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ABSTRACT

Meta-analysis is a subset of systematic review; a technique for systematically combining pertinent qualitative and quantitative study data from numerous selected studies to broaden a single conclusion that has more statistical power. This inference is statistically stronger than the analysis of any single study, due to increase numbers of topics, greater variety amongst subjects, or collected effects and outcomes. The aim of this review article is to highlight the definition, history, purpose, characteristics, use, advantage, disadvantage, validity, and steps in conducting meta-analysis.

Keywords: *Meta-analysis, checklist for meta-analysis, steps in conducting meta-analysis*

DEFINITION OF META-ANALYSIS

Meta-analysis is a statistical technique for combining the findings from independent studies. It is most usually used to evaluate the medical effectiveness of healthcare interventions; by the way of combining data from two or more randomized control trials which provide a unique estimate of treatment impact, giving due weight to the size of the different research studies. A perfect Meta analyses aim for complete coverage of all relevant studies, look for the presence of heterogeneity, and explore the robustness of the main findings by using sensitivity analysis (Glass, Barry & Smith, 1981).

A meta-analysis is a two-stage method. The first stage is the extraction of data from each study and the calculation of a result for that study (the 'point estimate' or 'summary statistic'), with an estimate of the chance variation. The second levels figure out whether or not it's far suitable to calculate a pooled average end result across studies and, if so, calculating and presenting such result. The type of data to be extracted from each study need to be determined in design phase and a standardized form is constructed to record the data (Egger, Smith & Sterne, 2001).

HISTORY OF META-ANALYSIS

The first meta-analysis was conducted in 1904 by Karl Pearson (Shannon, 2008). He was requested by the British government to review the evidence on the consequences of a vaccine against typhoid. The term "meta-analysis" was created by Gene V. Glass (1976), who was the first modern statistician to formalize that meta-analysis is the statistical analysis of a massive collection of analysis results for integrating the findings (Glass, 1976).

PURPOSE OF META-ANALYSIS

1. When more than one study has anticipated an effect.
2. Whilst there aren't any differences in the study characteristics that are in likelihood to drastically affect outcome.
3. When the final results has been measured in similar methods.
4. When the information are available with interpretation.
5. When poor quality of research are covered or while quality issues are overlooked.
6. When inadequate attention is given to heterogeneity.
7. When reporting biases are a problem: publication bias, time lag bias, duplicate publication bias, language bias, outcome reporting bias.

AIM OF META-ANALYSIS

1. To obtain a single estimate of effect of interest (effect size) from a few statistics observed in each of the several comparable studies.
2. All strategies estimated standard effect with the aid of computing weighted average of studies individual estimates of impact.

CHARACTERISTICS OF META-ANALYSIS

1. Numerical or statistical pooling of the study consequences: In meta-analysis, data from the studies are weighted and the effects are pooled to form a series of summary estimates to estimate an overall effect size.
2. Two Best Comparisons: At any time, only two interventions or alternative treatments are compared.

Those treatment/interventions can be a unique intervention versus a placebo, or a novel intervention versus any other intervention (treatment as standard), or two alternative interventions or two alternative conditions.

3. Included studies should be comparable: This is a crucial consideration in meta-analysis and a formal tactics exist to indicate the quantity to which studies are homogeneous or heterogeneous.

USE OF META-ANALYSIS

1. To set up statistical significance with studies that has conflicting effect
2. To develop an extra accurate estimate of effect magnitude
3. To deliver a more complicated analysis of harms, safety data, and advantages
4. To scrutinize subgroups individual numbers that is not statistically considerable
5. To reduce the subjectivity of the study comparisons by means of the using systematic and explicit evaluation technique
6. To discover statistical data gap in the knowledge base and endorse direction of future research

ADVANTAGES OF META-ANALYSIS

1. A clearer interpretation: allows integration of multiple studies, inclusive of smaller research that can have been inconclusive.
2. Bias: Less bias than an unsystematic review and present an unbiased synthesis of the empirical data.
3. Precision: Effect size can be more unique when trials are integrated; a larger sample size mean statistical power improved.
4. Transparency: It could be tough to absolutely get rid of bias, but a good meta-analysis will have a defined written protocol.
5. Quicker and much less expensive than undertaking a large randomized control trial
6. Consider as an Evidence-based resource.
7. Greater potential to extrapolate to general population affected
8. Confirmatory data analysis.

DISADVANTAGES OF META-ANALYSIS

1. Tough and time consuming to identify appropriate studies.
2. Not all studies offer adequate information for inclusion and analysis.
3. Requires advanced statistical strategies.
4. Heterogeneity of study populations.
5. Need to calculate combine effect size by appropriate statistical technique.

THE VALIDITY OF A META-ANALYSIS

The validity of a meta-analysis relies upon on the satisfactory of the studies included, and an evaluation of quality is a necessary a part of the process:

i) Internal validity

1. Meta-evaluation should include sufficient studies to provide strength for its test. The exact variety will rely on the purpose of analyses being performed.
2. For doing a meta-analysis, it should have at the least 30 studies.
3. The reliability should be published and must be reasonably high, preferably over 0.8.
4. Minimize selection bias, information bias and confounding.

ii) External Validity

1. The theoretical boundaries proposed by the authors: sometimes it can be too broad, such that the researcher combines numerous dissimilar studies. In other case it may be too narrow, such that the scope of the meta-analysis is smaller than the scope of the theories evolved within the research area.
2. Did the authors conduct truly exhaustive literature search?
3. Did the authors look in secondary literatures?
4. Did the authors include unpublished articles? In that case, how rigorous changed into the search? Or if they did not, then do they provide a justification for this decision?

LIMITATIONS OF META-ANALYSIS

1. Quality of a meta-analysis is only as good as the individual studies.

2. Bias (such as publication bias) can be carried in the process of locating and selecting studies for inclusion.
3. Criteria for including studies are important to comprehend the meta-evaluation
4. It may not be appropriate to combine studies.
5. Need to consider each clinical and statistical importance.

CRITICISMS OF META-ANALYSES

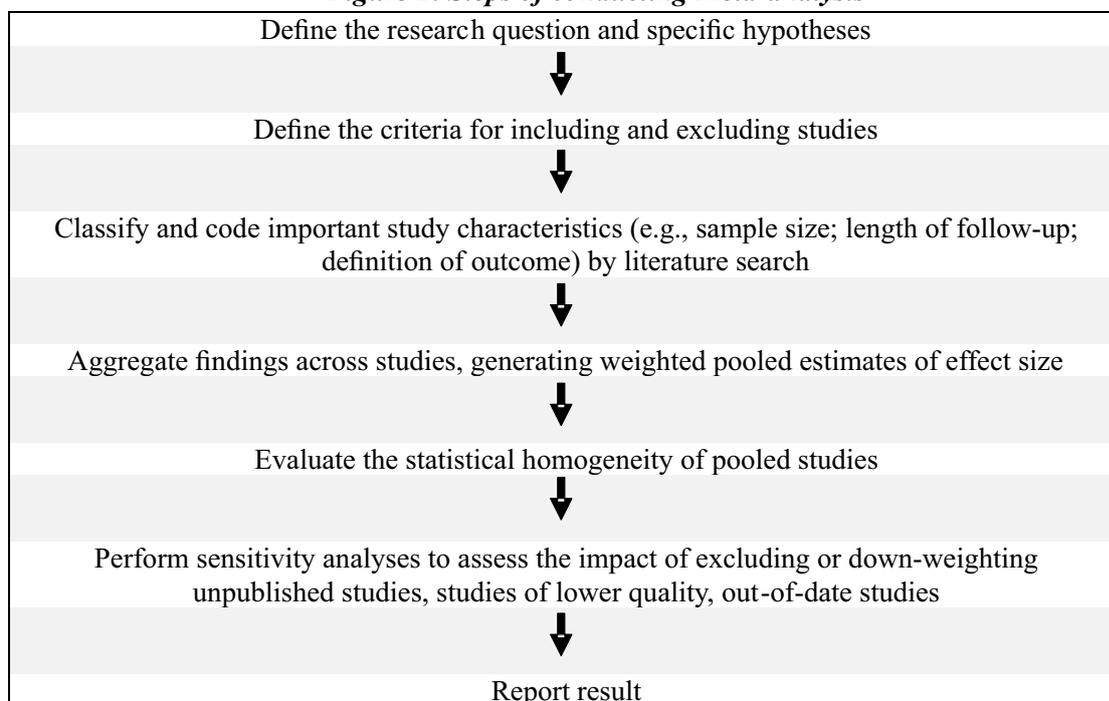
1. Meta-analysis provides collectively apples and oranges; over generalization does happen.
2. Meta-analysis ignores qualitative differences among studies; codes them as moderating variables.
3. Meta-evaluation is a garbage-in, garbage-out system.
4. Results from meta-analysis are interruptible due to the consequences from "poorly" designed studies are included with "true" studies.
5. Logical conclusions can't be drawn by way of

comparing and aggregating studies that include different measuring techniques, definitions of variables (eg. treatments, effects and outcome) and subjects because they are too dissimilar.

STEPS IN CONDUCTING META-ANALYSIS

As illustrated in Figure 1, meta-analysis can be conceptualized as a greater or less linear process inclusive of above sequential steps. These steps of meta-analysis indicate that a number of skills are needed and meta-analysis consequently is a multi-disciplinary team based activity (Russo, 2007). It presents a standardized approach for examining the present literature on a specific, possibly debatable, issue to determine whether or not a conclusion may be reached concerning the effect of a treatment or exposure. Consequences from a meta-analysis can contradict expert opinion or popular belief. If it is properly conducted, the strength of a meta-analysis lies in its ability to combine the effects from various small studies that may have been underpowered to distinguish a statistically significant difference in effect of an intervention.

Figure 1: Steps of conducting Meta-analysis



Source: Russo, M. W. (2007). *How to Review a Meta-analysis*. *Gastroenterology & Hepatology*, 3(8), pp 637–642.

The Quality of Reporting of Meta-analyses (QUOROM) statement was published to provide guidelines for conducting meta-analyses, with the purpose of improving the quality of published meta-analyses of randomized trials (Russo, 2007). A check list (Table 1) assessing the quality of a meta-analysis has been established by the QUOROM group and is available online (<http://www.consort-statement.org/>

QUOROM.pdf). The purpose of Observational studies in Epidemiology (MOOSE) which is also other protocols for the reporting of meta-analysis suggestions is to provide proper techniques for conducting a meta-analysis and to standardize the methods of reporting a meta-analysis. By using a standardized technique for critiquing a meta-analysis, the internal validity of the analysis can be determined.

Table 1: Check list for Meta-analysis

Study question	<ul style="list-style-type: none"> • Objectives clearly stated • Clinically relevant and focused study question included • Effectiveness of intervention not convincingly demonstrated in clinical trials
Literature search	<ul style="list-style-type: none"> • Comprehensive literature search conducted • Searched information sources listed (PubMed, Cochrane database) • Terms used for electronic literature search provided • Reasonable limitations placed on search (English language) • Manual search conducted through references of articles, abstracts • Attempts made at collecting unpublished data
Data abstraction	<ul style="list-style-type: none"> • Structured data abstraction form used • Number of authors (>2) who abstracted data given • Disagreements listed between authors and how they were resolved • Characteristics of studies listed (ie, sample size, patient demographics) • Inclusion and exclusion criteria provided for studies • Number of excluded studies and reasons for exclusion included
Evaluation of results	<ul style="list-style-type: none"> • Studies were combinable • Appropriate statistical methods used to combine results • Results displayed • Sensitivity analysis conducted
Evaluation of publication bias	<ul style="list-style-type: none"> • Publication bias addressed through evaluation methods such as funnel plot or sensitivity analysis
Applicability of results	<ul style="list-style-type: none"> • Results were generalizable
Funding source	<ul style="list-style-type: none"> • Funding source(s) stated • No conflict of interest seen

Source: Russo, M. W. (2007) (*How to Review a Meta-analysis. Gastroenterology & Hepatology*, 3(8): 637–642.

THE INDIVIDUAL STEPS ARE EXPLAINED AS FOLLOWS:

1. Step One: Frame a Study Question

Framing a research question is the first step in meta-analysis and the questions can be constructed by using Participants Intervention Comparator Outcome (PICO) format. The research question is formatted using participants [P], intervention [I] or exposure [E] relying on whether the meta analysis is about interventions to be tested against each other or whether the meta analysis being conducted is about association of a particular exposure for a particular outcome;

comparator [C] who or what is being under comparison with the intervention or the exposure underneath study, and the final specific health outcome [O] of interest, in that order (Khan *et al.*, 2003).

The objective of a meta-analysis and the research question being addressed must be clearly mentioned which may consists of primary and secondary objectives. The question at the point of interest of a meta-analysis should not have already been answered satisfactorily via the outcomes of multiple well conducted randomized trials (Khan, *et al.*, 2003). To make the study groups more homogenous, the research

question should be more focused. If the subjects throughout the studies are different, combining statistics from these studies isn't appropriate.

For example, a hypothetical meta-analysis on the effect of Helicobacter pylori eradication for reducing the chance of ulcer won't be beneficial or interesting due to the fact because several studies have already confirmed a benefit within the eradication of H. pylori while ulcer is present. Moreover, the study population might possibly consist of patient with both gastric and duodenal ulcers, making the population heterogeneous. On the other hand, a meta-analysis evaluating the efficacy of different antibiotic remedy regimens to eradicate H. pylori in patient with duodenal ulcers can be more appropriate and might constitute a greater homogenous study population.

The primary objective of a meta-analysis may not be entirely determining the effectiveness of an intervention. Consequences from a meta-analysis can be used to determine the appropriate sample size of a future trial, develop records for economic studies along with cost-effectiveness analyses, or exhibit the association between an exposure and disease. Frequently, the outcomes of a meta-analysis are used to highlight the weaknesses of previous research and to advise how to enhance the design of future trials.

2. Step Two: Searching Literature

After a research question is framed, the Meta analyst then proceeds to conduct a search of the literature databases. The specific terms and combinations of words used to search the databases rely upon the criteria already set up inside the scoping of the Meta analysis. Literature searches can encompass

computerized and manual searches, which involve reviewing the references of an article “ancestor search,” in addition searching through abstracts, normally over the previous 5 years.

The frequently used on line resources for literature searches include PubMed, Cochrane Database and Cancerlit. The Cochrane Collaboration was based in 1993 and produces the Cochrane database of systematic review, which has generated more than 2,500 systematic review and meta-analyses (<http://www.cochrane.org/opinions/index.htm>). Reviews from the Cochrane database are generally high quality and offer a beneficial resource for those who are interested to pursue systematic reviews and meta-analyses. PubMed became developed through United State National Library of Medicine and consists of over 17 million citations courting back to the 1950s. Cancerlit is formed through United State National Cancers Institute and is a database consisting of more than 1 million citations from over 4,000 resources dating back to 1963.

At least two reviewers should search resources for articles pertinent to the meta-analysis, and the keywords used in the on-line searches need to be provided within the article (Petticrew & Roberts, 2006). Common words, phrases and terms inside the text, name, abstract, and words/expressions in the managed vocabulary are used to effectively search these databases. Use of Boolean expressions of AND (narrows down the searches to simplest precise terms), OR (expands the searches to include all of the terms or phrases used), NOT (excludes the searches and narrow down to precise phrases) are used at the side of wildcard entries that's shown in Table 2.

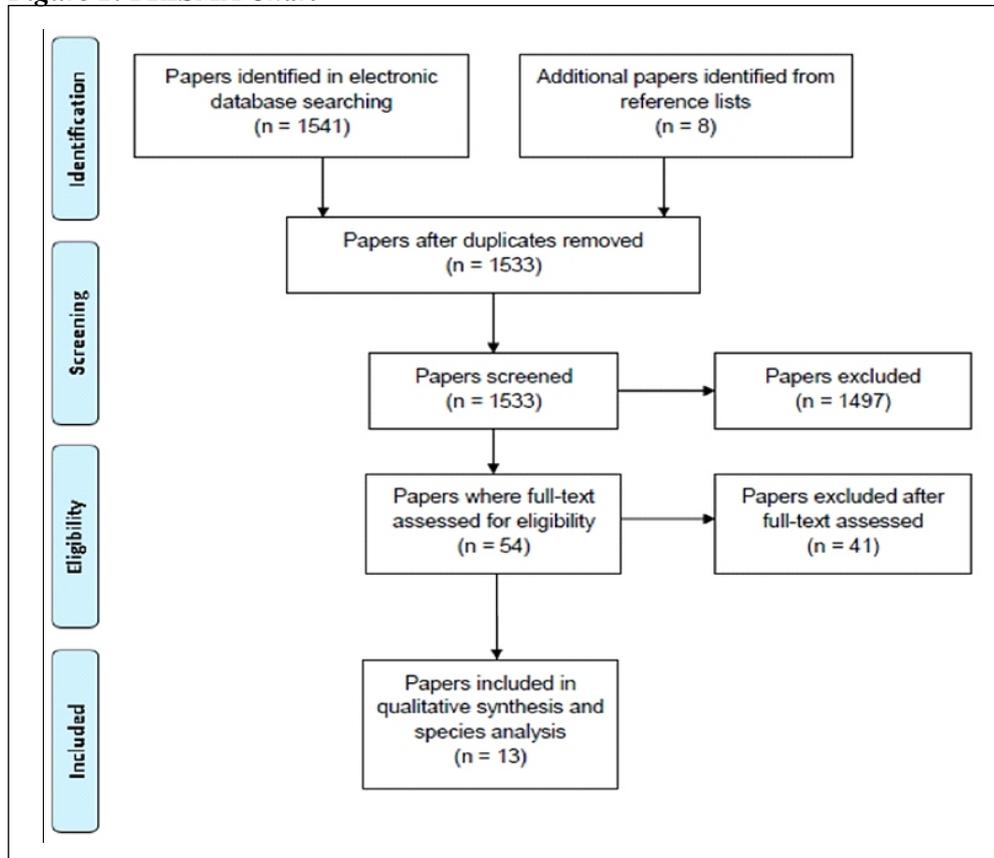
Table 2: Use of Boolean Operators for Searching Mindfulness Meditation related Studies

Boolean Operator	Example
AND	Mindfulness and Meditation will retrieve all citations that only have both “mindfulness” and “meditation” in it
OR	Mindfulness OR Meditation will retrieve all citations that have either Mindful OR Meditation or both mindfulness and meditation in it
NOT	Mindfulness NOT Meditation will retrieve all citations that have Mindfulness in it but not meditation

Many authors encompass only full-length article papers because abstracts do not always provide sufficient information to score the paper. The number of the studies that included and excluded must also be provided, as well as the reasons for exclusion. We use PRISMA chart for inclusion and exclusion criteria (Figure 2). A review of the titles and abstracts of the articles or publication retrieved and collected within

the first search are then reviewed based totally on their titles and abstracts. The flow chart starts with all of the retrieved publications in initial step, and then proceeds downwards slowly to expose the cause for exclusion of the publications, both at the level of most effective reviewing the titles and abstracts but additionally on evaluation of the overall text content of the articles (Basu, 2014).

Figure 2: PRISMA Chart



Source: Basu A. Introduction to Meta-Analysis. PeerJ PrePrints, 2014.

3. Step Three: Risk of Bias Appraisal of Full Texts

In meta-analysis, data from primary research studies are combined to create an instantaneous estimation of the association among variables, where the objectives are to estimate the general effectiveness of a particular treatment/intervention. This method involves pooling result from primary studies to arrive at a precise estimation to evaluate whether or not compared with alternative treatment or placebos or in comparison with no treatment at all, the treatment under review was effective in achieving the outcomes set out in the studies.

For observational studies, the purpose is to evaluate whether the pooled estimates of the odds ratios or relative risk estimates imply a valid association among the two entities. It follows that during meta-analysis, the analyst isn't only interested in the presence of the evidence however also whether the evidence is comparable across the studies included in the Meta analysis. As a result, if the studies themselves are of poor quality, then the overall quality of the Meta

analysis will not only be poor, it may also end up propagating the error that compromise internal validity in primary studies (Robert & Yeager, 2004). In assessment of randomized controlled trials, it is vital to significantly observe how participants had been allocated the treatment procedure and alternative conditions and how such allocations had been concealed from not only the participants within the study but also for investigator. Such concealment is regarded as “blinding” or “allocation concealment”. Studies that fail to demonstrate robust processes of allocation concealment are likely to report significant selection for biases or reporting biases and consequently these researches are at significant risk of studies with inaccurate estimations of the extent of associate between the treatment and consequences.

4. Step Four: Abstract Data from Individual Studies

Data abstraction is one of the essential steps in conducting a meta-analysis, and the methods of data abstraction that have been utilized by the authors should be defined in detail. In high quality meta-

analyses, a standardized data abstraction form is developed and utilized by the authors and can be shown in the paper as a figure (Corcoran, 2003). The reader of a meta-analysis should be provided with enough information to determine whether the studies that were included were appropriate for combined evaluation. However, the Cochrane handbook recommends the subsequent elements of data to be abstracted:

- Title of the review and name of the coder
- A key or identifier for every primary study included in the review
- The study is eligible or not at the point of interest of the author.
- Type of study design (RCT, others, before-after study, cross over)
- Allocation Concealment was done (adequate, uncertain, inadequate, not completed, not relevant)

5. Step Five: Assess Whether the Studies are Homogeneous

The differences in participant profiles are referred as “clinical heterogeneity” and differences in the technique of execution of the studies themselves are called “methodological heterogeneity”. Beyond those two sources of heterogeneity, variability is also determined within the magnitude and direction of the effect of size between the intervention or exposure group with respect to health outcomes (Gray, 2001). This diversity is known as statistical heterogeneity and refers to the extent at which the outcomes vary from each across the distinctive studies included in the meta-analysis. As long as these variations are so small that they do not significantly differ statistically from a centrally pooled estimate, these studies are referred to as “statistically homogenous”. Such homogeneity can be tested typically in two ways:

- a) Simple chi-square test of homogeneity
- b) I-square test of homogeneity.

So the statistical test for homogeneity, that is referred to as the test for heterogeneity, is frequently misused and misinterpreted as a test to validate whether the studies were similar, comparable and accurate (i.e., homogenous) to combine. The test can also complement the outcomes from statistics abstraction, helping the interpretation that the studies had been homogeneous and appropriate to combine. The test of homogeneity investigates the hypothesis that the size

of the effect is identical in all included study. $P < 1$ is taken into consideration to be a conservative estimate. If the test for homogeneity is significant, calculating a combine estimate might not be appropriate. If this is the case, the reviewer should re-look at the studies included in the analysis for considerable differences among study designs or characteristics of subjects.

6. Step Six: Conduct Fixed Effects or Random Effects Meta-Analysis

The purpose of meta-analysis is to reach at a precise measure of the overall effect estimate primarily based on individual study effect sizes. These individual studies are developed based totally on specified studies questions and intensive search of the literature databases and certainly different resources of records, as trial registries and often studies are obtained in consultation with individual authors and investigators.

The typically used statistical techniques for combining statistics consist of the Mantel-Haenszel method that is primarily based at the fixed effects theory and the Der Simonian Laird method that is primarily based at the random effects principle (Wallace *et al.*, 2004). One of the goals of these methods is to provide a summarised statistic of an intervention's effect or exposure, as well as a confidence interval. The fixed effects model examines whether or not the treatment/intervention produced a benefit in the study that have been carried out. In contrast, the random effects model assumes that the studies covered within the meta-analysis are a random sample of a hypothetical population of studies. The precise statistic is commonly reported as a risk ratio, but it can also be reported as a rate of difference, person-time data, or percentage.

Arguments can be made for the use of both the fixed effects and random effects models, and sometimes results from both models are protected. The random effects model affords greater conservative estimate of the combined statistics, with a much wider confidence interval, and the summary statistic is less likely to be significant. The Mantel-Haenszel model can be applied to odds ratios, rate ratios, and risk ratios, whereas the Der Simonian Laird method can be applied to ratios, as well as rate differences and incidence density (ie, person-time-data).

7. Step Seven: Evaluating the result

Data abstraction results should be clearly presented in order for the reader to determine whether or not the included studies must have been mixed in the first

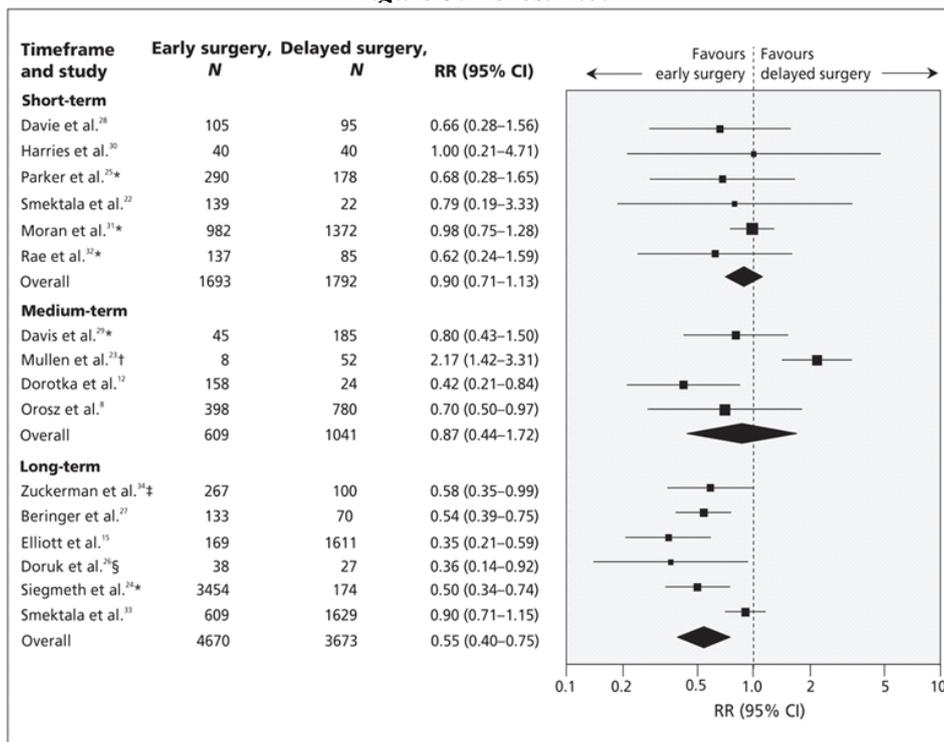
place. The meta-analysis should provide a table outlining the feature of the studies, as characteristics of subjects, study design, sample size, and intervention, which include the dose and duration of any drugs. Significant differences within the study design or affected patient populations signify heterogeneity and recommend that the data from the studies should not have been combined.

For example, a meta-analysis was conducted on the risk of malignancy in patient with inflammatory bowel disease who were taking immunosuppressant. The patients had either ulcerative colitis or Crohn's disease and were taking Azathioprine, 6-Mercaptopurine, Methotrexate, Tacrolimus, or Cyclosporine. Due to the differences in patient populations and kinds of

treatment among the studies, the outcomes from these studies should not have been combined (Evans, 2003).

Forest plot is a graphical presentation of meta-analysis data, in which the point estimate for the risk ratio is represented by a square or circle and the condense interval for each study is represented through a horizontal line. The size of the circle or square corresponds to the weight of the study in the meta-analysis, with larger shapes given to studies with large sample sizes or data of better quality or both. The 95% condense interval is represented by using a horizontal line except for the summary statistic, which can be shown via a diamond, the length of which represents the condense interval (Figure 3).

Figure 3: Forest Plot



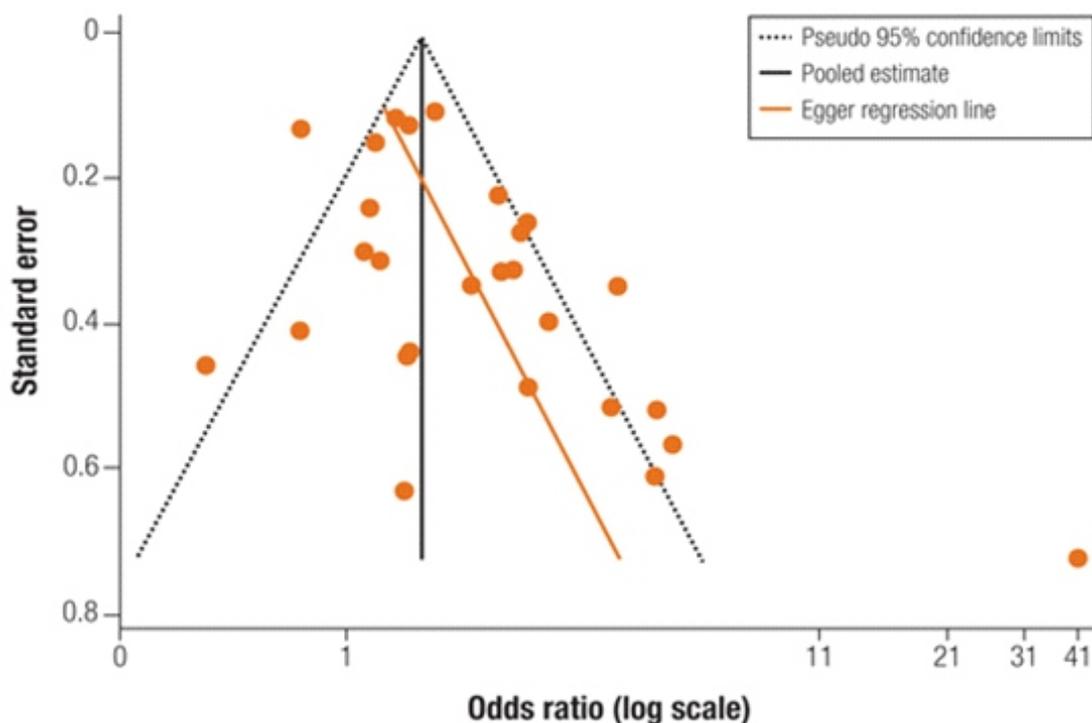
Source: Basu A. Introduction to Meta-Analysis. PeerJ PrePrints, 2014.

Funnel plots (Figure 4) showed that the studies included in the meta-analysis in a plot of effected size against sample size (or some other degree of the extent to which the findings might be affected by the play of chance) (Basu, 2014). As smaller studies have more chance variability than larger studies, the expected image is one of a symmetrical inverted funnel. If the plot is asymmetric, this indicates that the meta-analysis may have missed few trials, usually smaller studies

showing no effect.

The funnel plot has a few barriers; as an example, sometimes it can be difficult to find the asymmetry by eye. As a result formal statistical method has been evolved to test for heterogeneity. Egger's regression check has been broadly used to check for publication bias. It assesses whether small studies generally tend to have larger effect sizes than would be anticipated.

Figure 4: Funnel Plot

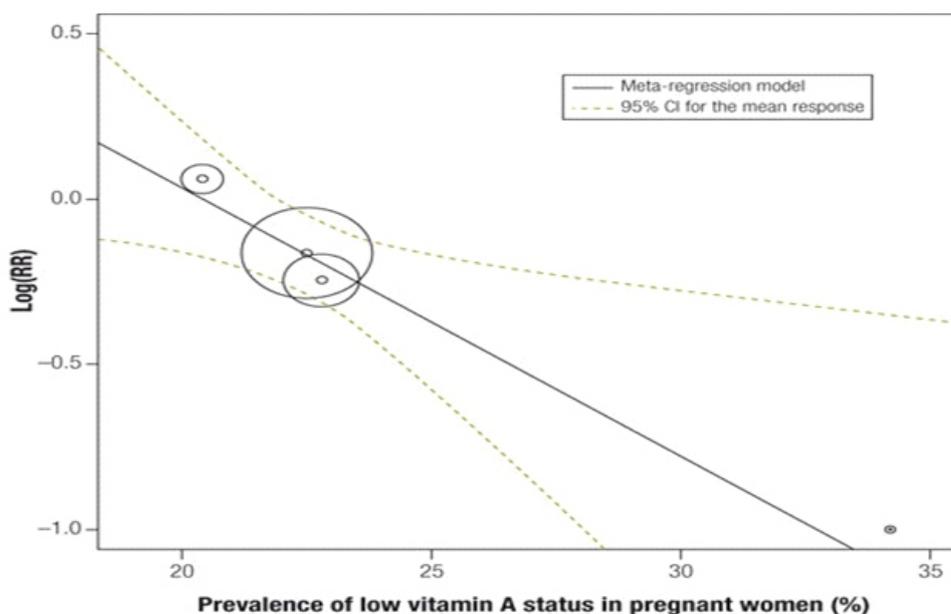


Source: Basu A. Introduction to Meta-Analysis. PeerJ PrePrints, 2014.

Meta-regression is a method which allows researchers to discover which kinds of patient-specific elements or study design factor contribute to the heterogeneity (Basu, 2014). The Meta regression uses summary data

from each trial, such as average effect size, average disease severity at baseline, and average length of follow-up. This approach is precious, however it has only limited ability to identify important factor.

Figure 5: Meta Regression



Source: Basu A. Introduction to Meta-Analysis. PeerJ PrePrints, 2014.

Sensitivity analysis is an evaluation method employed while there is uncertainty in one or more variables included in the model or while determining whether or not the conclusions of the evaluation are robust when a variety of estimates is used. A sensitivity analysis is usually included in a meta-analysis due to uncertainty regarding the effectiveness or safety of an intervention. The values at the extremes of the 95% confidence interval for risk estimates of key variables or areas with the maximum uncertainty may be included in additional modeling to determine the stability of the conclusions. For example, in a meta-analysis that author carried out together with his colleagues at the efficacy and safety of transjugular intrahepatic portosystemic shunt (TIPS), the rate of new or worsening encephalopathy ranged from 17% to 60%. This range was integrated into a sensitivity analysis to report the best and worst case situations for encephalopathy Post-TIPS (Loffroy *et al.*, 2013).

APPLICABILITY OF RESULT

The results of a meta-analysis, even though they are statistically significant, must have significant application in clinical practice or constitute a message for researchers for further studies. The outcomes should have external validity or generalizability and must impact the care of an individual patient. In addition, the studies included in the meta-analysis should encompass patient populations which might be typically seen in clinical practice. There have to be a balance between studies which are comparable and suitable to combine without becoming too focused, which will avoid study population that is too narrow.

CONCLUSION

Meta-analysis can be an effective tool to combine outcomes from studies with similar design and patient populations that are too small or under powered individually to illustrate a statistically significant association. As with clinical trials, having an appropriate study question and design are essential while performing a meta-analysis to ensure that there is internal validity and that the results are clinically meaningful. Heterogeneity among research in study designs or patient populations is one of the maximum common flaws in meta-analyses. Heterogeneity can be averted by thoughtful data abstraction accomplished by two or more authors who use a standardized data abstraction form. By means of applying a systematic method to meta-analysis, most of the pitfalls can be averted.

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