (2,12,13):

1. To provide an overview of a complex literature in order to guide policy decisions and direct future research
2. To improve the precision of estimates of the effect size by increasing the number of observations
3. To assess and resolve apparent conflict in the literature by investigating heterogeneity in study design and results
4. To enable more reliable subgroup analyses to be performed
5. To answer questions not posed at the start of individual trials
6. To define new research questions and assist in the planning of future trials

Figure 3. The Cochrane Collaboration logo shows how pooling data reveals the significance of treatment effects.

Method of Meta-analysis

A meta-analysis should first begin with a protocol, which clearly states its aim and methodology. The objectives, hypotheses to be tested, proposed methods and criteria for identifying and selecting relevant studies, and extracting and analyzing information must be described clearly. Actual study search, selection and appraisal follows, which involves applying specified procedures for locating and appraising studies that meet specified criteria for inclusion. Data are extracted and checked to see if they can be quantitatively combined. This involves clinical criteria and statistical procedures to investigate relations among study characteristics and findings. A brief description of the steps follow, a complete description and evaluation would be beyond the scope of this review.

1) Formulating questions and locating studies for inclusion

The review should begin with a focused question. By formulating the question properly, the criteria that primary studies need to meet to be included become clear. The investigators then must try to find every relevant report. This usually begins with a computerized search of MEDLINE and other electronic literature databases such as EMBASE and CANCERLIT. The Cochrane Controlled Trials Register (CCTR) is one of the best electronic sources for randomized clinical trials (RCTs) (14). The Cochrane Collaboration has an extensive programme of manual searches of medical journals published in English and many other languages, this has helped to identify many published RCTs not listed in Medline. Multiple overlapping search strategies should also be used and must be carefully

planned. It has to be decided whether the search will be extended to include unpublished studies, as their results may differ systematically from published trials. For locating published studies, electronic databases are useful but used alone, they may miss a substantial proportion of relevant studies (14). Searches should extended beyond electronic databases where possible such as manually searching journals and conference proceedings, searching bibliographies of articles, monographs, existing registers of studies, and contacting companies or researchers asking about unpublished work.

2) Selecting and data collection

To plan for study selection, reviewers refer to the focused clinical question and choose selection criteria that are consistent with it. The criteria can be itemized on customized data extraction forms and should at least specify:

1. design of the study
2. patient population
3. disease
4. interventions given
5. measurement of outcomes

The study data to be extracted are usually either binary or continuous measurements. Binary data can be summarized by the incidence risk, odds or rate and treatment effects are estimated by the risk ratio, odds ratio, risk difference or rate ratio. Continuous data can be summarized by the mean response and treatment effect by the difference between the treatment and control group means. It is also important to extract the standard errors or confidence intervals of all the study treatment effect estimates.

3) Appraising Studies

In planning the critical appraisal of included studies, reviewers decide which clinical and methodologic study features are important in order to adequately portray the validity and relevance of each study. Ultimately, primary studies should be appraised and reported in sufficient detail to allow readers to judge the quality of the study and the appropriateness of its inclusion. Blinding evaluators to the names of the authors and their institutions, the names of the journals, sources of funding, and acknowledgments may help reduce reviewer bias and lead to more consistent appraisal scores.

4) Calculating overall effect

Only when the studies are judged combinable because of homogeneity in design should an overall pooled effect be calculated by combining the data. Meta-analysis uses a method that gives the results of larger trials more weight than the smaller ones. There are two statistical techniques to do this, the **fixed-effects model** and the **random-effects model**. The difference between the two models is in the way the variability of the results between the studies is viewed. The fixed-effects model assumes that there is a single true effect to be estimated and considers that study result variability is exclusively due to random variation. The random-effects model assumes a different true effect for each study and takes this into consideration as an additional source of variation. These separate study effects are assumed to be normally distributed, and the mean of this distribution is what we are estimating by the random-effects pooled average. The additional variability measured make the random effects pooled estimates have wider confidence intervals. A substantial difference in the combined effect calculated by the fixed and random effects models will be seen only if studies are markedly heterogeneous. Another quantitative technique for combining data is the **Bayesian method**. This approach incorporates a prior probability distribution based on subjective opinion and objective evidence, such as the results of previous research. Bayesian analysis uses Bayes' theorem to update the prior distribution in light of the results of a study, producing a posterior distribution. This approach has many attractive features, but is controversial because it depends on opinions, and frequently they will vary considerably (15).

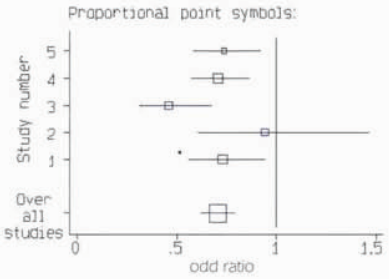

Figure 4. Odds ratios for vitamin A and confidence intervals

5) Presentation

The results of a meta-analysis are presented in a Forest plot (see Figure 4) that shows the point estimates and their confidence intervals (CIs). The presentation shows the extent of heterogeneity, and also the pooled estimate of the individual studies. This display was adopted by the Cochrane Collaboration as its logo. The example of data shown in Table 1 come from a meta-analysis of vitamin A supplementation in infectious disease from five community studies (16). Each study result is represented by a square and a horizontal line, which corresponds to the point estimate and the 95% confidence interval of the odds ratio (Figure 4). The area of the squares reflects the weight of the study. The solid vertical line corresponds to no effect of treatment (odds ratio = 1.0). If the confidence interval in-

Table 1. Vitamin supplementation in infectious disease, odds ratios and confidence interval. Adapted from Glasziou & Mackerras (16)

Study	Dose regime	Vitamin A		Control		Odds ratio	95% CI
		Death	number	Death	number		
1	200,000 IU six-monthly	101	12,991	130	12,209	0.73	0.56 to 0.95
2	200,000 IU six-monthly	39	7,076	41	7,006	0.94	0.61 to 1.46
3	8333 IU weekly	37	7,764	80	7,755	0.46	0.31 to 0.68
4	2000,000IU four-monthly	153	12,541	210	12,264	0.70	0.57 to 0.87
5	200,000IU once	138	3,786	167	3,411	0.73	0.58 to 0.93

cludes 1, then there is no significant difference in the effect of experimental and control treatment at $P<0.05$. The confidence intervals of all but one study (Study 2) exclude 1, indicating that the effect estimates were significant.

Results of a meta-analysis will vary depending on the overall study quality of the primary trials, on whether certain trials or subgroups of patients have been excluded and on which model for pooling the data is selected (2). Therefore, the robustness of the conclusions to different exclusion decisions and model assumptions should always be examined in a **sensitivity analysis**. The procedure simply involves the re-analysis of different subsets of the data and comparing the results for consistency. To avoid accusations of "data-dredging" there should be logical reasons for the choice of data subsets and models, preferably a priori specification in the protocol. If the sensitivity analyses do not change the results, it strengthens the confidence that can be placed in the original interpretation. If the results change in a way that lead to different conclusions, this indicates a need for great caution in interpreting the results and further investigation as to possible reasons for this.

The Advantages of Meta-Analysis

1) State-of the art literature review

In the past, when seeking advice in controversial topics, clinicians and scientists have relied heavily on narrative reviews. Traditional narrative reviews are often subjective, unsystematic, and inefficient in contrast to systematic reviews. Strategies for identifying and selecting information are also rarely defined. Collected information is often reviewed haphazardly with little attention to systematic assessment of quality. Once a set of studies has been assembled, usually a common way to review the results is to count the number of studies supporting various sides of an issue and to choose the view receiving the most votes. Such procedure ignores sample size, effect size, and research design. There is good evidence to suggest that these traditional methods are often misleading, biased and often reach opposite conclusions (19, 20). Consequently, it has been increasingly recognized that the traditional review article is a subjective method of summarizing research data and prone to bias and error (20,21). By employing pre-planned and specified statistical techniques with systematic qualitative review methodology, meta-analysis injects more objectivity and rigor into the review writing process.

2) Gain in statistical power for average estimates

Meta-analysis also provides a gain in statistical power when estimating average effects. If data from more than one study can be combined, the effective sample size and hence statistical power will increase. This is an advantage when the incidence of events is expected to be rare. However, we should never forget that we are not simply looking for statistical significance but also clinical significance. In order to interpret a pooled average fairly we should have an idea of the result difference that would be clinically significant in our context. It should be remembered that the inevitable gain in precision does not protect a meta-analysis from bias. Thus a large but poorly done meta-analysis could give us a very precise estimate of a very biased treatment effect.

3) Predictive ability

Meta-analyses have been examined for their ability to predict the results of large clinical trials. Villar *et al* examined 30 meta-analyses in perinatal medicine, comparing the results of a meta-analysis of several small trials with a single large trial addressing the same topic (20). Twenty-four of the 30 meta-analyses correctly predict the direction of effect in the largest trial. Cappelleri et al reviewed 79 meta-analyses and also found about 80% agreed with the results from the larger trial (21). The authors suggested that "researchers and funding agencies may use meta-analysis before recommending a clinical practice or to summarize results of three controlled trials before deciding on additional studies of promising interventions". The method of **cumulative meta-analysis** in which a meta-analysis is serially updated with the result of the latest study can help determine when additional studies are no longer needed and highlight the effectiveness of treatments much earlier (22).

Such cumulative analysis can help to determine whether the pooled estimate has been robust over time and can also determine the point in time when statistical and clinical significance were reached. For example, Figure 5 shows a cumulative meta-analysis of mortality results from randomized controlled trials of intravenous streptokinase in acute myocardial infarction. A significant ($P<0.01$) combined difference in total mortality had been achieved by 1973. The result of the subsequent 25 studies, which enrolled a total of 34,542 additional patients, reduced the significance level to 0.001 in 1979, 0.0001 in 1986, and finally to 0.00001. The cumulative method suggested that evidence of the life-saving efficacy of intravenous streptokinase had been in existence almost 20 years ago, long before its submission to and approval by the Food and Drug Administration and its general adoption in practice (22).

4) Explore and explain heterogeneity between studies

Heterogeneity of study results in a meta-analysis can be detected by visual inspection of the Forest plot and by a statistical test for heterogeneity. Result heterogeneity can be due to chance, but more often it is due to systematic differences in the design and execution of the studies. Qualitative appraisal of the studies will help identify these differences. The problem of heterogeneity can be further explored using sub-group analysis and meta-regression methods. The purpose of subgroup analysis is to try and identify a subset of studies that are more homogenous in design and hence combinable. **Meta-regression** uses linear regression as an exploratory tool to measure how specific study characteristic e.g. time of publication, quality of study and follow-up time influence the magnitude of the point estimate of the treatment effect across studies (23). The results are generally reported as slope coefficients with CIs. Once again the conclusions should be treated with caution because a typical meta-regression will involve only a small amount of independent data and would also be based on an unvalidated linear regression model.

5) Other Types of Data and Methods

Meta-analysis of Diagnostic Tests

Meta-analysis is potentially important in the assessment of the accuracy of diagnostic tests for both clinician and policy makers. Meta-analysis may (24) 1) provide an overall summary of diagnostic accuracy; 2) determine whether estimates of diagnostic accuracy depend on the study design characteristics (study validity) of the primary studies 3) determine whether diagnostic accuracy differs in subgroups defined by characteristic of the patients and test; and 4) identify areas for further research.

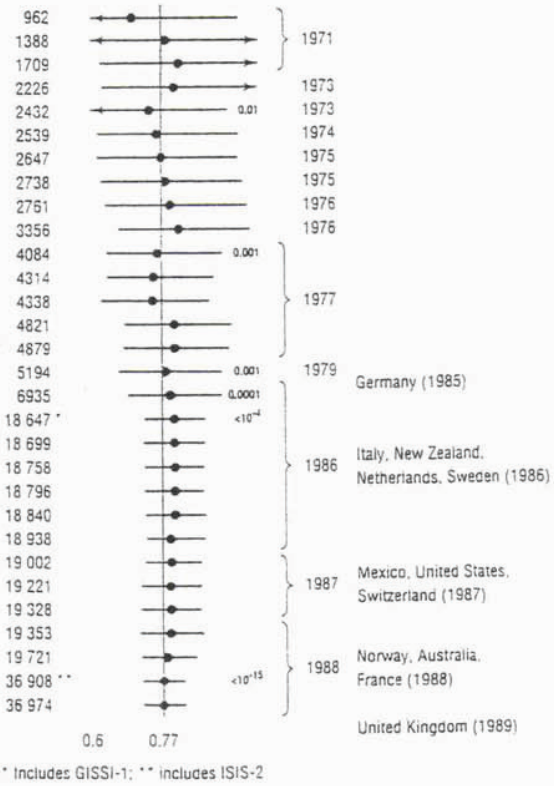

Fig 5. Cumulative meta-analysis of total mortality results from randomized controlled trials of intravenous streptokinase after myocardial infarction. Adapted from Lau *et al* (22)

Meta-analysis of Non-randomized Studies

Data from non-randomized study designs (observational studies) can also be combined in principle by using meta-analytical techniques. Typically such studies would include cohort, case-control and cross-sectional designs. Because of the great vulnerability of such non-randomized comparative studies to bias (15), even greater care must be taken in appraising studies, analysis and interpretation.

Meta-analysis of Individual Patient Data (IPD)

Meta-analysis can be conducted on IPD instead of being based on summary data. Meta-analysis of IPD uses detailed outcome and risk factor data for the individual patients involved in each study rather then relying on published study summaries. However, meta-analysis of IPD is more expensive and time-consuming than meta-analysis of published summary data because it requires the coordination of large teams of investigators (25). Stewart & Parmar (26) investigated the difference between meta-analysis of the literature and meta-analy-

sis of IPD. They concluded that the results of a meta-analysis of the literature alone may be misleading, this was attributed to publication bias, patient exclusion, length of follow-up and method of analysis. Therefore, meta-analysis of individual patient data probably represents the best form of meta-analysis (27). Among the advantages the approach brings are (2): 1) direct computation of survival curves, thus avoiding indirect and biased methods; 2) the ability to check assumption of constancy of treatment effect over time; 3) the ability to identify interactions between treatment effect and patient profiles.

Skepticism

When meta-analysis first appeared, it received a mixed reception. Today, despite its widespread and growing acceptance, meta-analysis continues to be controversial. While some exponents feel that meta-analysis should replace traditional review articles of single topic issues whenever possible (28), others think of it as "a tool that has become a weapon" (29). The common criticism of meta-analyses is that they often inappropriately combine information from multiple trials with different designs, interventions and subject populations into a single estimate of effect (8,30). Thus meta-analyses may generate misleading conclusions by the ignoring obvious heterogeneity among studies. Although we can use a chi-square test to test for heterogeneity of results among studies, this is not a valid way to judge study combinability because, combinable studies must be homogeneous (similar) by design, which is not the same as homogeneous in results. Meta-analyses should therefore state a priori design conditions for combinability in the protocol so that the reader can judge for himself whether they are logical and to what extent the combined studies meet these criteria.

A second problem with many overviews is that they are based entirely on published trials. In some areas of research there has been evidence that journals, perhaps unintentionally exert **publication bias**. This is the phenomena by which significant and positive results are more likely to be reported, than the non-significant and negatives ones. Results which are significant may be emphasized and non-significant results may be ignored by the investigators and editors as uninteresting or uninformative (31,32,33). Often authors and publishers make less effort to publish when the results are not significant. Furthermore, publication of unfavorable results may also be discouraged by the sponsor of research. Consequently, pooling the results of only published trials will perpetuate thisbias and distort the findings of meta-analyses. It is therefore suggested that conclusions based only on a review of published data should be interpreted with caution (33). However, it is usually difficult to locate and get information on the unpublished studies. The Cochrane Collaboration has initiated a scheme to encourage all trialists and drug companies to report all their study results regardless of whether it was a positive or negative finding.

Publication bias is difficult to eliminate, but some statistical procedures may be helpful in detecting its presence. A funnel plot may be used to visually explore the possibility that publication bias is present. It is a simple scatterplots of the trials' effect estimates against their precisions (inverse of the variance, standard error or sample size). Results from small (imprecise) studies will be scattered widely at the bottom of the graph. The spread will narrow as precision increases among larger studies. In the absence of bias, the plot should resemble a symmetrical inverted funnel. If the plot shows an asymmetrical and skewed shape (often a half-funnel), bias is indicated. Figure 6 shows the example of an inverted funnel plot from a meta-analysis of intravenous streptokinase for acute myocardial infarction (18). The risk ratio for the mortality reduction in each study is plotted against the weight of the study, represented by the sample size. The plot shown in the study reveals that there are fewer small studies with risk ratios greater than 0.8 than there are small studies with risk ratios less than 0.8, whereas the number of medium and large studies are fairly symmetrical. These results suggest that some small studies with negative findings were not published. Outlier studies may also be identified by using this plot.

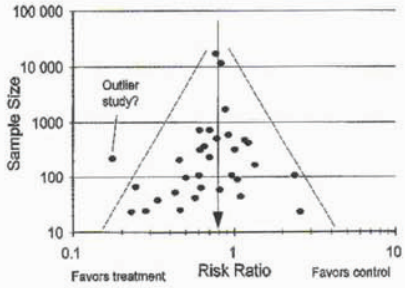

Figure 6. An inverted funnel plot to detect publication bias

In addition, among published studies, those with significant results are also more likely to be published in English, more likely to be cited, and more likely to be published more than once, leading to other biases such **English language bias, database bias, citation bias**, and **multiple publication bias**. Although studies might have been located and data obtained, potential for bias might still arise such as in establishing the inclusion criteria for a meta-analysis (**biased inclusion criteria**) and **bias due to poor study quality**. Any form of bias poses a serious threat to the validity of meta-analysis. While the meta-analyst can minimise the biases in his review methodology, there is little he can do about the biases within each study except to alert the reader to them.

Summary and Conclusions

Meta-analysis has made and continues to make major contributions to both medical research and clinical decision making. However, it is not a panacea and while it remains the most promising approach to reviewing clinical trials, it cannot "clean-up" dirty data. A well-done meta-analysis will in fact reveal the flaws in each study, allowing a more objective appraisal of the evidence than traditional narrative reviews. But it is still only a review of primary studies and therefore cannot be viewed as a substitute for them. In conclusion, for a good meta-analysis, thorough knowledge of the clinical problem, a priori specifications of inclusion criteria, pooling criteria and sub-group analysis, and careful search, appraisal and presentation of data are essential. Meta-analyses will often not give a final solution to a problem, rather it will reveal the progress that has been made and the flaws in present studies so that future ones can be better designed, conducted, analyzed and reported.

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