Meta-Analysis in Psychiatry Research

Fundamental and Advanced Methods

Mallikarjun B. Hanji

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META-ANALYSIS IN PSYCHIATRY RESEARCH

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LIST OF ABBREVIATIONS

CI	confidence interval
DL method	DerSimonian and Laird method
DOR	diagnostic odds ratio
DSM	Diagnostic and Statistical Manual
FN	false negatives
FP	false positives
ICD	International Classification of Diseases
ICMR	Indian Council of Medical Research
IPD	individual patient data meta-analysis
IPSS	Indian Psychiatric Survey Schedule
ML	maximum likelihood
MLE	maximum likelihood estimation
NIMHANS	National Institute of Mental Health and Neurosciences
NNT	number needed to treat
OR	odds ratio
QUOROM	quality of reporting of meta-analyses
RD	risk difference
REML	restricted maximum likelihood estimate
RevMan	review manager
RPES	Rapid Psychiatric Evaluation Scheme
RR	risk ratio
SE	standard error
TN	true negatives
TR	true positives
WHO	World Health Organization

PREFACE

This book is best suited for professionals, teachers, and post-graduate students in the field of psychiatry and allied fields. The main objective of writing this book is to introduce the latest meta-analytical methods developed and applications of suitable ones in the field of psychiatry with real examples in estimate pattern and prevalence of schizophrenia in India along with review of software to be used for the same in a precise and simple manner. The book contains most of the methods developed in meta-analysis, which are described in simple language and presented in a systematic and chronological order so that reader can easily understand the importance of individual methods.

Review of software: The software to be used for meta-analysis has been reviewed in a systematic way to assist the reader in choosing the required software. The commands of the software, namely, STATA, have been used extensively to demonstrate the examples in detail.

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—**Mallikarjun B. Hanji**

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CHAPTER 1

INTRODUCTION

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ABSTRACT

Meta-analysis can be defined as a systematic statistical method for analyzing and synthesizing results from independent studies, taking into account all pertinent information. Readers of narrative studies face problems such as lack of detailed description, the process that led to the review, and hence the readers cannot replicate and verify the results and conclusions of the review. Most effective mechanism for systematic review is to reduce bias and increase precision, by including maximum possible number of relevant individual studies and providing a detailed description of their strengths and limitations. Vote counting is clearly unsound, since it ignores sample size, effect size, and research design. Meta-analysis is trying to answer four basic questions, namely, (1) are the results of the different studies similar and to the extent that they are similar, (2) what is the best overall estimate, (3) how precise and robust is the estimate, and (4) can dissimilarities be explained. Exploratory analysis, such as regarding subgroups of patients who are likely to respond particularly well to a treatment, may generate promising new research questions. Meta-analysis identifies areas where further studies are needed. Meta-analysis provides robust evidence and may utilize a less biased sample of evidence. Physicians can now make decisions regarding the use of therapies or diagnostic procedures on the basis of a single article that synthesizes the findings of tens or hundreds of clinical studies. The Cochrane Collaboration which is an international organization involved in preparing meta-analysis of the effects of interventions in all aspects of health care. The science of meta-analysis is relevant to clinical and community psychiatry to evaluate the potential errors and sources of bias and offer guidelines for evaluation. The statistical basis of meta-analysis reached back to the 17th century wherein astronomy and geodesy intuition and experience suggested that combinations of data might be better than attempts to choose amongst them. Meta-analysis has had critics and criticisms over the years. Most prominent of which is publication bias, which refers to the tendency for journals and authors not to publish articles on research that has no significant findings. There is a danger that meta-analysis of observational data produce very precise but spurious results. The complex methods used in meta-analysis should always be complemented by clinical acumen and common sense in designing the protocol of a systematic review, deciding what data can be combined, and determining whether data should be combined.

Meta-analysis provides an opportunity for shared subjectivity in reviews rather than true objectivity. Meta-analyses are most easily performed with the assistance of computer databases and statistical software.

1.1 FEATURES OF META-ANALYSIS

1.1.1 META-ANALYSIS

Meta-analysis can be defined as a systematic statistical method for analyzing and synthesizing results from independent studies, taking into account all pertinent information. By synthesizing, scrutinizing, tabulating, and perhaps integrating all relevant studies, meta-analysis allows a more objective appraisal, which can help to resolve uncertainties when the original research, classical reviews, and editorial comments disagree. Meta-analysis is a scientific activity that borrows from both the expert review and the methodology of multicenter studies (Fisher et al., 1993). There are varieties of synonyms for meta-analysis used in the literature: overviews, aggregates, syntheses, integration, amalgamation, pooling, and combining. Quantitative is the heart of the meta-analysis and combining results is an essential ingredient in meta-analysis.

1.1.2 NARRATIVE STUDIES

Traditionally, individuals often considered experts in the field who have conducted narrative reviews of the literature, associated with a particular field using informal and subjective methods to collect and interpret information. Readers of narrative studies face problems such as lack of detailed description, the process that led to the review, and hence the readers cannot replicate and verify the results and conclusions of the review.

1.1.3 SYSTEMATIC REVIEWS

Reviews being the product of a scientific process to reduce bias, to increase precision and by providing detailed information to allow replication by others. Most effective mechanism for systematic review is to reduce bias and increase precision, by including maximum possible number of

relevant individual studies and providing a detailed description of their strengths and limitations.

1.1.4 VOTE COUNTING METHODS

Once a set of studies have been assembled, a common way to review the results is to count the number of studies reporting various sides of an issue and to choose the view receiving the most votes. This procedure is clearly unsound, since it ignores sample size, effect size, and research design.

1.2 SCOPE AND BENEFITS OF META-ANALYSIS

1.2.1 COMBINE RESULTS

A quantitative systematic review or meta-analysis use statistical methods to combine the results of multiple studies.

1.2.2 HETEROGENEITY

They are trying to answer four basic questions, namely: (1) Are the results of the different studies similar and to the extent that they are similar? (2) What is the best overall estimate? (3) How precise and robust is the estimate? and (4) Can dissimilarities be explained (Lau et al., 1997)?

1.2.3 EXPLORATORY ANALYSIS

Exploratory analysis, such as regarding subgroups of patients who are likely to respond particularly well to a treatment, may generate promising new research questions to be addressed in future studies. Meta-analysis can help us to investigate the relationship between study features and study outcomes. One can code the study features according to the objectives of the review and transform the study outcomes to a common metric so that comparison of the outcome is possible.

1.2.4 IDENTIFICATION OF RESEARCH AREAS

Meta-analysis may demonstrate the level of adequate evidence and this identifies areas where further studies are needed.

1.2.5 PROVIDING EVIDENCE

Meta-analysis can examine questions, provide formal standard of rigorous for accumulating evidence from different studies, formulize the process of policy making, increase statistical power, provide robust evidence, and may utilize a less biased sample of evidence.

Meta-analysis, if appropriate, will enhance the precision of estimates of treatment effects, leading to reduced probability of false negative results, and potentially timely introduction of effective treatments.

1.2.6 BENEFITS OF META-ANALYSIS

Physicians can now make decisions regarding the use of therapies or diagnostic procedures on the basis of a single article that synthesizes the findings of tens or hundreds of clinical studies. Scientists in every field can similarly gain a coherent view of the central reality behind the multifarious and often discordant findings of research in their areas. Meta-analysis of a series of small clinical trials of a new therapy often yields a finding on the basis of which physicians can confidently begin using it without waiting long years for a massive trial to be conducted.

1.3 SOME EXAMPLES

Sharma et al. (2003) has successfully employed meta-analytical procedures to determine the effect of inhaled steroids on bone mineral density. Shann (1997) has employed meta-analysis to obtain evidence of trials of prophylactic antibiotics for children with measles for adequate evidence. The meta-analysis (Gupta and Gupta, 1996; Gupta, 1997) was performed to determine the time trend in the prevalence of coronary heart diseases in India and age and gender specific changes.

The Cochrane Collaboration which is an international organization involved in preparing maintaining and disseminating highly structured, frequently updated, and good quality systematic reviews and meta-analysis of the effects of interventions in all aspects of health care (Cochrane Injuries Group Albumin Reviewer, 1998; Kennedy et al., 2002; Olsen and Gotzsche, 2001).

The national library of medicine defines meta-analysis as a quantitative method of combining the results of independent studies and synthesizing summaries and conclusions, which may be used to evaluate therapeutic effectiveness, plan new studies, etc. with application chiefly in the areas of research and medicine.

Meta-analyses are based on trials of parallel group design, but some trials assessing the treatment of interest may use other designs. This is particularly the case in certain chronic diseases whose treatment is often evaluated by cross over-trials; typical examples include hypertension, asthma, or rheumatic diseases. Parallel and cross-over trials both provide estimates of the same treatment effect (Curtin et al., 2002a,b).

Laird and Ware (1982) have discussed the random effects model for longitudinal data on health effects of air pollution. Malhotra et al. (2001) have conducted a meta-analysis of controlled clinical trials comprising low-molecular-weight heparins with unfractionated heparin in unstable angina. Pavia et al. (2003) have carried out a meta-analysis of residential exposure to radon gas and lung cancer. Ezzat et al. (2004) have carried out a systematic review on the prevalence of pituitary adenomas. Gisbert et al. (2003) have carried out a systematic review and meta-analysis to determine prevalence of hepatitis C virus infection in porphyria cutaneatarda. Devereaux et al. (2002) have carried out meta-analysis of studies comprising mortality rates of private for-profit and private for nonprofit hospitals.

1.3.1 PSYCHIATRIC RESEARCH

The science of meta-analysis is relevant to clinical and community psychiatry to evaluate the potential errors and sources of bias and offer guidelines for evaluation. Meta-analysis is a specific technique that was developed in social sciences, but was soon adapted as a fundamental tool in psychiatric research with a number of aims.

The relevance of meta-analysis to psychiatry stems from one of the earliest meta-analyses ever undertaken, which evaluated efficiency of various forms of psychotherapy. Since the 1980s, meta-analysis has increasingly appeared in the medical literature, and scarcely a month now passes without the publication of a meta-analysis of relevance to clinical psychiatry in general medical journals or in mainstream psychiatric literature (Tharyan, 1998).

Whitehead (1997) has applied a prospectively planned cumulative meta-analysis to a series of concurrent clinical trials. Meta-analysis permits investigation of generalizability and consistency, improved transparency of methodology, and enhance reproducibility in psychiatry fields.

Harrison et al. (2003) have carried out a meta-analysis to answer the question whether brain weight is decreased in schizophrenia patients and concluded that the brain weight is slightly, but significantly, reduced in schizophrenia, consistent in duration and magnitude with MRI volumetric findings.

Based on fitting a model to the funnel plot, Shi and Copas (2004) have discussed a method for random-effects sensitivity analysis that deal with the problems of heterogeneity and publication bias and applied on the effect of alcohol on the risk of breast cancer. Hall and Roter (2002) have conducted a meta-analysis to answer a question: Do patients talk differently to male and female physicians. Reynolds et al. (2003) have carried out a meta-analysis and concluded that heavy alcohol consumption increases the relative risk of stroke while light or moderate alcohol consumption may be protective against total and ischemic stroke.

Ananth et al. (1999) have applied meta-analysis of observational studies on incidence of placental abruption in relation to cigarette smoking and hypertensive disorders during pregnancy and concluded an increased associationship.

Herbert and Cohen (1993) have conducted a meta-analysis and concluded that clinical depression was associated with several large alterations in cellular immunity.

The meta-analytical approaches have wide applications in making diagnosis, deciding on the course and method of treatment, predicting the outcome of treatment, and determining the course of mental disorders in order to prevent them.

1.4 HISTORICAL BACKGROUND

The statistical basis of meta-analysis reached back to the seventeenth century wherein astronomy and geodesy intuition and experience suggested that combinations of data might be better than attempts to choose amongst them.

In 1904: Professor Karl Pearson reported the use of formal techniques to combine data from different studies. G. V. Glass set up a process for synthesizing research studies that used statistical methods, including the use of probabilities and effect sizes, for aggregating results.

Late 1970: Two other coherent methods have been formulated as elaborations of Glass's approach. These five separate and coherent methods are Glassian meta-analysis, study effect meta-analysis, combined probability meta-analysis, meta-analysis using approximate data pooling with tests of homogeneity, and meta-analysis using approximate data pooling with sampling error correction. They indicate the present moment in the continuing evolution of review methodology and can be distinguishable on four factors: purpose, unit of analysis, treatment of study variation, and products of the meta-analysis (Glass, 2000).

In 1976: The same year, that Glass (1976) first coined the term "Meta-analysis," Rosenthal published his book "experimental effects in behavioral research," and Schmidt and Hunter were working on a validity generalization technique. These three concurrent efforts established three distinguishable meta-analytic approaches.

In 1984: Hedges and Olkin (1984) have extended the logic of non-parametric estimators of effect sizes in meta-analysis.

In 1989: Alexander et al. (1989) have developed statistical and empirical examination of the chi-square test for homogeneity of correlations in meta-analysis. From the statistical point of view, meta-analysis is a straight forward application of multifactorial methods (Blend, 2000).

In 1990: The foundation of Cochrane Collaboration facilitated numerous developments (Egger et al., 2001). Researchers have answered the difficulty by supporting methods to test the statistical significance of results combined from separate experiments. They sought ways to combine probability values from tests of significance.

In 1995: Stewart et al. (1995) have conducted a meta-analysis of published studies to identify factors, which explained variation in estimates of migraine prevalence.