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Meta-Analysis: A Higher Quality of Evidence in Clinical Research Pyramid

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Abstract: ***Meta-analysis is a statistical tool used to systematically and quantitatively estimate the pooled effect of earlierindividual research studies to obtain conclusions about that research subject. The outcomes from a meta-analysis are more precise estimate of the effect of treatment or risk factor for disease, than any individual study. One of the potential advantages of conducting meta-analysis is to obtain an accurate and quantitative review of a large, complex and generally controversial topic in literature. Meticulously conducted meta-analyses are potential tools in evidence-based medicine. The small clinical trials (small sample size) might have inconclusive results on individual basis however, while combining these trials met-analysis increases the statistical power and thus more precise estimate of effect size. Moreover, meta-analysis is also useful for exploring sources of publication bias and quantifying between-study heterogeneity.***

Keywords: meta-analysis, systematic review, evidence-based medicine, effect size, forest plot, publication bias, heterogeneity

1. Introduction

1.1 Definition

Meta-analysis is defined as a systematic review which provides quantitative estimate for the treatment effect of an intervention or exposure on a specific topic of interest in the literature.[1]Meta-analysis use statistical methods to calculate an overall or 'absolute' effect by pooling the findings of single, independent studies.[2] The main criteria to design a high quality meta-analysis is to recognize a medical area with ambiguity in the effect of the treatment or exposure but a moderately homogenous availability of literature exists. Meta-analysis aims at standardized research based process for investigating the existing literature on a particular and controversial clinical issue to achieve a conclusion vis-à-vis the effect of a treatment or exposure.[1]

1.2 Importance of Meta-analysis in Medical Research

In medical research, evidence-based medicine (EBM) is the best form of evidence and the excellent evidence in EBM is from meta-analyses. Meta-analyses are advantageous as they are less biased with more precision in calculating an "absolute" effect of different studies on a clinical issue, increase the statistical strength by merging the results of previous studies thereby solving the problem of small sample sizes and insufficient statistical strength. [3, 4]Researchersutilize a recognised and systematic methodology to identify for differences in sample size, heterogeneity in the selected studies and treatment effects and determines the sensitivity of the results with regards to systematic review protocol (study selection and statistical analysis). [2]Aproperly conducted meta-analysis of clinical studies is ranked at topmost level in the hierarchy of evidence and is considered as decisive evidence in medical research.[3,4]

1.3 Systematic Reviews and Meta-analysis

A systematic review process comprises of collecting all potential studies related to a given clinical topic and design, and analyzes their results. The quality of studies is evaluated and a statistical meta-analysis of the study results is performed on the basis of their quality. Generally, systematic reviews include a meta-analysis constituent to synthesize the data from several studies into pooled summary of effect size (Figure 1). Often, a meta-analysis is conducted on randomized controlled trials (RCTs) which have a high level of evidence to attain high accuracy and reliability of the results.[5]

1.4 Hierarchy of Quality of Evidence of Meta-analysis in Evidence-based Medicine

The hierarchy ranking of studies by evidence-based practice (EBP) is based on the rigour (strength and precision) of their research methods. [6]According to quality of evidence pyramid, the animal research and laboratory studies constitutes the base of the pyramid (where ideas are first developed). On progressing up the pyramid, the volume of information available decreases but relevance to the clinical setting increases. There is less bias on progressing up the pyramid with each level of evidence compared to the level below it. Therefore, meta-analyses can be seen as the apex of evidence-based medicine with least possible bias.[7]

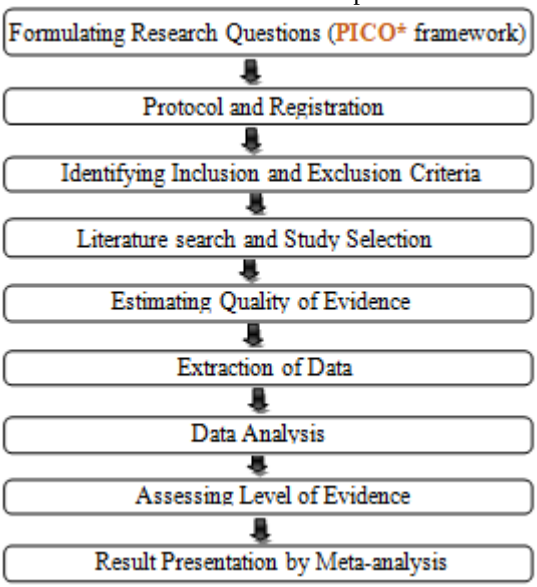

Figure 1: Schematic flow of steps involved for conducting a systematic review[5]

***PICO: Participants Interventions Comparisons Outcomes**

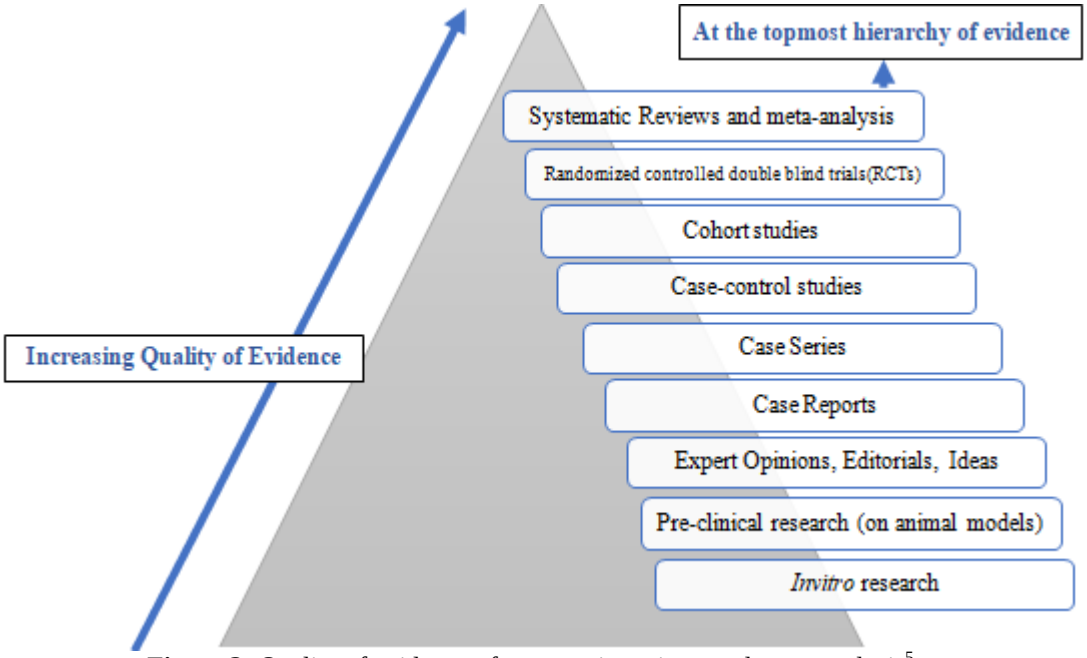

Figure 2: Quality of evidence of systematic reviews and meta-analysis[5]

The process flow for conducting a Meta-analysis

There are mainly eight steps to conduct a systematic review and meta-analysis (Table 1).

Table 1: Essential steps for conducting a high-quality meta-analysis

Steps for meta-analysis	*Procedure*
1. Formulate the review question[1,8,9]	• Define objectives clearly[1] • Include only clinically relevant and focused study questions [1] • Focus on effectiveness of treatment not credibly demonstrated in clinical trials[1]
2. Identify inclusion and exclusion criteria[10]	Done by Cochrane acronym: ***PICO(S)*** question format[3]
3. Create a search strategy and identify studies[1, 8, 9]	• **From search engines:** PubMed, EMBASE, The Cochrane Central Register of Controlled Trials (Cochrane CENTRAL)[3] • Ideally, identify and select randomized, controlled clinical trials(RCTs)[4]
4. Determine quality of evidence of studies	• Criteria used is ***Grading of Recommendations, Assessment, Development and Evaluations*** (GRADE) system(http://www.gradeworkinggroup.org/) [9]
5. Data Extraction	• Create a simple data extraction form/table to assimilate the information extracted from each study • The information should include: authors, publication year, number of participants, age range, study design, outcomes. • Data extraction by at least two reviewers is advised for more inter-rater reliability and avoiding data entry errors.[2, 9]
6. Analyzing and interpreting data (Statistical analysis)	Create forest plots[3] Utilize fixed and random effects model[3] **Assess between study- heterogeneity :** Cochrane Q test, I^2[3]
7. Determining publication bias	By methods such as funnel plot or sensitivity analysis [1]
8. Disseminating results	Based on preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[3]

2. Study Planning

a) Formulating a research question utilizing PICO(S) structure

The global format for formulating the question for reviews on interventions is the PICO(S) question (European Food Safety Authority (EFSA), 2010). PICO(S) stands for ***P***opulation(the patient or problem),***I***ntervention or exposure, ***C***omparison, clinical ***O***utcome of interest and possibly ***S***tudy design(S). The PIT (population, index test and target population) format is considered useful for formulating research question for diagnostic test accuracy and the PO format (population, outcome) for research questions for descriptive parameters (such as incidence or prevalence), respectively (EFSA, 2010).[10]

Even though other models exist such as SPIDER (sample, phenomenon of interest, design, evaluation, research type) and SPICE (setting, perspective, intervention, comparison, evaluation), the PICO model is most reliable and widely used for creating clinical questions. There are three advantages of using PICO model: 1) It makes the questioner to emphasize on what the patient/client believes to be the one most important outcome 2) Iteases the next step in the process, the computer based search by allowing to select language or key terms for their search 3) It aids in clear identification of the problem, intervention, and outcomes related to specific care provided to a patient.[11]

b) Identify inclusion and exclusion criteria

An established and predefined inclusion and exclusion criteria is a mandate for the studies included in the meta-analysis.[1]One objective of defining inclusion and exclusion criteria is to identify a homogenous set of study population

for the meta-analysis. The rationale for choosing the criteria should be clearly stated, as it may not be perceptible to the reader. [1]It is a difficult exercise to choose a selection criteria meeting all the requirements for a quality meta-analysis.[1]A wide inclusion criteria is required to demonstrate safety and effectiveness in a large group of patients and a number of ethical and scientific reasons should be stated to define exclusion criteria. However, if the inclusion criteria are too wide, there is a risk of selection of poor quality studies which can hamper the confidence in the final result. But if the criteria are too stringent, risk of availability of only few studies thus making results nongeneralizable.[12]The optimization and finding a balance between these two conditions result in subjective selection of inclusion and exclusion criteria.[12]The main factors for creating an inclusion criteria are study design, sample size, and subject characteristics. Exclusion criteria include studies not published in English or as full-length manuscripts. Generally, a large percentage of studies (90% or more) are excluded by the systematic reviewers. The main reasons for exclusion are: (1) clearly meet one or more of the exclusion criteria, (2) incomplete or unclear methods, (3)failure to meet a pre-established threshold for quality, or (4)not providing sufficient statistics or data for estimating effect sizes.[12]

c) Create a literature search strategy and identify studies

A broad and comprehensive search is indispensible to secure proper basis for evidence-based research that includes maximum studies meeting the inclusion and exclusion criteria.

Classically, five bibliographic databases Medline[5], Embase[5], and Cochrane Central Register of Controlled Trials (CENTRAL)[5],Cochrane Database[1], and Cancerlit[1]are used to perform a comprehensive search of the available studies. As a first step the abstracts of all probable studies should be extracted followed by full review of that study appearing to meet inclusion criteria. This process of review is often done by at least two reviewers to establish inter-rater reliability. It is advised for authors to maintain a record of all reviewed studies with reasons for inclusion or exclusion, and information needed for data pooling (e.g., means, standard deviations). [8]There are eight key stages that relate specifically to literature searching in systematic reviews. [13]

The following criteria should be considered for a comprehensive literature search for trials:

- A search not limited to English language[13]
- Cochrane CENTRAL or at least two other electronic databases(such as MEDLINE or EMBASE) should be searched [13]
- For unpublished trials, conference abstracts, theses, trials registers; and contacts with experts in the field should be searched. If not all four , at least one of the search methods should be used. [13]

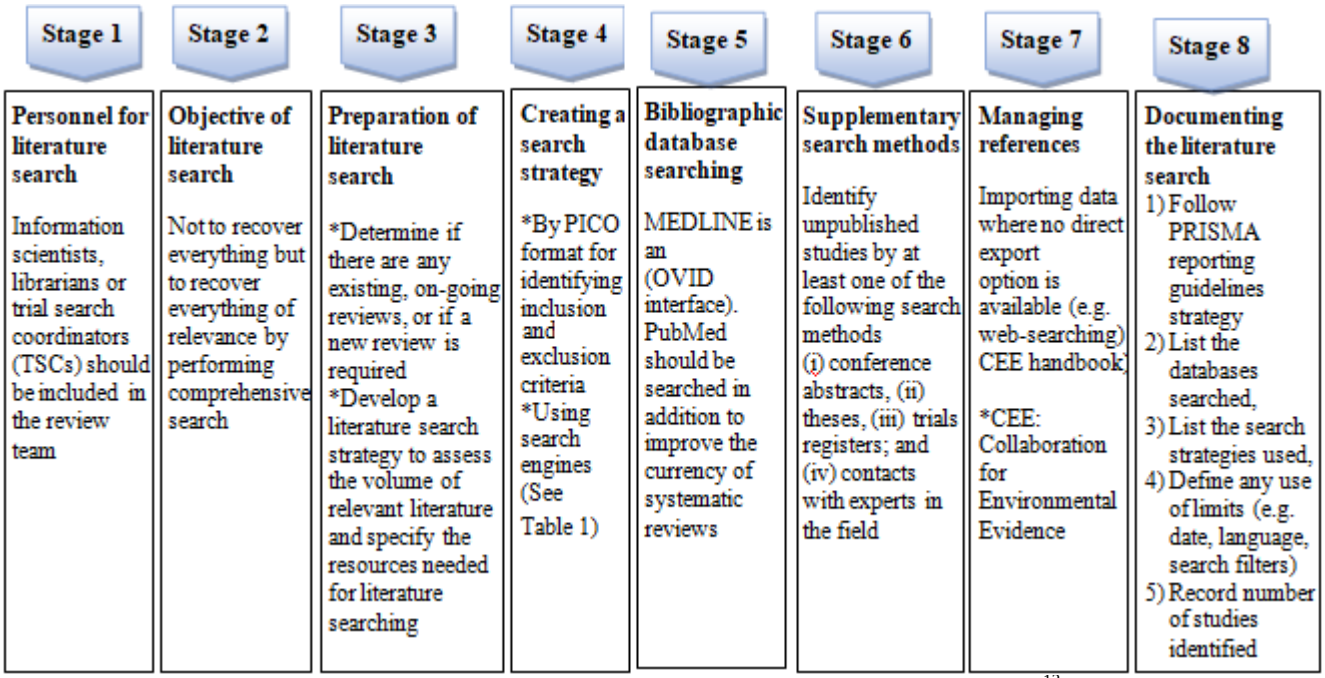

Figure 3: Schematic procedure of literature searching- Eight step process[13]

3. Quality of Evidence

Despite how well the systematic review or meta-analysis is planned, the quality of meta-analysis gets hampered or inaccurate results are obtained if the quality of evidence in the studies is low. Even the analysis involves RCTs of high quality, assessing the quality of evidence specificallyaids in determining the strength of recommendations in the meta-analysis. The evaluation of the quality of evidence of studies is done by the ***Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system***.[5]

Key recommendations from GRADE for evaluating quality of evidence

- GRADE proposes four levels of evidence quality: high, moderate, low, and very low.[14]

- RCTs depict as high quality evidence and observational studies as low quality evidence. [14]
- The main factors downgrading the quality are: limitations in study design, ambiguity of estimates (wide confidence intervals), indirectness of evidence, variability in results or publication bias. [14]
- The main factors upgrading the quality are: very large magnitude of effect, a dose-response gradient, and if all plausible biases would reduce an apparent treatment effect. [14]

The 5-point Oxford Quality Rating Scale is used for drug trials. This measure is considerably influenced by double-blinding and is commonly used in Cochrane reviews for assessing RCTs-related study quality.The standard recommendations of CONSORT (Consolidated Standards of Reporting Trials statement) are used for psychological interventions.[8]

Extracting the data

A simple data extraction form or table can be created to extract required information in an organized manner from each reviewed study (e.g., authors, publication year, number of participants, age range, study design, inclusion/exclusion criteria and outcomes). Data extraction should be conducted by at least two reviewers for establishing inter-rater reliability and evading data entry errors.[8]

Due to difference in the size and format of each variable, the size and format of the outcomes are different, and minor changes may be required while combining the data. If the differences in the size and format of the outcome variables cause difficulties in combining the data (for example: the use ofdifferent evaluation instruments or different evaluation time-points), then meta-analysis should not be conducted and the analysis may be limited to a systematic review only. [9]

4. Data Analysis

1) Effect Size

Effect sizes provide mean change in the dependent variable in each study in a standardized manner. These can include considerations of sample size. Moreover, in pooled effect sizes as in meta-analysis, these can be weighted by the variance of the estimate, so that the studies with lower variance (i.e. tighter estimated effect size) are given more weight in the data set. As there is inverse relationship between variance and sample size (decrease in variance will cause increase in sample size) therefore effect sizes based on larger study populations are given greater weight. [15]

The three most common statistical methods used to obtain reliable and comparable effect sizes for meta-analysis:

a) For continuous response variables between control and experimental groups, the mean difference(MD) between the groups is considered as an appropriate method to calculate effect size. [15]
b) For testing for an effect of a continuous or ordinal categorical variable on a continuous response variable, the correlation coefficient can be used. [15]
c) For dichotomous response variables the risk ratio (RR) or odds ratio (OR) provides a measure of effect size. [15]

2) Type I(α) and type II (β)errors

There are two types of errors affecting the quality of meta-analysis:

a) Type I error (α) occur which rejects the null hypothesis when it is true.
b) Type II error (β) which fails to reject the null hypothesis when it is false.

A β = 0.2 (power 80%) generally reflects high power and should be the targeted minimum value. The parameters on which power mostly depends include the overall effect size, the average group size, the number of included studies and their heterogeneity. [15]

3) Dichotomous variables and continuous variables

The outcome variables can be broadly discussed in terms of dichotomous variables and continuous variables.

Effect measures for continuous outcomes

The two most common effect measures for continuous outcomes are mean difference (MD) and standardized mean difference or effect size (SMD)(Table 2).[5,16]

MD = Absolute difference between the mean value in two groups[5]

$$SMD = \frac{\text{Difference in mean outcome between groups}}{\text{Standard deviation (SD) of outcome among participants}}$$

The MD is defined as the absolute difference in mean values between the groups, and the SMD is the mean difference between groups divided by the standard deviation (SD). [5, 15] Depending on the method of calculation of SD , the SMD has several variations such, as Cohen's d, Glass's Δ, and Hedges' g.[17]When results are in the same units(scale) in all the studies the MD can be used, but when results are presented in different units(scale), the SMD should be used. [5,16]

Interpretation of MD and SMD

- **A value of zero (0):** Effects of the new and the existing treatment method are the same.[5]
- **A value lower than zero (0):** the new treatment method is less effective than the existing method. [5]
- **A value greater than zero (0):** the new treatment is more effective than the existing method. [5]

Effect measures for dichotomous outcomes

For pooling data for dichotomous variables, the OR, RR, or risk difference (RD) can be used. The RR and RD can be used as effect measures for RCTs, quasi-experimental studies, or cohort studies, whereas the OR are appropriate for other case-control studies or cross-sectional studies. The dichotomous variable can be presented as the number needed to treat (NNT), which signifies the minimum number of patients needs to be treated in the treatment group for an identified event to occur in at least one patient compared to the control group. [5,18]

4) Fixed-effect models and random-effect models

The analysis of effect size can be done by using two models: a fixed-effect model or a random-effect model.[5, 19]

Fixed-effect models

According to the fixed-effect model theory the effect of treatment is the same in all the studies and any variation is due to random error. Therefore, the fixed-effect model is ideal to use for the studies with same design and methodology, or the variability in results within a study is small, and the variance in the studies is considered due to random error. Three common methods used to analyse effect size in a fixed-effect model are: 1) inverse variance-weighted estimation, 2)Mantel-Haenszel estimation, and 3) Peto estimation (Table 2). [5, 19]

Random-effect models

A random-effect model presumesheterogeneity(variation) between the studies being combined.An important feature of the random-effects model is that there is a distribution of true effect sizes. [5, 19]The methods commonly used to analyse effect size in a random-effect model are: 1) the DerSimonian and Laird method is mostly used for dichotomous variables, 2) inverse-weighted estimation is used for continuous variables.[5]

Differences between fixed- and random-effects models

- The random-effects models have wider confidence interval (CI) for the summary effect.[19]
- More similar study weights in the random-effects model (small studies gain influence and large studies lose influence). [19]
- There is difference in the estimate of the effect size under the two models.[19]

If the binary outcome variables are used, deciding for the right model for analysis is crucial, as fixed and random effects models give different results. In case of continuous variables, fixed or random models are often produce identical results in meta-analyses.[5,19]

Table 2: Recommended pooling methods [5]

Data outcome variable	Effect measure	Fixed-effect models	Random-effect models
Dichotomous	Odds ratio (OR)	Mantel-Haenszel (M-H) Inverse variance (IV) Peto	Mantel-Haenszel (M-H) Inverse variance (IV)
	Risk ratio (RR), Risk difference (RD)	Mantel-Haenszel (M-H) Inverse variance (IV)	Mantel-Haenszel (M-H) Inverse variance (IV)
Continuous	Mean difference (MD), Standardized mean difference (SMD)	Inverse variance (IV)	Inverse variance (IV)

5) Heterogeneity

Heterogeneity is calculated by homogeneity test which tells if the degree of heterogeneity is greater than would be expected to occur naturally when the effect size calculated from several studies is higher than the sampling error. Mostly three types of homogeneity tests can be used: 1) forest plot, 2) Cochrane's Q test (chi-squared), and 3) Higgins I^2 statistics.[5, 20]

In the forest plot a higher homogeneity is there if there is greater overlap between the confidence intervals. In the Q statistic method, if the P value of the chi-squared test is less than 0.1, a statistical heterogeneity is considered and a random-effect can be used.[5,20]

However, the best approach is the I^2 statistics because it provides the quantitative estimate of the effect of heterogeneity and a measure of the degree of inconsistency in the studies' results.[5, 20]

The formula to calculate I^2:

$$I^2 = 100\% \times (Q - df)/Q$$

where Q= Cochran's heterogeneity statistic
df= the degrees of freedom.

The degree of heterogeneity as defined by the values for I^2can be categorised into three grades of low, moderate, and high with I^2 values of 25%, 50%, and 75% respectively. [5,20]

Advantages of I^2

- Pays attention on the effect of any heterogeneity on the meta-analysis. [20]
- Simple to calculate and can be generally obtained from published meta-analyses. [20]
- Does not inherently depend on the number of studies in the meta-analysis. [20]
- Interpretation can be similar regardless of the type of outcome data (eg dichotomous, quantitative, or time to event) and type of effect measure (eg ORor hazard ratio (HR)). [20]

Heterogeneity causes an asymmetry funnel plot if it induces a correlation between study sizes and intervention effects. For example, considerable treatment benefits might be observed only in high risk patients and these may be preferentially included in early and small studies. Contrarily, the intervention may have been employed less thoroughly in larger studies, resulting in smaller effect estimates compared with smaller studies.[21]

6) Publication bias

The most common type of bias in meta-analyses is the publication bias. This denotes to the misrepresentation of meta-analysis outcomes due to the higher probability of publication of statistically significant studies rather than non-significant studies. [5]

Reasons for Publication Bias

- Unpublished studies. [21]
- Journals may be biased toward positive results because negative results are less likely to be published. [21]
- Some studies get initiated but do not complete. These studies are available in the form of conference abstracts but not in the clinical trial study databases. Therefore they are missed. [21]
- There occurs language bias because while literature searches for systematic review, generally publications in one language are considered (preferably only English).[21]

Funnel Plot

A funnel plot is a type of scatter plot of the effect estimates from distinct studies against some measure of each study's

precision. The standard error (SE) of the effect estimate is plotted on the vertical axisand generally used as the measure of study precision with a reversed scale that places the larger, most powerful studies towards the top. Effect estimates include relative risk(RR), risk ratio(RR), OR, absolute risk and logarithmic transformations of these measures. [22]

When the publication bias is absent, the points will be symmetrically distributed around the true effect in the form of an inverted funnel (Figure 3). [23]

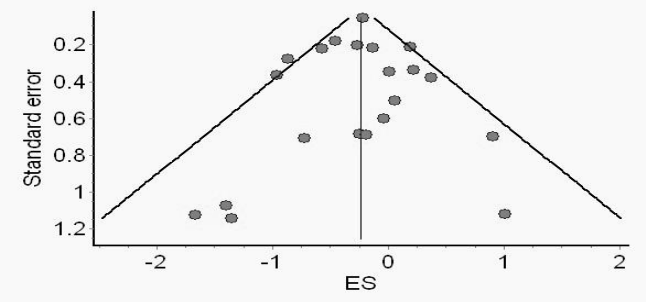

Figure 3: A symmetrical funnel plot

When the publication bias is present the funnel plot will be asymmetric. The pooled effect estimate will be diverged from the true effect due to negative effect estimates from smaller studies missing from the plot. [23]

Egger's Test

This test uses linear regression instead of correlation and estimates for asymmetry of the funnel plot.[21]

If publication bias is absent, all studies on X axis (1/SE) will be nearby the regression line of Y axis (effect size/SE), with large sample studies away from origin and small sample studies near origin. This indicates that there would be lesser publication bias if the regression line has intercept value close to zero.[21]

Begg and Mazumdar's rank correlation test

The Begg and Mazumdar rank correlation test uses the correlation between the ranks of effect sizes and the ranks of their variances.[21]The four important properties of this test are:

a) Difference between concordant and discordant ranks.[21]
b) Kendall's rank correlation for testing the interdependence of variance and effect size. The method utilizes Kendall's rank correlation rather than the ordinary product moment correlation, because normal distributions of effect sizes are improbable here.[21]
c) *z*-value.[21]
d) *p*-value for this correlation.[21]

In meta-analysis containing 75 or more studies this test for estimating publication bias is powerfulbut shows low power when meta-analysis has less than 25 studies. Therefore, for small meta-analyses the results of this test must be interpreted carefully.

7) Sensitivity analysis

A sensitivity analysis is defined as repeat of the primary meta-analysis in which alternative decisions or ranges of values for decisions that were unclear while performing meta-analysis are substituted. There are many decision nodes within the systematic review process which can generate a need for a sensitivity analysis.If results remain same across the different analyses, the results reflect the robustness as even with different decisions they remain them similar. However, if the results differ across sensitivity analyses, then interpretation of the results need caution.The best way to report sensitivity analyses in a systematic review is by producing a summary table. It is generally not informative to create individual forest plots for each sensitivity analysis undertaken.[24]

Various decision nodes for performing a sensitivity analysis in a meta-analysis include:[24]

a) Study Search
b) Eligibility criteria
c) Type of data to be analysed
d) Data analysis methods

Some examples for sensitivity analysis:

a) Exploring the effect of using different meta-analysis models (random or fixed effect models). [24]
b) Exploring the effect of exclusion or inclusion of studies in meta-analysis based on sample size, methodological quality, or variance. [24]
c) If the eligibility criteria of some studies in the meta-analysis arenot fulfilled due to lack of complete required details, sensitivity analysis might involve performing the meta-analysis twice: first, including all studies and second, only including those that are definitely within eligibility criteria.[24]

8) Interpreting and analysing "forest plot"

The results of a meta-analysis are typically represented as 'forest plots'.These meta-analysis graphs can primarily be divided into six columns. The rows represent the results of individual studies (Figure 4). [25, 26]

a) The first column represents the individual studies included in the meta-analysis. Generally the first author and year are shown. [25, 26]
b) The second column displays intervention/treatment groups. [25, 26]
c) The third column indicates the control groups. [25, 26]
d) The fourth column represents visual display of the study results. The contents of the fourth column can be interpreted as follows: [25, 26]
   - The middle line is called 'the line of no effect or null effect', which has the value of either 0 for continuous outcome variable (eg. WMD) or 1 for binary/dichotomous outcome variable (eg. ORorRR). If if OR or RR = 1 or WMD = 0, it indicates that no difference between the intervention and the control group. [25, 26]
   - Each box represent the "weighting" of that individual study in the meta-analysis. These boxes indicate sample size of the study. The bigger is the box the more are the participants in the study. The boxes are situated in line with the outcome value of the individual studies, also called the effect sizes (eg. OR, RR or WMD). The value axis is situated at the bottom of the graph.[25, 26]
   - The whiskers (horizontal lines) through the boxes portray the length of the confidence intervals (CI). The CI is defined as: "**The range of values within which**

you can be 95% certain the true value lies." These CI lines can aid in identifying the precision of the study results. The longer lines depict wider CIs and thus the less precise the study results. A study shows greater weight if the bigger the sample size and the narrower the CI.Numerically, the CI does not include 0 for continuous outcome variables and 1 for binary outcome variables.[25, 26]Fundamentally:

- The bigger the study, the bigger is box and the smaller the horizontal line representing the point estimate. This can be understood that the probability of these studies of crossing the line of null effect is less because 95% CI should have a much smaller range. [25, 26]
- The smaller the study, smaller is box and the wider the horizontal line representing the point estimate. This can be understood that the probability of these studies of crossing the line of null effect is high because 95% CI have much bigger range. [25, 26]

e) The fifth column represents the weight (in %) indicates the influence ofthe study on the overall results of the meta-analysis of all included studies. The influence of the study on overall meta-analysis results will be more if the percentage weight is higher and the box is bigger. [25, 26]

f) The sixth column shows the numerical values for each study (eg. OR or RR or WMD and 95% CI) which are same to the graphical results in the fourth column. [25, 26]

The diamond represents the pooled result of the meta-analysis. The middle of the diamond sits on the value for the overall effect sizes (eg. OR, RR or WMD) and the width of the diamond depicts the width of the overall CI. Statistical significance of the overall result is also expressed by p value in the 'test for overall effect' which is considered as statistically significant if $p<0.05$. Also, in case of binary variables, effect values are always greater than 0 but in case of continuous variables values can be negative or positive. [25, 26]

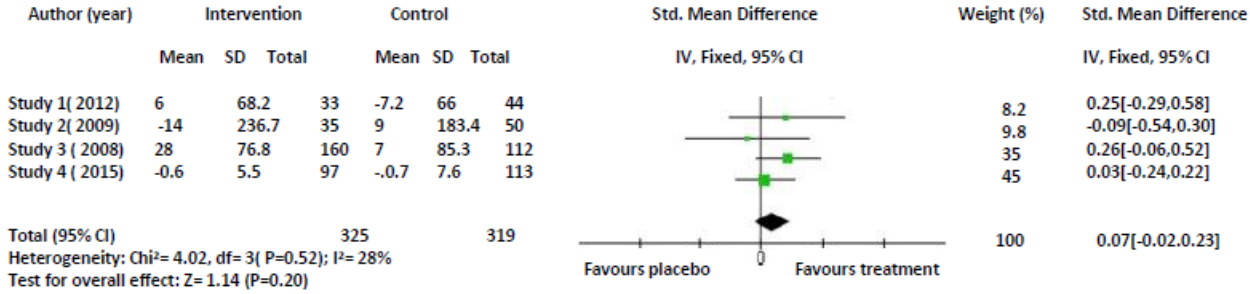

Figure 4: Example of Forest Plot
(This example is only for representation purposes to interpret forest plot)

Softwares for Creating Forest Plots
Forest plots in Review Manager (RevMan)

RevMan provides a flexible framework for preparation of protocols and full reviews, together with text, characteristics of studies, comparison tables, and study data. The meta-analysis of the data entered can be performed and results are graphically represented as forest plots in the 'Data and analyses' section. The review types which can be performed in RevMan 5.3(recent version) include intervention reviews, diagnostic test accuracy reviews, methodology reviews, overviews of reviews, review properties, licence for publication and flexible reviews. [27]

RevMan offers multiple selections for data analyses (e.g. choosing between fixed and random-effects meta-analyses), or using different effect measures and graphics (e.g. scale of axes and ordering of studies). Default analyses are shown unless options are ignored. The defaults are Mantel-Haenszel odds ratios for dichotomous data, fixed-effect meta-analyses of mean differences for continuous data, Peto odds ratios for 'O–E and Variance' outcomes and fixed-effect meta-analyses for generic inverse variance outcomes.[28]

The most commonly used version is RevMan 5.3 which has comprehensive features for data analyses. The following tabs are available for data analyses:[27]

- Constructing a comparison table
- Comparison properties
- Outcome properties
- Adding studies to an analysis
- Entering data
- Calculating data
- Generating and Analysis forest plots
- Funnel plots
- Sensitivity analysis

Go to the following link to download user guide and get more information on all tabs/ selections available in the software:
https://community.cochrane.org/sites/default/files/uploads/inline-files/RevMan_5.3_User_Guide.pdf

Steps for creating forest plot in RevMan
(These screen shots are created for explaining the steps only and are not the part of any existing review)

Step 1- Creating a RevManoutline for review

1) Start RevMan
2) Select the "Close" button on the right-lower corner of the first prompt.
3) Select "New"in Filemenu on the menu bar on the top.
4) Select "Next"in New Review Wizard
5) Select type of Review and then click "Next" (Figure 5)
6) Input in PICO Short Title in the last field
7) Select Review stage, and then select "Finish"

Figure 5: Type of Review

Step 2-Entering details of included studies

1) Click "Studies and References" in left side-bar
2) Click "Add Study" on the main screen under "Included Studies"
3) Input study details: Author, year , then click "Next"
4) Select Published data only (which is automatically selected) and then click "Next"
5) Input year if not automatically populated and then click "Finish"
6) Repeat all the above steps for all individual studies included in the meta-analysis

Step 3-Creating forest plots

1) Click "Data and analyses" in left-sidebar (Figure 6)
2) Click " Add comparison" on the main screen below "Data and Analyses"
3) Input Name of PICO in New Comparison Wizard, eg "Hydrotherapy vsTraditional Physiotherapy in Osteoarthritis (OA) in relieving pain" then click "Next"
4) Select "Add an outcome under the new comparison" and then click "Continue"
5) Select "Dichotomous or Continuous" based on Data Type, then click "Next"(Figure 7)
6) Input Outcome Name, eg. "Relieve in OA pain"
7) Edit Group Label 1, eg. "Hydrotherapy" then, Label2, eg. "Traditional Physiotherapy" and then click Next
8) Select the method for effect-measure "Risk Ratio" or "Odds Ratio", " Mean Difference" whatever is applicable as per data type and then click "Next"
9) Select Results of meta-analysis, "Total and subtotals", "90%, 95 % CI" and then click "Next"
10) Enter Forest Plot labels, then click "Next"
11) Select "Add study data for the new outcome", then click "Continue"
12) Select all studies with the outcome under review (for relieving OA pain), then "Finish"
13) Enter the numerical values of outcomes for each the controland treatment groupsin the white boxes on the center of the screen.
14) Click the blue forest plot icon to the right of the FE button above the forest plot which is created.
15) Click "Add as Figure"**(A plot similar to Figure 4 will be displayed on the screen)**
16) Click "Figures"in left-side bar to see a list of forest plots
17) Use the"File" menu to save your RevMan forest plot file

Figure 6: Data and analyses for creating forest plot

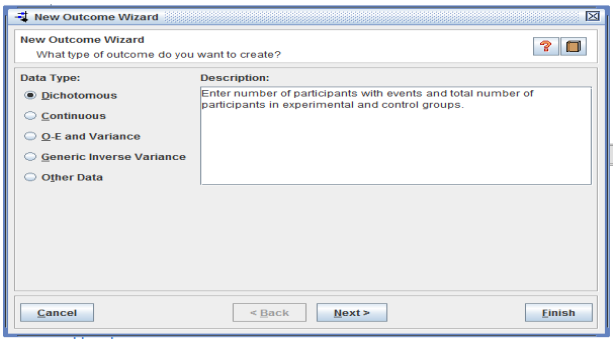

Figure 7: Data type selection in RevMan

Forest Plots in R Studio

R package ***meta*** is a user-friendly package providing standard methods for meta-analysis.[29]
For more information go to the link:http://meta-analysis-with-r.org/

R package ***meta*** provides the following statistical methods for meta-analysis:

1) For fixed effect and random effects model [29]

- For continuous outcome data (metacont)
- For binary outcome data (metabin)
- For incidence rates (metainc)
- For generic inverse variance meta-analysis (metagen)
- For single correlations (metacor)
- For single means (metamean)
- For single proportions (metaprop)

2) Offer different types of plots for meta-analysis[29]

- Forest plot (forest)
- Funnel plot (funnel)
- Galbraith plot / radial plot (radial)
- L'Abbe plot for meta-analysis with binary outcome data (labbe)
- Baujat plot to explore heterogeneity in meta-analysis (baujat)
- Bubble plot to display the result of a meta-regression (bubble)

3) Statistical tests for funnel plot asymmetry (metabias) and
4) Trim-and-fill method (trimfill) to evaluate bias in meta-analysis[29]
5) Cumulative meta-analysis (metacum) and leave-one-out meta-analysis (metainf)[29]
6) Meta-regression (metareg)[29]

Standard Practice for Reporting of Meta-analyses- The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines

The PRISMA Statement comprise of a 27-item checklist and a four-phase flow diagram for researchers to re-use. The

objective of the PRISMA Statement is to support authors to improve thereporting of systematic reviews and meta-analyses.

For 27-item checklist go to the link:
http://prisma-statement.org/PRISMAStatement/Checklist.aspx

For four-phase flow diagram go to the link:
http://prisma-statement.org/PRISMAStatement/FlowDiagram.aspx

5. Conclusion

Meta-analyses are generally conducted by pharmaceutical companies for obtaining marketing authorization from regulatory authorities for new drugs if sometimes demand a meta-analysis as part of the approval process. For clinicians and applied researchers in medicine, education, psychology, criminal justice, meta-analysis is a tool to find out which interventions work and comparisons with other interventions to identify the superiority of a specific drug. Other domains where meta analysis is widely used to assess the evidence include sociology, social psychology, sex differences, finance and economics, marketing, political science ,ecology and genetics,. [31]The conventional medical practice trends have been changed by the use of randomized, blinded, multicenter clinical trials and meta-analysis, leading to development of "EBM". The key players in initiating this change have been the Cochrane Collaboration who have developed standard practice guidelines for conducting systematic reviews and meta-analyses and more recently the PRISMA statement has been introduced to improve reporting of systematic reviews and meta-analyses. One major issue in determining whether studies can be pooled is the extent of heterogeneity among individual studies. The graphical statistical tools for assessing heterogeneity such as Cochrane's Q test (chi-squared), and Higgins I^2 statistics have been found appropriate approaches for conducting high quality meta-analyses. Publication bias is anotherbasic issue which can be estimated by funnel plot, Begg and Mazumdar's rank correlation, and Egger regression methods. Despite of all these, meta-analysis is an infallible tool with apex hierarchy in clinical research pyramid with least possible bias.

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