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# META - ANALYSIS

*Ivana Ilic*

Meta-analysis is a statistical and analytical method which combines and synthesizes different independent studies and integrates their results into a common result. In the past few years, there has been an increasing interest in meta-analysis from both medical researches and statisticians. One of the main targets of clinical research is to obtain reliable results, although clinical trials with the same topic often give contrasting results. Medical practice is strongly influenced by the results of clinical studies, if they are brought to light through important scientific journals. This large amount of information often contains scattered data, and discordant conclusions, and sometimes it is very hard to define the quality and validity of each study. Today, a great number of biomedical journals gives importance to articles using meta-analysis in their researches. By using meta-analysis as a method of summarizing, integrating and analyzing a great number of independent studies on the same topic and finally pooling their results into a common result, a researcher can achieve relevant, objective and unbiased conclusions, if the procedure is well-conducted and controlled by the experts. The aim of this paper is to provide the clinical researcher with the basic principles of meta-analysis and its concepts in order to perform a valid clinical study and to report results in the correct way. In today's evidence-based medical practice, it is crucial for anyone who wants to deal seriously with the scientific work in the biomedical field to learn mathematical and statistical principles that build meta-analysis. In that way, this statistical method could be of great importance to the researcher who wants to respond to new demands of modern medical science. *Acta Medica Medianae 2009;48(2):28-31.*

***Key words:*** *meta-analysis, statistics, analytics*

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## Introduction

### Definition

Meta-analysis is a statistical and analytical method which combines and synthesizes different independent studies and integrates their results into a common result. It can be very powerful tool when well-designed and appropriately performed. Meta-analysis has mathematical and statistical principles well defined for the critical evaluation of medical data. Therefore, the results obtained by a well-conducted meta-analysis can be considered as valid and there would be no need for further investigation on this issue.

### Brief history

As a scientific method to accomplish valid results by synthesizing independent researches, meta-analysis has a long and old history, although the term meta-analysis was introduced not earlier than 1976 by Gene Glass. Since the introduction of the term, the use of combined experiments and obtaining generalized conclusions has become very wide in the fields of education, psychology and the biomedical sciences. First example of this method appeared in Legendre in 1805 and his invention of the principle of least squares (these results were used by Stigler in 1986 later in his research in astronomy). Important example of meta-analysis in the field of medicine was a study by Karl Pearson in 1904 who analyzed the data from five studies on the correlation between the vaccination for enteric fever and its mortality. He observed separate sets of data from different geographical locations. It is an early example of meta-analysis, and yet it has all the features of a correct meta-analysis. The first written work on the methodology of combining the results of different studies was given by Tippett in 1931, then shortly after Fisher in 1932 and Pearson in 1933, who independently proposed a method for combining tests of statistical significance based on the product of the p values across studies. Also, Cochran in 1937 and Yates and Cochran in 1938 in their early work combined information across experiments in the agricultural sciences in order to

derive estimates of treatment effects and test their significance. See also Mosteller and Bush in 1954, Glass, McGaw and Smith in 1981, then Hunter, Schmidt and Jackson in 1982, Rosenthal in 1984, Hedges and Olkin in 1985 and Cooper and Hedges in 1994 for further investigation on the history of meta-analysis.

### When to perform a meta-analysis

The domain of applicability of meta-analysis is wide, but somewhat circumscribed. It can be applied only to empirical research studies that produce quantitative findings. It can not summarize and integrate findings that are theoretical and reported in the qualitative form rather than quantitative. Also, it is very important that those findings can be meaningfully compared. It means that they are dealing with the same constructs and relationships and also to be configured in the similar statistical forms.

### Why to perform a meta-analysis

Medical practice is strongly influenced by the results of clinical studies, if they are brought to light through important scientific journals. This large amount of information often contains scattered data, and discordant conclusions, and sometimes it is very hard to define quality and the validity of each study. Among the reasons for this is the lack of knowledge concerning the use of mathematical and statistical tools. Therefore, the knowledge of methodology of statistics is crucial for all medical researchers in order to obtain correct results. That is why the interest in meta-analysis in biomedical world is growing rapidly. Today, a great number of biomedical journals gives importance to articles using meta-analysis in their researches. By using meta-analysis as a method of summarizing, integrating and analyzing great number of independent studies on the same topic and finally pooling their results into a common result, researcher can achieve relevant, objective and unbiased conclusions, if the procedure is well conducted and controlled by the experts (1).

### Planning a meta-analysis

Every stage in planning meta-analysis has its own rules defined precisely in order to avoid bias in the analysis and to provide more accurate results. It is necessary to work in team constituted by the experts of the topic under investigation and by the experts of the statistical methods applied to the medical fields.

***The first step*** is to define hypothesis, i.e. careful statement of the topic to be investigated or the question to be answered, and also according to that hypothesis, to define excluding and including criteria for the research studies. This hypothesis will guide the selection of research studies, the coding of information from those studies, and the analysis of the resulting data. The problem hypothesis needs to be straightforward and complete but, at this stage of the process, need not be highly detailed (that will come later, in the next steps).

***The second step*** is searching for the topic of interest in all available scientific literature, and thorough literature search is crucial to retrieve every relevant study. It is important to choose correct key words that will lead us to the target issue. The researcher has to investigate all reliable and available medical sources of scientific journals, such as Medline, Embase, Index Medicus, and with the consultation with the leading experts in the field also consider published journal articles, books, dissertations, technical reports, unpublished manuscripts, conference presentations, etc. Of course, it is necessary to check the references cited in each article and start new searches on that basis. It is obvious that more persons should be included in this stage of the process, in order to achieve accuracy and effectiveness. Finally, the complete procedure and the criteria for excluding or including studies from the analysis should be described in details (2).

***The third step*** is to choose adequate statisti-cal software, and perform meta-analysis. First, we must say that it's quite difficult to integrate all those different studies into one study, and perform mathematical and statistical formulas as those studies are using the same measurement procedures for their key variables. That is why we have to code these quantitative findings in a way that allows them to be statistically compared and combined. The central notion in meta-analysis is the so-called effect size. Practically, it is the basic parameter of interest, the value that we are trying to estimate. It can be: odds ratio, risk ratio, correlation coefficient, mean difference, standard mean difference, depends what is our target in the analysis. We have to standardize it, so it can be comparable across studies.

Also, the number of elements in the sample varies from study to study, so that different effect size values will be based on different sample sizes. But, statistically speaking, effect size values based on larger samples are more precise estimates than those based on smaller samples. Therefore, those estimates are more powerful and have greater impact on final result than those based on smaller samples. This problem is solved by giving "weight" to each study according to its precision. In fact, if the precision is estimated according to the dispersion, namely the variance, then the weight of each study is given by the inverse of the variance:

$$W_i = \frac{1}{V_i}$$

where $W_i$ is the weight and $V_i$ the variance of the outcome of the study, where and $n$ is a number of studies involved in the analysis. In other words, if a study has a wide variance (greater imprecision), it will have a small weight in determining the final

result of the analysis (the integrated result of the meta-analysis), while a study with a small variance (greater precision) will have a greater weight. The general formula of the meta-analysis expresses the global outcome *D* in terms of a weighted mean:

$$D = \frac{\sum_{i=1}^{n} W_i d_i}{\sum_{i=i}^{n} W_i}$$

with the sum extended to *n* studies, and where $d_i$ represents individual outcomes from each study.

***Fixed and random effects models***. The statistical procedures that we are going to use in the calculation may be divided into two categories depending on the assumptions that we made about the available studies. If the effects evaluated are expected to be a part of the same distribution, we are choosing the fixed effect model for our calculations. If this assumption is not met, it means that the studies are sampled from a population that includes several different populations, each provided with its own mean. In this case, it could be necessary to use a random effect model.

***Final step*** is interpretation of the results of meta-analysis, in the sense that we should estimate and evaluate the effect size of integrated studies, i.e. give an answer to our hypothesis, explain the causes of possible heterogeneity, justify the studies that are considered, analyze the reasons for excluding some studies from the analysis, evaluate the stability of meta-analysis, i.e. test if the common effect changes significantly by adding new studies into analysis, and calculation of the number needed to be treated (3).

## Advantages and disadvantages of meta-analysis

The strength of meta-analysis lies in the fact that it produces effect size estimates with considerably more statistical power than individual studies. Further, it improves the estimation of the effect of a treatment. Meta-analysis combines results of studies that are contrasting, in a way that it weights them, i.e. it gives importance to each study according to their accuracy, in the sense of variance. More, it is always possible to update analysis, when new studies are published on the topic under investigation. Meta-analysis is based on the exact mathematical and statistical rules; therefore, it is an objective method, less influenced by the author's personal opinion. Each step in the analysis must be documented and open to the consumer who can access to the procedures and conclusions and check the validity of results (4).

We must say, though, that this method is not always the best tool, and there are some authors who criticize it (5-7). First, this method demands a great deal of effort, in searching, collecting, analyzing and including or excluding studies. Perhaps the most persistent criticism of meta-analysis has to do with the mixing of involved studies. The problem is known as «apples and oranges». It occurs when we want to put together different types of studies which are not comparable and average them together in a grand mean effect size. Then, some critics argue that we should base our research only on high quality studies and to set more strict criteria for the inclusion of studies. The meta-analysis, based on methodologically flawed studies, cannot result in good statistics (8). Since usually only studies where a significant difference is found are published, this implies that some completed studies are not published and therefore cannot be considered in the meta-analysis and that can also lead us to a so-called publication bias (9,10). Of course, for all these weaknesses of the method, there are solutions that can handle the problems and they could be solved by the strong collaboration between the experts both in medical and statistical field (11-13).

## Conclusion

Nowadays, in the evidence-based medical practice, it is recommendable to anyone who wants to deal seriously with the scientific approach in biomedical sciences, to understand these mathematical and statistical principles of meta-analysis. In summary, knowing how to read, understand, have a critical opinion, and finally perform, a meta-analysis will be a valuable tool for the researcher who wants to participate in modern biomedical researches (7).

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# META-ANALIZA

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Meta-analiza predstavlja statistički i analitički metod koji kombinuje i sintetizuje različite medjusobno nezavisne studije i integriše njihove rezultate u zajednički, jedinstveni rezultat. U poslednjih nekoliko godina raste interesovanje statističara za meta-analizu, a takodje i istraživača u oblasti medicinskih nauka koji koriste statistiku. Jedan od glavnih ciljeva medicinskih istraživanja je dobijanje pouzdanih rezultata, a klinička istraživanja odredjenog problema ne daju uvek saglasne rezultate. Medicinska praksa se sprovodi pod snažnim uticajem rezultata kliničkih studija ukoliko su one objavljene u važnim naučnim časopisima. Velika količina objavljenih radova često sadrži nepotpune ili netačne podatke, kontradiktorne ili nesaglasne zaključke i ponekad je veoma teško odrediti kvalitet i validnost svake studije. Danas veliki broj biomedicinskih časopisa pridaje veći značaj onim radovima koji su svoje hipoteze dokazali kroz meta-analizu. Korišćenjem meta-analize kao metode sumiranja, integracije i analize velikog broja nezavisnih studija koje obradjuju istu temu i konačno izvodjenje zajedničkog rezultata, istraživač može postići relevantne, objektivne i precizne zaključke, ukoliko je procedura pažljivo osmišljena i kontrolisana od strane eksperata. Cilj ovog rada je da upozna istraživača u oblasti medicinske prakse sa konceptom meta-analize i njenim osnovnim principima kako bi mogao uspešno da sprovodi dobre kliničke studije i prezentuje rezultate na ispravan način. U savremenoj medicinskoj praksi baziranoj na statističkim dokazima potrebno je da svako ko želi da se ozbiljno bavi naučnim radom u oblasti biomedicinskih nauka usvoji matematičke i statističke principe na kojima se zasniva meta-analiza. Na taj način, ovaj statistički metod može postati nezamenljiv alat za istraživača koji želi da odgovori na nove zahteve moderne medicinske nauke. *Acta Medica Medianae 2009;48(2):28-31.*

***Ključne reči**: meta-analiza, statistika, analitika*