

Meta-Analysis: A Review Article

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Meta-Analiz: Bir Derleme

ABSTRACT

Meta-analysis is a frequently used statistical technique which uses to combine data from several studies to evaluate the effectiveness of treatment interventions. By combining results from independent studies, we can both increase power of the study (over individual studies) and improve estimates of the size of the effect. The processes of conducting meta-analysis include developing a protocol, selecting articles, developing inclusion criteria, collecting data, data analysis and interpreting results. A major limitation of the meta-analysis is that only relevant studies which have retrievable data can be included for analysis. This causes concern for publication bias. It is obvious that metaanalysis is a useful scientific method that can provide important information when summarizing medical literature. However, there can be misleading if the studies included are non-similar in their research question or collect different types of outcome data.

Keywords: Meta-analysis, systematic review, evidence-based medicine

ÖZ

Meta-analiz, birçok çalışmadaki verileri birleştirmek ve tedavi müdahalelerinin etkinliğini değerlendirmek için sık kullanılan bir istatistiksel tekniktir. Bağımsız çalışmalardan elde edilen sonuçları birleştirerek hem çalışmanın gücünü artırabilir (bireysel çalışmalara göre) hem de effect size tahminlerini iyileştirebilir. Meta-analiz yürütme süreçleri arasında bir protokol geliştirmek, makaleler seçmek, dahil edilme kriterleri geliştirmek, veri toplamak, veri analizi yapmak ve sonuçları yorumlamak bulunmaktadır. Meta-analizin önemli bir limitasyonu, sadece analiz için geri alınabilir verilere sahip ilgili çalışmaların dahil edilebilmesidir. Bu durum publication(yayın) bias için endişe yaratmaktadır. Meta-analizin, tıp literatürünü özetlerken önemli bilgiler sağlayabilecek tam olarak faydalı bir bilimsel yöntem olduğu oldukça açıktır. Bununla birlikte, dahil edilen araştırmaların araştırma sorusuyla aynı olmadığı veya farklı sonuç verileri topladığı takdirde yanıltıcı olabilir.

Anahtar kelimeler: Meta-analiz, sistemik derleme, kanıta dayalı tıp

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Meta-analysis can be defined as “A kind of scientific review of original studies/articles in a specific subject which is aimed to combine separate statistical results into a single estimation.” Although there are some differences between them, overview, systematic review and pooled analysis are other synonymous terms that have been used with meta-analysis ⁽¹⁾. Evidence-based medicine uses the published medical studies to guide clinical practice and decision. A meta-analysis is a study which combines the results of multiple studies and performs a statistical reanalysis. Meta-analysis determine the quality of research, compares the studies to determine the strongest evidence in the field for clinical decision making, and also gives directions for future research. Along these lines, meta-analysis has some advantages and

disadvantages as with any other research type. As an example, meta-analysis compares results from different studies and identifies relations between study results ⁽²⁾. It is most useful when the studies are controversial and with limited sample sizes to support conclusions. By combining results from independent studies, we can both increase power of the study (over individual studies) and improve estimates of the size of the effect. Also clear the way to interpret the results, in case of controversial results and summarize large volumes of literature. Most importantly methodology should be systematic, clear and replicable by others.

The British statistician Karl Pearson seems to be the first to combine results of observations from diffe-



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rent studies. The earliest meta-analysis was published by Karl Pearson in 1904 ⁽³⁾. However, meta-analysis has been applied for other fields of the science. Then, the first meta-analysis of medical treatment is probably that of Henry K Beecher on the powerful effects of placebo, published in 1955 ⁽⁴⁾. In the medical Archie Cochrane is also an important scientist in development of the meta-analysis and he advocated that use of randomized control trials make medicine more effective and efficient. His advocacy eventually concluded with the development of the Cochrane Library database of systematic reviews ⁽⁵⁾ science, conducting meta-analysis started to increase in 1980s.

Meta-analysis is designed to evaluate retrospectively all available published studies. Additionally, data that are based on the summary statistics could be extracted from previous published manuscripts. Hereby, it is possible that meta-analysis bring potential validity problems. A major limitation of the meta-analysis is that only relevant studies which have retrievable data can be included for analysis. Namely, published studies generally include statistically significant results (basically positive results have the chance of getting published more than negative studies). This causes concern for publication bias. A meta-analysis which is planned needs to

be registered, which has many advantages such as helping transparency, reducing potential bias and avoiding unintended duplication of reviews ⁽⁶⁾. Meta-analysis can be easily interpreted when the important concepts are known such as effect size, odds ratio, relative risk, fixed effect model, random-effect model, confidence interval etc (Table 1).

There are 3 most common and popular meta-analysis approaches; and are named as the Hunter and Schmidt, Glass, and Hedges and Olkin meta-analysis procedures. Regardless of the different approaches used for meta-analysis, basically, there are several common steps exist for doing a meta-analysis ⁽⁷⁾:

1. Defining the research topic and developing a protocol.

Meta-analysis requires teamwork. Therefore, while conducting a meta-analysis, a technically equipped statistician and knowledgeable medical experts should be included into the study. First step is to perform a detailed research of literature to define the research topic and prepare a study protocol. Description and the rationale of doing the study is needed, and to be followed by significance of addressing the problem. Basically defining what is already known and unknown is important. The protocol of meta-analysis should include a clear hypothesis of the study with outcomes. In the protocol, general information of the investigated disease or condition should be mentioned. Also, results of the previous studies should be discussed and the reasons for conducting the current meta-analysis should be presented. The purpose of a meta-analysis should have proper answer to important clinical questions or identify areas of high clinical significance that are still unreported in the medical literature ^(8,9). An appropriate question should be unique and focused on the certain identification of the Participant(s), Intervention(s), Comparison(s), Outcome(s), and Study design. These are components of PICOS criteria which need to be defined in the study. The protocol should be registered and made easily accessible to readers and investigators.

After identifying the study aim and questions, the investigator must determine the inclusion and exclu-

Table 1. Major Components of a Meta-analysis

Concept	Definition
Effect size	Indicates that both direction and magnitude of the treatment effect
Odds ratio	Ratio of the probability of an event occurring compared to the event not occurring in a particular group. The odds ratio is the ratio of the odds between 2 groups
Relative risk	Relative risk is equal to the risk among exposed subjects divided by the risk among unexposed subjects
Fixed-effects model	A model that assumes that each study included in the meta-analysis is estimating the same population treatment effect
Random-effects model	A model that assumes that the treatment effects of the included studies are part of a distribution of treatment effects
Confidence interval	Confidence intervals (CIs) provide upper and lower limits that capture the range of values around the true

sion criteria of the study. PICOS criteria might be useful to decide the inclusion and exclusion criteria as a part of study protocol of the meta-analysis. A PRISMA (Preferred Reporting Items in Systematic Reviews and Meta-analysis) flow chart should be created. This should demonstrate the identification and screening of available studies and also determines the final number of studies included for statisti-

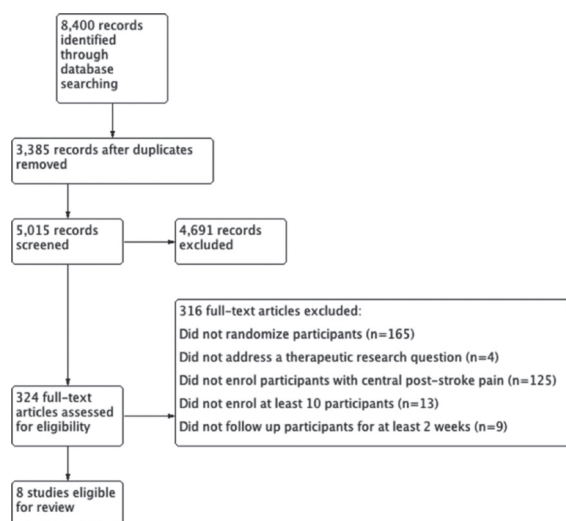


Figure 1. Study flow chart

cal analysis. As an example, Mulla et al performed a meta-analysis of randomized controlled trials to evaluate therapies for central post stroke pain ⁽¹⁰⁾. The study flow chart can be seen in Figure 1. The question must be specific; however, author should try to avoid being too specific. Trying to be more specific for the inclusion criteria's might limit the heterogeneity of the studies in the final analysis. If the posed question is too specific (eg, "Is having 120 mg dl⁻¹ blood glucose better than having 115 mg dl⁻¹ blood glucose for the patient admitted to the intensive care unit?"), then it is highly possible to not find enough published manuscripts available to answer the question. On the other hand, depending on the study topic, specificity makes study homogeneous. However this might decrease the number of studies included and analyzed for the meta-analysis. Thereby, inclusion and exclusion criteria should be carefully determined. If investigator needs to do changes regarding established inclusion and exclusion criteria, it is possible to alter the criteria as the study search strategy requires. The person doing the literature search should be defined (could be a librarian or independent researcher). Important information is to include dates of the literature search performed.

Oxford Quality Scoring System
1. Was the study described as random? <input type="radio"/> Yes <input type="radio"/> No
2. Was the randomization scheme described and appropriate? <input type="radio"/> Yes <input type="radio"/> No
3. Was the study described as double-blind? <input type="radio"/> Yes <input type="radio"/> No
4. Was the method of double blinding appropriate? <input type="radio"/> Yes <input type="radio"/> No [11]
5. Was there a description of dropouts and withdrawals? <input type="radio"/> Yes <input type="radio"/> No

Figure 2. Oxford quality scoring system

Then, after a systematic search, at least two investigators independent from each other should screen the retrieved studies and exclude irrelevant data. Each eligible study also should be read by another investigator regarding adequacy of the blinding, description of withdrawals and randomization according to Oxford scale ⁽¹¹⁾ (Figure 2).

2. Searching for relevant studies

Searching the literature is very important step in meta-analysis. The person doing the literature search should be defined (could be a librarian or independent researcher). Important information is to include dates of the literature search performed. Selecting the correct keywords/synonyms is crucial, authors should have consensus on this. Authors can combine few of the keywords using OR (expands search)/AND (narrows search).

There are several free of charge and available electronic databases for the extraction of studies which are included in meta-analyses. Also investigators can access pay-per-use databases. Suitable search filters should be created by the investigators at this stage such as type of studies (experimental or human), language etc. Using only a single database to extract the appropriate studies is insufficient. Investigators should search for studies that have addressed the same research question, using some different electronic databases such as the COCHRANE, MEDLINE, PubMed, Institute for Scientific Indexing (ISI), Embase, Web of Science, Scopus and PsycINFO ⁽¹²⁾. These databases can be used not only to find article but also to identify authors in the field. PubMed is a free database which uses the MEDLINE database provided by the United States National Library of Medicine of the National Institutes of Health. The Cochrane Library is an accumulation of several databases provided by John Wiley & Sons Ltd., which contains thousands of systematic reviews. Regardless of the databases used, main purpose of the searching relevant studies is to ensure that whole eligible and important studies are included to the meta-analysis. Another important point is that investigator should make sure to avoid duplication of studies might be related to language or any other reason. It might be easy to determine by checking the articles material and method section reporting the enroll-

ment date of the patients.

As soon as all the eligible articles have been found and full text copies are obtained, the title of each article should be read and irrelevant ones should be removed. This is generally done by two investigators. Any article that is not compromised at this stage should be retained. The abstracts of all the remaining articles must then be read to eliminate further articles. Articles which are not meeting the inclusion criteria must be removed. After finishing the selection of the article, full text of all articles must be read to evaluate whether they are eligible or not. Also, the following important step is to check the references of the included articles to identify other eligible studies. It can be helpful to find related studies by checking the references based on the original inclusion criteria ⁽¹²⁾.

There is large variation of type of data that can be used and available for a meta-analysis. As an example, while data of all individual patients might be used, summary statistics obtained from publications also might be used. Although they are time consuming, meta-analyses based on individual patient data have advantages over those based on summary statistics of published paper. Because of difficulties to obtain individual patient data, meta-analyses are generally performed by using summary statistical data from included studies. However, if the required data is not available in the manuscript then the investigators should contact corresponding authors and try to obtain the information, and this should also be reported in the manuscript.

3. Publication bias

Publication bias is an important limitation of meta-analysis. Journals generally publish significant finding more than non-significant findings. Because reviewers intend to reject manuscripts which contain negative or non-significant findings ^(13,14). This is described as publication bias ⁽¹⁵⁾. This bias is very important; positive or significant findings are predicted to be eight times more likely to be submitted than negative or non-significant findings ⁽¹⁶⁾. Also, studies which have positive findings are approximately seven times more likely to be published than studies with results supporting the null hypothesis

⁽¹⁷⁾. As long as negative findings or unpublished studies have not included in meta-analytic reviews, the effect of this bias will overestimate population effects. Furthermore, effect sizes will be smaller in unpublished studies compared with published studies ⁽¹⁸⁾. Additionally, if an investigator wants to minimize the publication bias, the search can be extended from published manuscripts to relevant conference abstracts. This search strategy highlights the use of varied resources to ensure all potentially relevant studies are included and to reduce bias due to the file-drawer or publication bias problem. If a meta-analysis includes only positive studies and does not include the negative ones, then conclusion will be over-optimistic estimate regarding the true treatment effect.

4. Collecting data

Data collection should be done as described by study protocol. Data collection can be performed either using a printed paper checklist or electronic spreadsheets. There are different checklists which were published by some academic institutions and private companies. Investigators should choose an eligible one which is suitable for their study design, research question and outcomes. In a flow diagram, include numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage. Relevant information might be sought from eligible studies such as study details, study methodology, details of the participants and outcomes. As an example, study details should include study author(s), year of publication, journal, years of patient enrollment, level of evidence, study design (prospective, retrospective, randomized controlled study etc.) and number of sites (single or multicenter study). Details of the participants should include number of the patients enrolled in the study, demographic data of the patients (such as age, gender, etc.), number and characteristic of intervention etc. Report, should include clear description of all outcomes, number of complications, adverse events encountered and number of repeated interventions ⁽¹⁹⁾.

5. Data analysis-calculating mean correlations, variability, and correcting for artifacts

Heterogeneity is a term that describes variability

among studies. Variation in treatment effect in studies is expected but statistical heterogeneity refers to the amount of variation in treatment effect present beyond chance. Basically studies with methodological flaws and small sampled studies overestimate treatment effect and cause statistical heterogeneity. High heterogeneity may be a reason not to combine studies and perform meta-analysis. There are two statistical methods to analyze statistical heterogeneity; the Cochran Q test (chi-square test for homogeneity) and the I² (Higgins I²).

One of the most important aspects of meta-analysis is to combine data. There are different statistical approaches for combining multiple studies called fixed effects estimates, random effects estimates and mixed model ⁽²⁰⁾. The fixed effects method makes the presumption that there is no relevant heterogeneity. Therefore, it can be concluded that all studies are measuring the same variant. In fact, the fixed effect measure can give you a good summary of the results, if you observe that heterogeneity is low. The random effects method presumes that heterogeneity is present, and the differences among studies are due partly to statistical random variability, but also due to differences in the “true” treatment effect that each study is measuring, as it is not assumed that all studies are measuring the same thing. The main difference between random effects method and the fixed effects method is that random effects estimation gives more weight to small studies which present different results. However, Interpreting the results of random effects meta-analyses is difficult than fixed effects method. Because, random effects method gives an estimate of the average effect. It means that treatment effect might depend on specific characteristics of the retrieved studies ⁽²¹⁾.

A graph known as a Forest Plot is one of the most common way to show the results of meta-analyses (Figure 3a,b). Current figure shows the results of a meta-analysis which was done by Komatsu et al. ⁽²²⁾. This meta-analysis compared remifentanyl to other opioids for general anesthesia. When the forest plot graph is investigated carefully, one can obtain significant information from the graph. The details of each study can be seen, including the number of patients, the name of the authors and the number of events. Also, the results are presented both graphically and in

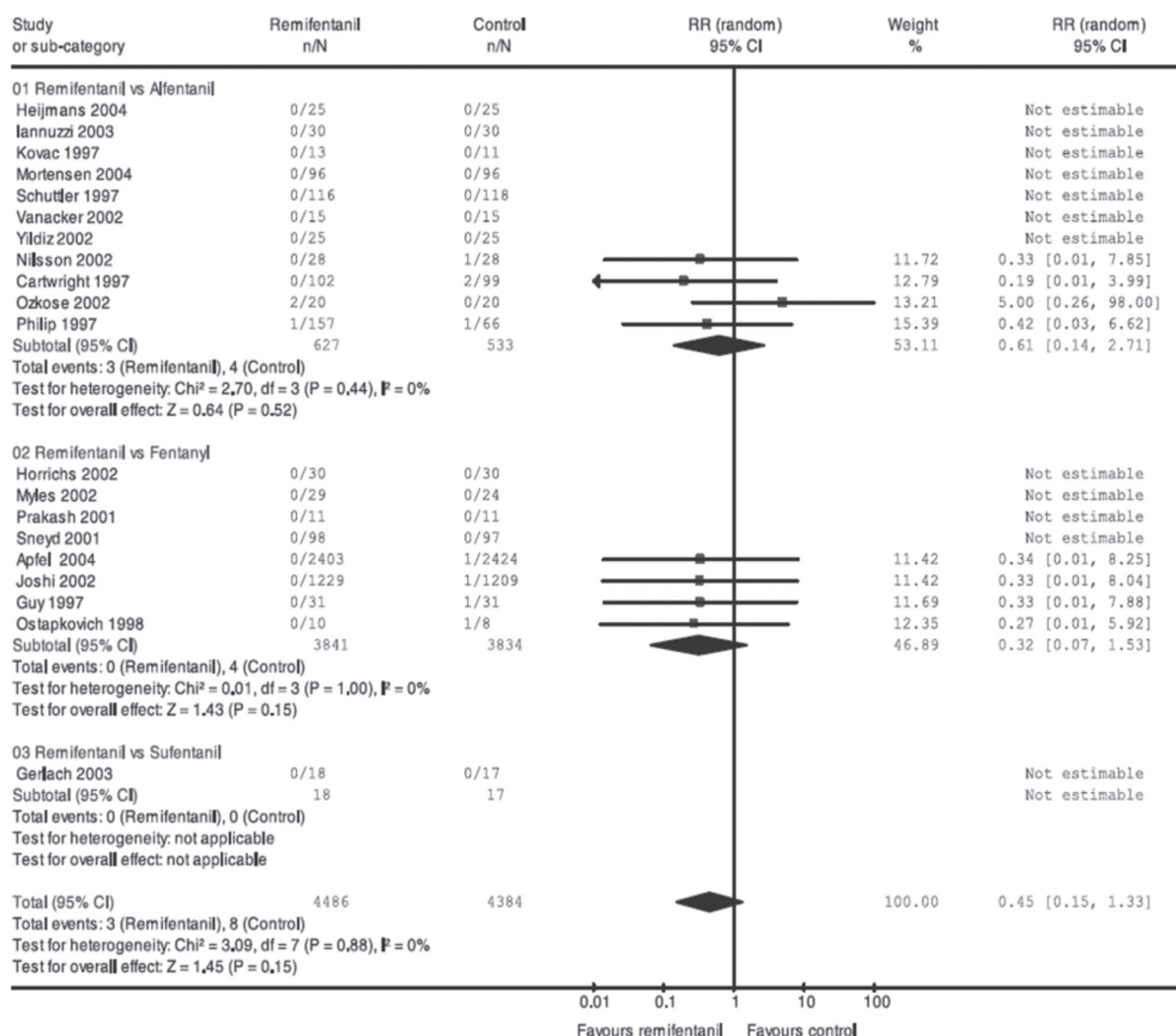


Figure 3a. Forest plot graph

text form. The central blob of each line indicates the estimated relative risk of each study, and the horizontal line indicates the 95% confidence interval. The size of the central blob indicates how much weight the study puts on. The bigger the blob means that this study contributes more to overall analysis. Then, the 95% confidence interval and weight of the study can be seen in a text form on the right part of the graph. The overall estimate can be seen at the bottom which is the most important number to take away from meta-analyses. However, it may be difficult to interpret in the presence of a significant heterogeneity between studies. The forest plot offers another way of evaluating heterogeneity by monitoring the spread of estimates from individual studies ⁽²¹⁾.

Analyzing subgroups of interest is also possible; especially in a particular subgroup of patients effect can also be compared.

6. Interpreting results and making conclusions

When the outcome of interest is rare or small, interpreting the results of meta-analysis becomes difficult and more prone to misinterpretation. The quality of a meta-analysis is as good as the studies which are included and analyzed. Level of evidence within studies included in meta-analysis should be described according to the strength of the evidence. For instance, systematic reviews, meta-analyses, randomized controlled trials are considered as Level I evidence. Two groups, nonrandomized studies such

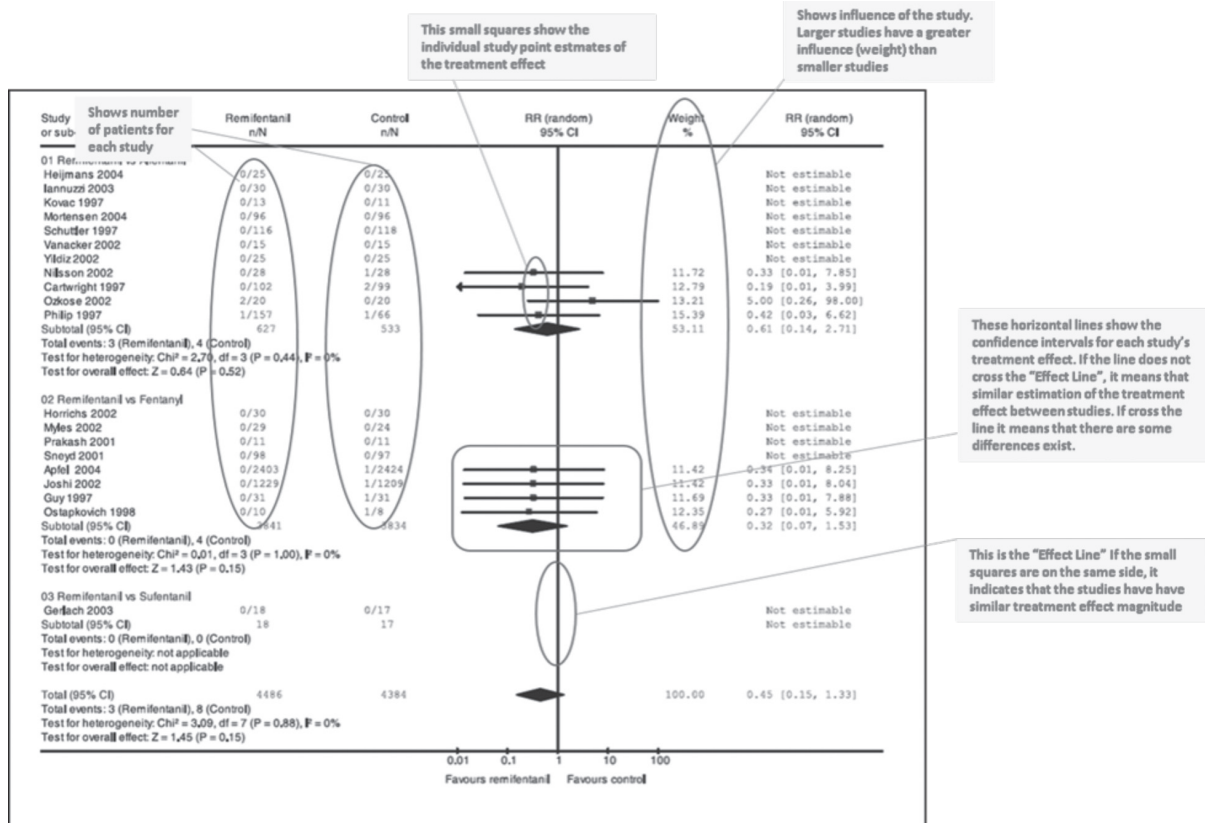


Figure 3b. Interpretation of a forest plot graph

as cohort and case-control studies are considered as Level II evidence. Only one group, and nonrandomized studies are considered as Level III evidence. Descriptive studies such as case series are considered as Level IV evidence. Case reports are considered as Level IV evidence. Therefore, a meta-analysis only with randomized controlled trials with level I evidence is a level I meta-analysis. Additionally, a review of multiple level I randomized controlled trials and multiple level III nonrandomized studies is a level III review. It is important as mentioned above that, searching for eligible studies and study selection should be done by at least 2 reviewers. Also, study quality should be assessed by at least 2 reviewers as well. The importance of the quality evaluation of the studies is that it describes the potential bias within studies such as detection, selection etc. ⁽¹⁹⁾. There are different assessment tools for grading the evidence level and evaluating the quality of the studies such as Strength of Recommendation Taxonomy (SORT) ⁽²³⁾, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) ⁽²⁴⁾,

Assessment of Multiple Systematic Reviews (AMSTAR) ⁽²⁵⁾ and Methodological Expectations of Cochrane Intervention Reviews (MECIR) ⁽²⁶⁾. This kind of tools could be used to grade the studies which are used in meta-analyses instead of the individual study quality assessment.

A meta-analysis has limitations which can make its result unreliable to interpret and coming to conclusion. First, the publication bias is an important limitation for a meta-analysis since it is considered that 25% of meta-analyses in the psychological sciences may have publication bias problem ⁽²⁷⁾. Second, the search strategy used by the authors and the resources they searched might not be enough comprehensive to provide that they did not miss the appropriate studies. Third, the data collection and interpretation might have some difficulties. In this case, investigator may need the whole raw data to interpret them accurately ⁽²⁸⁾.

CONCLUSION

It is obvious that meta-analysis is precisely a useful scientific method that can provide important information when summarizing medical literature. But one has to be cautious; if a meta-analysis includes poor and inadequate quality studies, the result can misleading and questionable.

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