

Introduction to Meta Analysis

Meta analysis refers to secondary data analysis where information from individual research articles are synthesised to arrive at a summary estimate. Meta analysis thus refers to several related steps of framing a question or a problem, formulating search strategies, collection of journal articles or primary studies, abstraction of data from the studies, critical appraisal of studies, judging homogeneity of studies, and synthesis of information from them. In this paper, we describe the key processes of how to conduct each of these steps to conduct a meta analysis.

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Health information has grown exponentially in recent years and evidence-based practice is the new paradigm of health care. As a result, health professionals in all disciplines are expected to be up-to-date with the most relevant and with the best current evidence. However, it is impossible to keep up with the sheer volume of information. This calls for careful curation of available information. In the absence of robust information synthesis, non-systematic, narrative information or reviews that are based only on the reviewers' prior experience or expert opinions cannot be reproduced and as a result, these reviews cannot be updated and with the rapid pace of innovation and new studies that supersede old information, such reviews are at a risk of getting outdated. In addition to this, the well-established dictum of best evidence positions meta analysis of randomised controlled trials for interventions at the peak of evidence on which one can base one's practice of healthcare [4]. Consequently, carefully conducted, reproducible reviews that employ framing of relevant research questions, well-specified algorithms to search literature databases and research databases of primary studies, and synthesis of information are very important to conduct knowledge synthesis and develop practice guidelines. Such explicit reviews of the literature are known as systematic reviews. In

meta analysis, findings from similar but unique studies are statistically synthesised. In this chapter, the principles and practice of meta analysis will be presented.

In general, health professionals conduct three different types of reviews depending on the aim or goal of the review. Where the goal of the review is to collate all available evidence or information on a particular topic of interest (“omnibus review”), a comprehensive narrative review of the topic from different perspectives is usually conducted. For example, Sonia Ancoli-Israel et al (2003) conducted a comprehensive review of the literature to identify studies on the role of actigraphy in the study of sleep and circadian rhythms that addressed management of ambulatory care sensitive conditions[1]. The aim of this review was to provide a large, comprehensive compendium of the role of actigraphy. Another purpose of conducting a review may be to identify the best evidence to manage a particular disease or health condition (“Best Practice Reviews”). In these reviews, the reviewers not only compare benefits of the different treatments or assess the association between different exposure conditions and health outcomes, but also compare and contrast risks. The reviewers thus compare the relative effectiveness and harms and their costs and effectiveness associated with those treatments or approaches. Thirdly, the most popular type of review in medicine and public health is where investigators aim to summarise the association between exposures and health outcomes or effectiveness of different treatments for specific conditions either in contrast with no treatments, placebos, or alternative treatments, but such associations are studied using a well-defined approach. The authors, adhering to evidence-based principles, stepwise frame answerable questions, identify relevant studies, critically appraise the studies and on the basis of that critical appraisal, abstract key information from the studies and summarise the findings from individual studies to arrive at an evidence based answer to the question posed. The comparisons can be conducted among three or more diagnostic or treatment approaches. In terms of

methodology, narrative synthesis of information or narrative reviews are conducted to narratively summarise key information contained in the articles considered for review.

Meta analysis thus refers to a specific type of systematic review that has the following three characteristics:

Numerical or statistical pooling of the study results. — In meta analysis, data from the studies are weighted and the results are pooled to form a series of summary estimates to estimate an overall effect size

Only Two Comparisons. — At any time, only two interventions or alternative conditions are compared. — Another distinguishing feature of meta analysis is that, here at any point, only two alternative treatments are compared. These treatments can be a novel intervention versus a placebo, or a novel intervention versus another intervention (treatment as usual), or two alternative interventions or two alternative conditions. This is true of parallel arm meta analysis that we shall discuss in this chapter; however, in network meta analysis, a growing field, where networks of studies that make direct and indirect comparisons among each other allows for multiple comparisons of studies. However, discussion of network meta analysis is beyond the scope of this chapter.

Included studies should be similar. — This is an important consideration in meta analysis and formal approaches exist to indicate the extent to which studies are homogeneous or heterogeneous.

In addition to these distinguishing characteristics, the steps of meta analysis follow those of any systematic review: in selecting explicit research question, and methodology that is reproducible and synthesis of information. The steps of meta analysis are explained below.

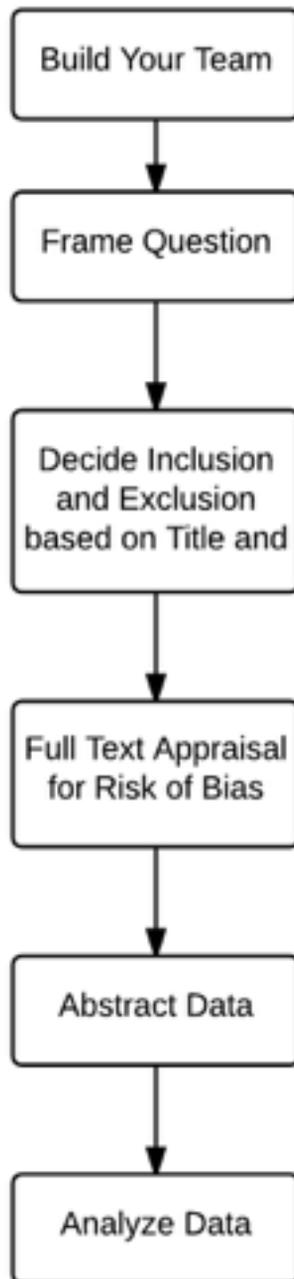


Figure 1. Steps of Conducting Meta Analysis

As illustrated in Figure 1, meta analysis can be conceptualised as a more or less linear process consisting of the following sequential steps:

1. Framing of a research question;
2. Searching of literature;
3. Initial screening of studies based on their titles and abstracts;
4. Critical appraisal of studies based on a close reading of their full texts to identify key data elements and appraise their risk of bias;
5. Abstraction of data from individual studies;
6. Assessment of the homogeneity of the included studies both from a statistical and other perspectives (methodological and clonal homogeneity)
7. Statistical pooling of the results abstracted from each of the identified studies (step 5) to arrive at a summary statistic;
8. Examination of the different subsets of studies (based on step 4 on their quality appraisal or other characteristics) - sensitivity analyses or subset analyses (also referred to as meta regression).

These steps of meta analysis indicate that a range of skills are needed and meta analysis therefore is a multi-disciplinary team based activity. Consider for example, that you are planning to conduct a meta analysis for available evidence on the effectiveness of meditation plus medications as opposed to medications alone for the control of hypertension. In order to conduct such a meta analysis, you will need the skills of a physician who is knowledgeable about management of hypertension, but also of an expert who can advise on mindfulness meditation, an expert who can conduct literature

search on the topic, and a statistician who can statistically combine data for arriving at a summary estimate. In addition, you will need researchers who can maintain a database full of articles, and abstract data from the articles for further processing. In summary, meta analysis is an interdisciplinary team work. Framing of a research question include domain knowledge and skills, while at the same time, critical appraisal of the studies to identify risks of biases will need skills where the researcher should not allow domain knowledge to be biased at conclusions of specific studies. Therefore a study team should include both experts and non-experts. Given the “explosion” of information in literature and research studies, search of literature to narrow down to the exact quanta of literature needed for a successful meta analysis will need inclusion of a person with skills of literature search (a health information specialist can bring on board such skills). Hence before a meta analysis can be conducted, it is important for the analyst to put together a team consisting of individuals at least the following set of skills:

1. One or more domain experts who can identify and scope the health problem of interest
2. A health information specialist who will bring on board skills of literature search and retrieval of studies
3. A statistician who will analyse complex data from the studies as studies can present data in different ways and often sophisticated statistical skills are required in identifying or estimating key data elements for meta analysis
4. A database expert who can store and curate records or bibliography records

Also, since meta analysis is based on previously conducted studies and studies whose results have already been obtained, this is necessarily retrospective. Besides, in a

primary study, the trialist or the investigator works with individuals. The meta analyst on the other hand, accesses the primary studies and these primary studies rather than individuals are the source of information. Therefore, quality of meta analysis depends on the quality of the primary studies: if the original studies are of poor quality, then either the meta analysis cannot be conducted or if conducted, that meta analysis is open to the same biases and subsequently leads to propagation of errors in the original studies. The individual steps are explained as follows.

Step One: Frame A Study Question

How to Select Questions. — Framing a research question is the first step in meta analysis. In general, health problems where answers are not always clear or where increased precisions are needed are good candidates for meta analysis. For example, Peck et.al. (2013) conducted a meta-analysis to assess the magnitude and direction of the difference in blood pressure response to ACE inhibitors between black and white populations [7]. In another example, Babu et.al.(2013) addressed whether job stress factor was associated with hypertension as previous studies were too diverse and therefore pooling of studies would enable framing a response [2]. These examples show the power of meta analysis that it is possible to pool together results from small studies which themselves may be underpowered or inconclusive, yet when combined with each other in a meta analysis, the overall conclusions or figures provide stronger estimates of the association between interventions or exposure and outcomes. Thus, questions that are either “not settled”, or are based on small but inconclusive studies are good candidates for meta analysis. The questions can be best framed using the Participant-Intervention-Comparator-Outcomes (PICO) format as follows.

PICO Format. – A well-formatted question directs the course of action and specific steps taken in a meta analysis. The research question is formatted using participants [P],

intervention [I] or exposure [E] depending 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 specific exposure (against another) for a particular outcome; comparator [C] — who or what is being compared with the intervention or the exposure under study, and finally outcome [O] — the specific health outcome of interest, in that order. The role of participants is important in meta analysis as the same topic can result in different research questions depending on the participant profiles. For example, if your interest is in studying the risks of hormone replacement therapy for breast cancer, the studies can be very different depending on whether you are only going to be interested in pre-menopausal or post menopausal women (age as participant character become important). Similarly if you are interested to study roles of antihypertensive therapy, gender can be an important variable. The intervention or exposure will need to be specified as the scope and relevance of a meta analysis, and often, whether a meta analysis can at all be attempted, depend on how broadly or how tightly the intervention is defined. For example, imagine you are planning to conduct a meta-analysis comparing a combination of mindfulness meditation based stress reduction and drugs with drugs alone for the control of stress related symptoms among breast cancer survivors. While this is a well-defined intervention in itself, the number of studies that you can identify may be limited. On the other hand, you could retrieve a larger number of primary studies if you were to relax the intervention to include “any form” of meditation rather than MBSR. Then again, you would have to sacrifice homogeneity of studies (loosely, similarity of studies, explained later) and in turn, this consideration alone might lead to a different form of summarisation rather than conducting a meta analysis; for instance, you could shape up the review not as a meta-analysis but as an omnibus review or an overview of the effectiveness of any form of meditation for the control of hypertension. You might have to abandon a meta analysis

and end up doing a systematic or narrative review. Therefore, precision in the definition of intervention or exposure criteria can be a major decider for the meta analysis. Likewise comparators and outcomes to be studied for a research are crucial to its success.

An Example of PICO formatted research question (Table 1). —

Table 1 shows the PICO criteria for a meta analysis of the effectiveness of mindfulness based stress reduction for control of hypertension among elderly (64+ year old) hypertensives

Table 1. Explanation of PICO

Condition	Definition or Explanation
Participant	Mention the participants, e.g., all hypertensive adults both sexes age 64 years and above
Intervention	Mindfulness Based Stress Reduction plus medications
Comparator	Medication Alone
Outcomes	Blood Pressure Control (Systolic and Diastolic)

Too Narrow versus Too Broad Meta Analysis. — Framing of the research question sets the tone for a meta analysis. A meta analysis can be very narrow in scope; a too narrowly defined meta analysis can result in retrieval of too few studies. Scoping a meta analysis is not necessarily an easy task as this involves taking into consideration several factors: availability of supporting information, background data on the problem being studied, composition of the team and resources, and also the potential impact of the meta

analysis on the problem being studied (cite the Higgins review). If the meta analysis is too narrow, then the results cannot be generalised to larger population. For instance, generalisability of the results is a problem with randomised controlled trials as they tend to be very specific, and using few randomised controlled trials in a meta analysis may not be very helpful for generalisation of the study findings. This is almost akin to conducting a subgroup analysis in a meta analysis where only a select subgroup of available studies are considered; additionally, too narrowly focused meta analysis often results in selection bias of studies particularly with experts who are prone to exclude studies that do not meet their inclusion and exclusion criteria as these are very tightly defined.

On the other hand, if the meta analysis is too broadly defined, it becomes a very time consuming exercise, as the number of search results are very large, and takes time to analyse the volume of studies that are retrieved. Additionally, as studies would be very diverse, risks of studies being heterogeneous is high, and in turn leads to problems of interpretation of data. Large number of studies that are dissimilar to each other because of the diversity and over inclusive nature of the search results in what is often referred to as “mixing of apples and oranges”. In a tutorial on conducting Cochrane Reviews, Higgins et.al.(2000) have stated that such mixing is fine when the object of the study is to know about “fruits” but not when finer characterisation about either apples or oranges is the objective of the study [5]. Given this dilemma, a possible middle path for a large or broad based question might be to start with a series of smaller meta analyses that compare only two conditions or two interventions at a time and subsequently adding the studies to a thematic whole so that the overall large topic can be addressed from a robust methodological perspective.

Step Two: Searching Literature

After a study question is framed, the meta analyst then proceeds to conduct a search of the literature databases. The exact phrases and combinations of words used to search the databases depend on the criteria already set up in the scoping of the meta analysis. In general, more than one databases are searched with different techniques and combination of keywords, and use of boolean logic are used. For biomedical literature, [Pubmed] (<http://www.pubmed.org>) is a large and widely used database. Many academic and research institutions and universities have libraries that in turn host their own selection of databases that they buy licences. In addition, meta search engines such as Google Scholar provide excellent starting point for exploration of the studies.

Use of Controlled Vocabulary . — Meta analysis depend on retrieval of primary studies, and authors can express titles and abstracts in many different styles and use different types of headlines to express the core messages. Although how to write titles and structure abstracts are now quite standardised, authors are free to use expressions and statements that they best know. As a result, there is a need for specific key words or expressions when articles and journals are deposited to electronic databases so that publications can be easily retrieved. These keywords together make up what is known as controlled vocabulary. Controlled vocabulary therefore lists specific keywords under which primary studies are curated by database curators. For example, in Pubmed MeSH (Medical Subject Headings) constitutes such a vocabulary where different medical terms are organised in hierarchical order. Use of controlled vocabulary is an extremely useful strategy to identify studies. The most widely used controlled vocabulary for biomedical studies is used by the National Library of Medicine, the Pubmed or the Medline Database. The controlled vocabulary is known as Medical Subject Headings. The curators or maintainers of the Pubmed/Medline Database have described the MeSH vocabulary as such on their website as follows, “(the vocabulary) imposes uniformity

and consistency to the indexing of biomedical literature. MeSH terms are arranged in a hierarchical categorized manner called MeSH Tree Structures and are updated annually “ [see http://www.nlm.nih.gov/bsd/disted/pubmedtutorial/015_010.html] for more information.

Use Specialized Databases. — For meta analysis of intervention trials, randomised controlled trials and clinical trials are included and data from these trials are abstracted and analysed. For observational epidemiological studies such as cohort and case control studies, these studies are sought in literature databases, and data are abstracted from these studies and synthesised. Therefore, curated databases that contain specifically randomised or non-randomised trials are useful for location of trials for conducting meta analyses. While Pubmed/Medline and EBSCO (Europe focused) are two major sources of both observational studies and randomised controlled trials for all conditions, two major sources of clinical trials are clinicaltrials.gov and controlled clinical trials registry database. These databases not only contain information about completed trials but also additional information about ongoing trials and trials that are currently recruiting participants. These make searching for studies not only easy but also provides opportunities to easily search for grey literature or studies or trials that may have been completed but whose results are not yet available in published format.

Use Boolean Logic based searching of literature.— While availability of the specialised databases and generic databases have made it easy to access articles and original data for analyses, these would still need strategic and careful searching using a range of techniques. Generally, words and phrases in the text, title, abstract, and words/expressions in the controlled vocabulary are used to effectively search these databases. Use of Boolean expressions of AND (narrows down the searches to only specific terms), OR (expands the searches to include all the terms or phrases used), NOT (excludes the searches and narrows down to specific terms) are used along with wildcard entries

(Table 2). A common strategy for searching of articles is to start with terms describing “outcomes” first, then adding terms describing the “intervention” or “exposure” related terms, and finally terms that define or describe the “study design” related terms. For example, if you were to search for all studies on mindfulness based meditation and control of hypertension, you might start with “hypertension” or “high blood pressure”; then follow up the search with “mindfulness based meditation”, and then terms descriptive of “randomised controlled trials” or “controlled clinical trials”. Finally, use of years, and languages often limit the searches. In addition to manually constructing search terms, the researchers also frequently make use of specialised search terms and combinations of search terms that are made available for specifically conducting searches. Specifically, researchers who conduct Cochrane Reviews can avail of the services offered by the Cochrane Trialists or Cochrane Coordinators who maintain and curate databases of search terms that are validated for specific types of studies to be retrieved and these are used (cite the website).

Table 2 shows an example of Mindfulness Meditation for the control of hypertension and use of Search Operators

Table 2. Shows the 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

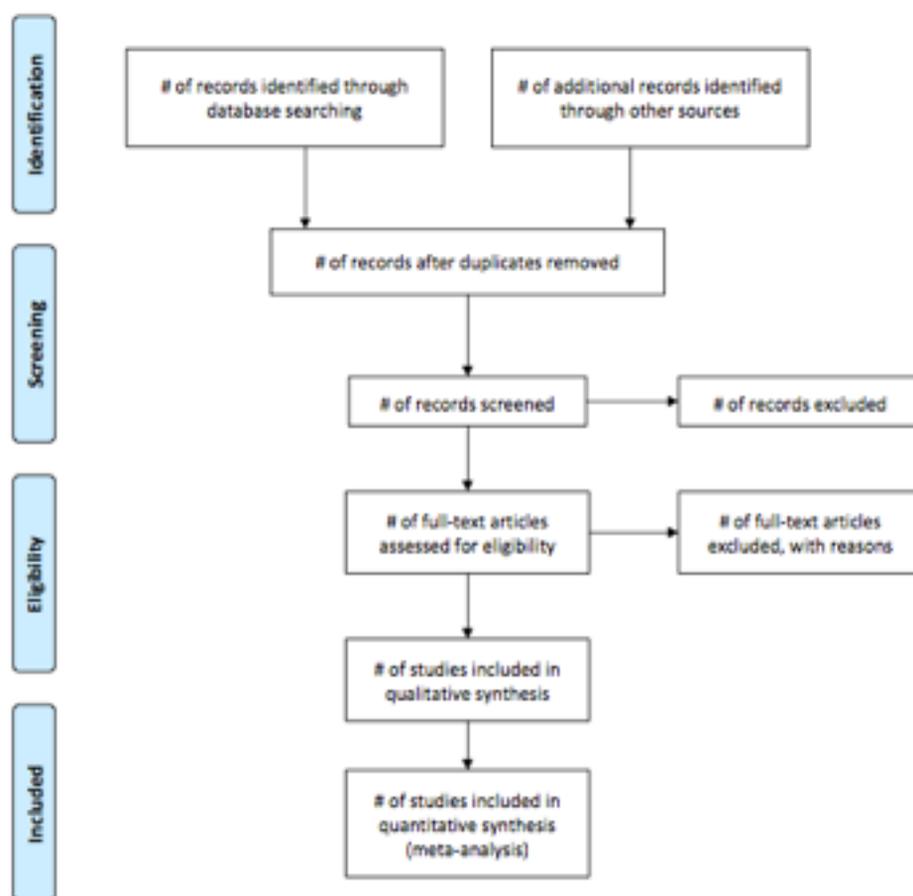
Use validated search filters. – Search algorithms can become quite complicated as different databases have different types of controlled vocabulary, but also there are issues around usage of wildcards, and other notations that help researchers to search individual databases. Increasingly, specialised search algorithms to search specific types of articles for data analysis are becoming available. The ISSG search filter resource is a large repository where search filters are made available for different types of study designs and different databases for researchers to use. For more information, check out the ISSG Search Filter Database site.

Grey Literature and Hand Search. – In searching for information, relying only on published articles in peer reviewed journals often cause a problem in that there is a bias where articles or publications that have positive findings are over represented (cite Cochrane and mention page). As a result, if only those studies that were published in peer reviewed journals or published in public domain are included in the meta analysis, and publications that were either not published because they failed to present positive

findings and therefore not included in the meta analysis, the meta analysis would itself be biased and would result in potentially erroneous estimates. Therefore, the meta analyst must conduct an active search for all publications and data which may not have been published or otherwise in archives or in authors' personal collection which although the research was completed still remained unpublished. Such publications are known as "grey literature" and must be included in any meta analysis. While it is not easy to retrieve such publications, usually contact with known experts, and active searching of conference abstracts, contacting first authors, or searching of trial registers are warranted to identify these sources of information. Omission of grey literature leads to "publication bias" (also referred to as "file drawer problem") meaning that articles or publications that are otherwise publishable (they are well conducted trials of good quality of evidence) but they never see the light of day (and consequently likely to be confined to the file drawers of the individual investigators for a variety of reasons. Perhaps the articles submitted to the journal are rejected because the editors of the journals do not have any interest in publishing negative findings, or the investigator decides not to send such articles to any journal as the journal is perceived not to publish them. Irrespective of the reason, publication bias must be formally examined during meta analysis. At present, rather than formal testing of the extent of publication bias, visual methods such as construction of "funnel plots" are available and should be reported in any meta analysis.

Besides reporting of publication bias, the reference lists of all the retrieved articles must be read and then the titles and abstracts of each reference article on that list should be read and attempt must be made to identify additional studies. This is known as "hand searching" and involves searching where necessary library archives or paper copies of journal articles. Thus, in summary, searching for publications involve teamwork, careful construction of search filters and algorithms, and is a recursive process where the

articles are searched exhaustively till a number of studies are finally retrieved that can answer the research question.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 2. PRISMA Chart

Need for Inclusion and Exclusion Criteria (Figure 2). – A review of the titles and abstracts of the articles or publications retrieved and collected in the first pass are then reviewed based on their titles and abstracts. The flow chart starts with all the retrieved publications in the first pass, and then moves downwards progressively to show the reason for exclusion of the publications, both at the stage of only reviewing the titles and abstracts but also on review of the full text of the articles. A rule at this stage is to follow the inclusion and exclusion criteria strictly and in cases, where the analyst is in doubt whether an article or publication can be included or excluded, the advice is to include the article, as it can always be excluded on close reading in the second pass. The list of excluded articles are then kept separately at another database and the analyst proceeds with the included studies. For each included study at this stage, the full text is obtained and data are abstracted from the studies and the studies are also assessed for their risk of bias. Additionally, in systematic reviews, not all article are included for meta analysis, and therefore, a separate listing of the number of articles that are kept for narrative synthesis versus articles kept for more detailed quantitative syntheses are indicated at this stage.

Risk of Bias Appraisal of Full Texts

In meta analysis, data from primary studies are combined to arrive at a summary estimate of the association between two variables. Where the objective is to estimate the overall effectiveness of a particular treatment, this process involves pooling results from primary studies to arrive at a summary estimate to assess whether compared with alternative treatments or placebos or compared with no treatment at all, the treatment under review was effective in achieving the outcomes set out in the studies. For observational studies, the aim is to assess whether the pooled estimates of the odds ratios or relative risk estimates indicate a valid association between the two entities. It

follows that in meta analysis, the analyst is not only interested in the presence of the evidence but 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 errors that compromise internal validity in primary studies.

In order to establish internal validity of a trial or an observational study, the investigators of studies should address three related entities – play of chance (the study should have sufficient number of participants to rule out random association), biases that can arise in course of conducting the study, and controlling for confounding variables. As an example, consider an investigator who is interested to study the association between excessive coffee drinking and the risk of pancreatic cancer and decides to conduct a case control study of individuals with and without pancreatic cancer and will measure their coffee consumption and with this measurement, the investigator will investigate whether excessive coffee consumption as defined under conditions of the study is associated with pancreatic cancer. In order to establish internal validity in such a study, she must specify ahead of conducting the study how many participants should be included in each arm (cases and controls). She should also consider alcohol drinking or other variables that are associated with both pancreatic cancer and alcohol intake, as potential confounding variables. Additionally, such observational epidemiological studies are open to selection and response biases. In case of randomised controlled trials, the process of randomisation ensures controlling of known and unknown confounding variables. However, for both randomised controlled clinical trials and observational studies, several different types of biases are possible. These include:

1. Selection Bias. – Indicates systematic differences in comparison groups that occur as a result of how the groups being compared were selected for the study. A similar bias results if the respondents of a study differ in which they respond to

survey questions (response bias). Selection bias is a particularly important problem in meta analysis and in appraisal of risk of bias, it is important to keep in mind two forms of biases: A. In case of randomised clinical trials and other forms of clinical trials it is important to ensure that true randomisation was done by way of using random numbers table rather than leaving chances for systematic allotment of treatments and alternative conditions. B. A very important point is to ensure that the allocations to the intervention and control arms were truly concealed (that is neither the investigator nor the patient was aware of where the intervention and control arms were allocated. This principle is known as double blinding). Allocation concealment is particularly important in clinical trials to ensure chances of selection and performance bias.

2. Performance Bias. – This results from systematic differences in the care provide between the intervention and the comparison group in case of randomised controlled trials.
3. Attrition Bias. – This results from systematic differences in how participants have withdrawn from the trials.
4. Detection Bias. – Systematic differences in which the outcomes are assessed.

In review of randomised controlled trials, it is essential to critically examine how participants were allocated to treatment and alternative conditions and how such allocations were concealed from not only the participants in the study but also for investigators. Such concealment is referred to “blinding” or “allocation concealment”. Studies that fail to demonstrate robust processes of allocation concealment are likely to report significant selection biases or reporting biases and therefore these studies are at significant risk of studies with inaccurate estimations of the extent of associate between the treatment and outcomes.

Step Four: Abstract Data from Individual Studies

Abstraction of data from individual study is critical for data analysis, and the process is now fairly standardised when specific summary of findings forms (SoF forms) are used. These forms have been developed by the GRADE Working Groups and provide detailed instructions as to how to use the data abstraction forms. These forms are also standard components of software such as RevMan Software used to conduct meta-analysis published by the Cochrane Collaboration. In general, the abstraction of information from primary studies include the first (or corresponding) author of the study, the year the study was reported, the population on which the study was conducted, the intervention or the exposure that was studied, and comparison groups, the outcomes, the effect estimates, and elements of information that indicate quality of the study. In general, the Cochrane Handbook recommends the following elements of data to be abstracted:

1. Title of the review and name of the coder
2. A key or identifier for every primary study included in the review
3. A field where you indicate that the study is eligible or not (this is somewhat redundant as you can sense that all studies included in the review are included here, but also there may be misses and this is where this extra field is helpful particularly if you have more than one coder for your project)
4. Type of Trial or Study Design (RCT, others, before-after study, cross over)
5. Whether Allocation Concealment was done (Adequate, Unclear, inadequate, not done, not relevant)
 - Participant characteristics
 - Depend on the study or review itself, if it is reasonable to believe that participant characteristics might influence the outcome or research in some ways then that

characteristic must be included. Example: in your study on the efficacy of mindfulness meditation for hypertension, you may want to include ethnicity of the participants on whom studies were done (unless you restricted) as an element of the data

1. Age
2. Gender
3. Settings (hospitals, emergency rooms, offices, nursing homes, prisons, others, community setting)
4. Diagnostic Criteria for the Outcome of Interest. – this is important for a number of reasons, particularly for hypertension or others as to what or how did the investigators ascertain the outcome? What criteria were used?
5. Interventions. – for drugs used route of administration, dosage, timing; for other kinds of interventions, who administered the intervention, how often,
6. Comparator Condition. – As in above
7. Outcomes. – See the GRADE forms and use them 13 Effect Estimates. –

Outcomes. – In both intervention research (randomised controlled trials, clinical trials) and in observational studies (case control studies, cohort studies, others) health effects or health related phenomena that depend, or arise out of an intervention or result of an exposure are referred to as outcomes. Examples of outcomes include recovery from an illness (whether patients recovered from an infection or not), death or survival (whether the patients survived after five years from the detection of breast cancer or did not survive), or length of stay at a hospital following an intervention; it can also be measured or expressed in terms of grades of responses from patients or participants in a trial (on a scale of one through five, where is a patient in terms of pain following a

procedure. The number that the patient expresses is the outcome of the procedure on a scale of one through five and is expressed in an ordinal measure and an outcome of the procedure). In general, five common types of outcomes are described in the literature. These are:

1. Dichotomous or binary outcomes. – Dichotomous outcomes indicate one of the two states of existence. For example, “survival” in the form of reporting of either dead or survived a procedure or a disease. Another example might be if the patients or participants in a trial or a study report whether they were diagnosed with a disease or was not diagnosed with disease, that outcome would be an example of a binary outcome, or dichotomous outcome. These outcomes are measured in terms of proportion of the participants with desired outcomes in a sample. For example, Brewer et.al. (2011) conducted a randomised controlled trial on 88 nicotine dependent adults to test the efficacy of mindfulness based training (MT) and compared this with American Lung Association’s Freedom From Smoking treatment. They measured the effectiveness of MT using self report of participants on their smoking behaviour and calculated rates of smoking cessation following either treatment. This is an example of how dichotomous or binary outcomes are reported [3].
2. Continuous outcomes. – These include outcomes that are measured on a scale where the boundary of the levels of the measurement of outcomes overlap. Such examples include measures of systolic and diastolic blood pressure measured in mmHg, measures of blood sugar control measured by mmols/L or measured by HbA1c, etc. The measures are reported in terms of either mean differences or standardised mean differences (explained below).

3. Ordinal Data. – These outcomes data are measured on rank ordered scales. Examples include quality of life on a scale between say 1 and 5 where 1 indicate very low values and 5 indicate very high values. These are again measured in terms of percentages of participants who are in each of the scores on the scales.
4. Time-to-event. – A time to event outcome denotes a length of time between initiation of the intervention (for clinical trials or intervention trials) or initiation of the observation (for observational epidemiological studies). For example, if in a study the objective of the investigators to compare the length of time from admission to discharge between intervention and control arm participants, then that outcome is a “time-to-event” outcome. Similarly, in cohort studies, often investigators are interested to study the length of time before the first case of disease appear following exposure (and those who were not exposed to specific exposure variables). Here as well, the length of time to the emergence of disease in participants is considered as a “time-to-event” outcome. In this chapter, we shall discuss binary and continuous outcome but skip other outcomes (“time to discharge” and ordinal outcomes”) as beyond the scope for this chapter.

How to abstract Data for binary outcomes and continuous outcomes

For abstraction of data from binary outcome variables, it is helpful to construct a two by two table and fill in the cells as follows:

Table 3. Abstraction of Data Elements for Studies that have binary outcome variables

Exposure or Intervention	Outcomes	Outcome Did
	Occurred	Not Occur
Exposure/Intervention Occurred	A	B

Exposure/Intervention Did Not Occur	C	D
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In the above table, A == number of participants who received the intervention or who were in the exposure arm of the study and ended up with the outcome of interest. Likewise B, C, and D refer to the number of participants in the trial or study where corresponding relationships between exposure or intervention and outcomes were recorded. Accordingly the risk ratios are defined as Rate Ratio or Relative Risk Estimates = $[A / (A + B)] / [C / (C + D)]$ (Or, rate of outcome among the exposed or intervention group versus rate of outcomes among the control group) Odds Ratio = $A * D / B * C$ For randomised controlled trials, clinicians are also interested in studying risk differences and associated numbers needed to treat that are expressed in the form of inverse of risk difference (1 / Risk Difference). The Risk Difference is given in the following formula: $[A / (A + B)] - [C / (C + D)]$.

However, the interpretation of risk difference requires that the baseline risk should be kept in perspective. For example, Nissen et.al. (2004) conducted a randomised controlled trial to compare the effect of intensive versus moderate lipid-lowering therapy on progression of coronary atherosclerosis. In order to do this, they conducted a double-blind, randomised active control multi-centre trial (Reversal of Atherosclerosis with Aggressive Lipid Lowering [REVERSAL]) at 34 community and tertiary care centers in the United States comparing the effects of two different statins administered for 18 months. Intravascular ultrasound was used to measure progression of atherosclerosis. Between June 1999 and September 2001, 654 patients were randomised and received study drug; patients were randomly assigned to receive a moderate lipid-lowering regimen consisting of 40 mg of pravastatin or an intensive lipid-lowering regimen consisting of 80 mg of atorvastatin. They found that C-reactive protein decreased 5.2% with pravastatin and 36.4% with atorvastatin. Based on this information alone, the risk

difference for reduction of C-reactive protein was $36.4\% - 5.2\% = 31.2\%$ and favoured atorvastatin over pravastatin. When translated to numbers needed to treat, this would indicate about 3 patients would be needed to be treated with atorvastatin (compared with pravastatin) to register one additional person's benefits for C-reactive protein [6] .

In cases where outcomes variable is “continuous”, two measures are mean difference and standardised mean difference. The formulae for these two measures are as follows:
Mean Difference = Mean of the outcome variable for participants in the treatment arm - Mean for the outcome variable for participants in the control arm
Standardised Mean Difference = Mean for those in the treatment arm - mean for those in the control arm / Pooled Standard Deviation

The standardised mean difference is used for those outcome variables where the units of measurement for the same outcome variable are different for different studies. Consider a meta analysis of control of blood sugar among diabetics where the outcome variable is concentration of HbA1C . This variable can be reported as measured in National Glycohemoglobin Standardization Program (NGSP) percentage values; alternatively, this can be measured in terms of International Federation for Clinical Chemistry (IFCC) reference method in mmol/mol units. As these are different units of the same outcome, a common comparable measurement strategy of the outcomes is in the form of standardised mean difference in the measure.

In general, different software packages are used for meta analysis, and these software packages often specify the level of outcome variable and entities required for analysis. For example, in the popular software package STATA, if you conduct meta analysis using the routine referred to as “metan”, you will need to provide either three variables, or four variables, or six variables, depending on the type of information you can provide the software. If you decide to use Odds Ratios, Hazard Ratios, or Rate Ratios or Relative Risks along with their 95% Confidence Intervals, then you will need to provide the

software three measures of effect estimates: the Odds Ratio (or the Relative Risk or Rate Ratio or Hazard Ratio; the upper, and the lower boundary estimates of the confidence interval). Usually these values are provided after transforming them to their logarithmic values, and the software in turn provides the estimates after converting the figures. On the other hand, if you can construct the two by two tables, then the four data points as outcome variables can also be provided; finally, if the effect estimate of interest is mean difference or standardised mean difference, then the software needs to be provided with the sample size, the mean difference between treatment and control group and the corresponding standard deviations.

A common problem is that, often study authors present data in the form of numbers of participants, relative risk estimates and p-values alone, rather than providing the readers data enough to abstract the numbers of participants in each arm to enable construction of two by two tables for the concerned study. In these cases, depending on the sample size presented, either z-values or t-values are estimated and then from these estimates standard deviations are worked out (these are the situations where statistical advices become essential to proceed). In other instances, you can easily construct a two by two table for some studies, while for others, authors may present only risk ratio estimates with 95% confidence intervals indicating lower and upper limits of the confidence intervals and the number of participants in the study (in each arm). In these cases, the analyst needs to estimate the point estimates of effect and associated standard deviation (SD), but all studies for the meta analysis should use the same measures. If in some studies report relative risks and other studies report numbers that would enable estimation of two by two tables, then for all studies relative risks are reported along with standard deviations to estimate the summary effect measure.

Step Five: Assess Whether the Studies are Homogeneous

In a meta-analysis, the researchers answer the following three questions:

1. What is the overall (summary) relationship between the treatment/intervention/exposure and the health outcomes? Or put in another way, is there evidence that the intervention is associated with the outcomes under study?
2. Is this association consistent across the studies that constitute the meta analysis?
3. Are all studies that would have been captured contribute to the pooling of results? Is there a bias introduced in the way studies were collated to introduce selection bias because of the way studies were selected for publication (publication bias)?

The first two questions are addressed in a meta analysis by pooling of data from studies and by statistically testing for the presence of heterogeneity in the study findings. In general, when a meta-analysis is conducted, a number of different studies with diverse populations and different measures are included. These studies are based on different population and as such are different from each other in several respects (they do share commonalities such as study design, and study aims and objectives). As a result, although studies are so selected to have very similar interventions (as a matter of fact, identical or same interventions or same exposures) and outcomes (health outcomes), there can still be differences in profiles of participants or differences in the quality of the studies, or the methods used in the studies. The differences in the participant profiles are known as “clinical heterogeneity” and differences in the method of execution of the studies themselves are known as “methodological heterogeneity”. Beyond these two sources of heterogeneity, variability is also observed in the magnitude and direction of the effect size between the intervention or exposure and health outcomes. This diversity is referred to as statistical heterogeneity and refers to the extent that the results differ from each across the different studies included in the meta

analysis. As long as these differences are so small that they do not statistically significantly differ from a centrally pooled estimate, these studies are known as “statistically homogenous”. Such homogeneity can be tested commonly in two ways:

1. Simple chi-square test of homogeneity. – Here, the number of studies are tested in a framework of hypothesis testing. The null hypothesis states that the effect sizes of individual studies are same, while the alternative hypothesis states that the effect sizes are different from each other (heterogeneity). In the chi-square test (the measure is also known as “Cochran’s Q”) with $N - 1$ degrees of freedom (where N = number of studies included in the meta analysis) provides a measure of heterogeneity. If the p-value is less than 0.05 (or less than 0.10 or a pre-specified cut-off), then the studies are considered to be statistically heterogeneous. However, measurement of heterogeneity in this manner has the problem that if the meta analysis includes a large number of studies, then the chance of statistical heterogeneity also proportionately increases even if the studies are similar to each other to a large extent. To address these concerns, another test, I-square test of heterogeneity is used.
2. I-square test of homogeneity. – The I-squared test of heterogeneity is expressed by the following formula, $I\text{-squared} = [(Q - df) / Q] * 100$ and expressed as a percentage, where Q = Cochran’s Q (see above), and df = degrees of freedom where given by $N - 1$ where N = number of studies. According to Higgins et.al. (2002), I-squared is interpreted as thresholds as follows:
 3. 0-40%: the heterogeneity might be important
 4. 30-60%: may represent moderate heterogeneity
 5. 50-90% may represent substantial heterogeneity, also 75% and above: considerable heterogeneity

Interpretation of tests of homogeneity. – Use the p-values carefully and if the p-value is greater than 0.05 or 0.10, this indicates that the studies cannot reject the null hypothesis. The null hypothesis in this case indicates that the studies are not heterogeneous or that the studies are homogeneous. This interpretation needs caution as if there are large number of studies, then the p-value can be less than the cut off yet the studies may be homogeneous [5].

What Happens When the test of homogeneity fails. –

In case of statistically significant heterogeneity, the analyst must explore features of studies that explain such heterogeneity. This can be done through careful review of the methods and results of individual studies or studies in groups; also, analysis of subgroups of studies based on predefined criteria (also quality assessments) are important. A common statistical way to conduct subgroup analyses is to conduct meta-regression, where the pooled effect estimate is regressed on identified features of the studies and searched for regression lines that explain how individual study features might be associated with the variability in the effect estimates.

In case of significant heterogeneity where there are also significant differences in the directions of the effect estimate, an average estimate of the effectiveness may be misleading (for example, imagine conducting a meta analysis on the effectiveness of an intervention on survival for post-operative patients; now, in that meta analysis, you found statistical heterogeneity; over and above, some studies indicate that interventions have protective effects on the survival (that is, they increase survival) while other studies indicate that the interventions actually increase the risk of death or reduce the survival probability). In this situation, a meta analysis is best not conducted by statistically pooling data from the studies, but a narrative review can be attempted to summarise the key features of the studies and summarise study findings; also, a

systematic review need not contain meta analysis. It is sufficient to conduct a narrative synthesis of data and explore the causes of such heterogeneity. Another option might be to perform a random-effects meta analysis – the studies are assumed to be part of a “universe of similar studies” and therefore this meta analysis can accommodate the fact that the studies can be so dissimilar with each other that their effect sizes may vary significantly. In summary, in presence of statistical heterogeneity, in all cases, an exploration of the causes of heterogeneity should be attempted, using subgroup analysis; additionally, if there is also additional variability in the direction of the effect measures, then it is best not to pool the study results but conduct a thorough exploration of the causes of such heterogeneity. In case where the direction of effect measures do not vary, in addition to exploration of the causes of such heterogeneity, a random effects meta analysis may be conducted.

Step Six: Conduct Fixed Effects or Random Effects Meta Analysis

In those situations where formal statistical pooling of the study results are warranted, the goal of meta analysis is to arrive at a summary measure of the overall effect estimate based on individual study effect sizes. These individual studies are obtained based on specified research questions and active search of the literature databases and indeed other sources of information, such as trial registries and often studies are obtained in consultation with individual authors and investigators. In establishment of the association between an intervention and an outcome (alternatively an exposure and an outcome), two questions that aim to characterise the nature of this association are:

1. Is this association summarised here in the meta analysis a definitive based on the studies that have been studied? Or
2. Is the association summarised is an indicator of the direction and magnitude of the association in a general sense that is expected in such an association?

These questions may seem pedantic. Consider the first question: in a meta analysis this question is based on an assumption that the studies included in the meta analysis by themselves sufficiently summarise the relationship between the intervention (or exposure) and the outcome. Such a model of meta analysis to characterise the relationship is known as “fixed effects model meta analysis”. The second question, on the other hand, indicates that the studies included in the meta analysis actually constitute a sample of studies out of all studies possible in a universe of similar studies. According to Diana Petitti (1999), these two models of meta analysis answer two different questions [8] . While fixed effects model answer a question for instance, whether intervention X was associated with the outcome O in the studies analysed, a random effects model answers quite another question: whether intervention X is likely to be associated with the outcome O. In turn, random effects meta analysis results in summary estimate that is closer to the null estimate and that, the associated confidence interval is wider than what is obtained in a fixed effects meta analysis.

Example: Do Whites Responds better than Blacks to ACE Inhibitors for the treatment of Hypertension?

Peck et.al.(2011) conducted a meta analysis of randomised controlled trials to test the relative responses to ACE Inhibitors of Whites compared with Blacks, and identified 16 studies where the authors investigated differences in systolic and diastolic blood pressures of Whites and Blacks. For this particular illustrative example of pooling data for meta analysis, we pool only results of diastolic blood pressure differences between Blacks and Whites and conduct a meta analysis. We presume that the initial steps of meta analysis, framing of research question, searching of the literature, identification of the studied, and critical appraisal of the studies themselves and identification of the risk of bias were all completed so these are not repeated [7]. Here, we are interested in three aspects of meta analysis:

1. What evidence or effect size exists to suggest that there is a difference in response for Blacks and White respondents in their diastolic blood pressure to ACE Inhibitors?
2. Is this response or effect size consistent among the studies considered for this meta analysis?
3. Is there a significant publication bias in the studies?

We first test whether the studies were sufficiently homogeneous or whether the studies were grossly heterogeneous. The readers are encouraged to read the main meta analysis (see reference section), but in this case, our interest is only on statistical tests of heterogeneity. We note that otherwise in terms of recruitment of the participants, the methodology of research, the studies were similar (that is, the studies were clinically and methodologically similar). Let's review the statistical tests of heterogeneity:

- Heterogeneity chi-squared = 36.75 (d.f. = 15) $p = 0.001$
- I-squared (variation in WMD attributable to heterogeneity) = 59.2%

These figures suggest statistically significant heterogeneity. In both chi-square tests and I-squared tests (see above), we also note that the studies are moderately heterogeneous. However, as the studies were otherwise found to be similar and this question (whether there is difference in response to ACE-Inhibitors for different races is a generic question), therefore, a random effects meta analysis may be appropriate for this question, rather than attempting either a fixed effects meta analysis or discarding meta analysis altogether. This leads us to answer the second question, "What evidence exists about the pooled response of the White and Black races in response to ACE Inhibitors as measured by diastolic pressure?"

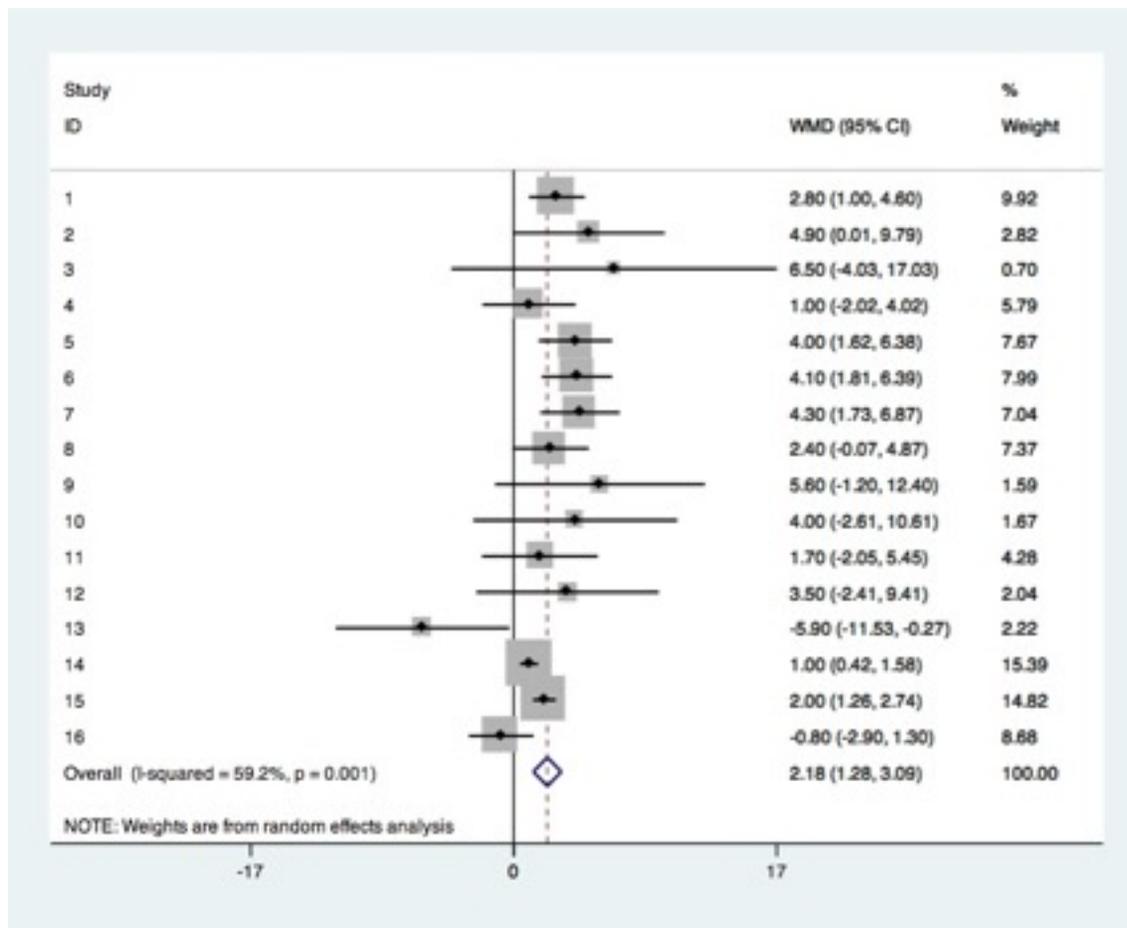


Figure 3. Forest Plot

This graph is known as a “Forest Plot”. Here, individual studies are plotted on the y-axis. The Pooled estimate or the summary effect size is presented in the form of a diamond shaped figure is known as “Forest Plot”. The sample size of each study is indicated by a shade around their point estimate. The dark straight line around which the studies are arranged indicate the null. In this case the mark is “0”, indicating no difference in diastolic blood pressure changes recorded between Blacks and Whites; while positive direction indicates that Whites have recorded larger changes and negative values indicate Blacks have recorded larger changes. The dotted line with a “diamond

shaped figure” at the bottom indicates the pooled estimate, in this case measured using the DerSimonian-Laird method of random effects meta analyses. This figure shows that the pooled estimates indicate that compared with Blacks, whites registered a larger change in the diastolic pressure (2.18 mmHg, 95%CI:1.28 - 3.09) and thus, this figure suggests that Whites, compared with Blacks, are more likely to respond to ACE inhibitors in their diastolic blood pressure measurements. In this meta-analysis, studies that have a larger sample size were given larger weights compared with smaller studies.

Is this conclusion is based on considering all relevant studies?

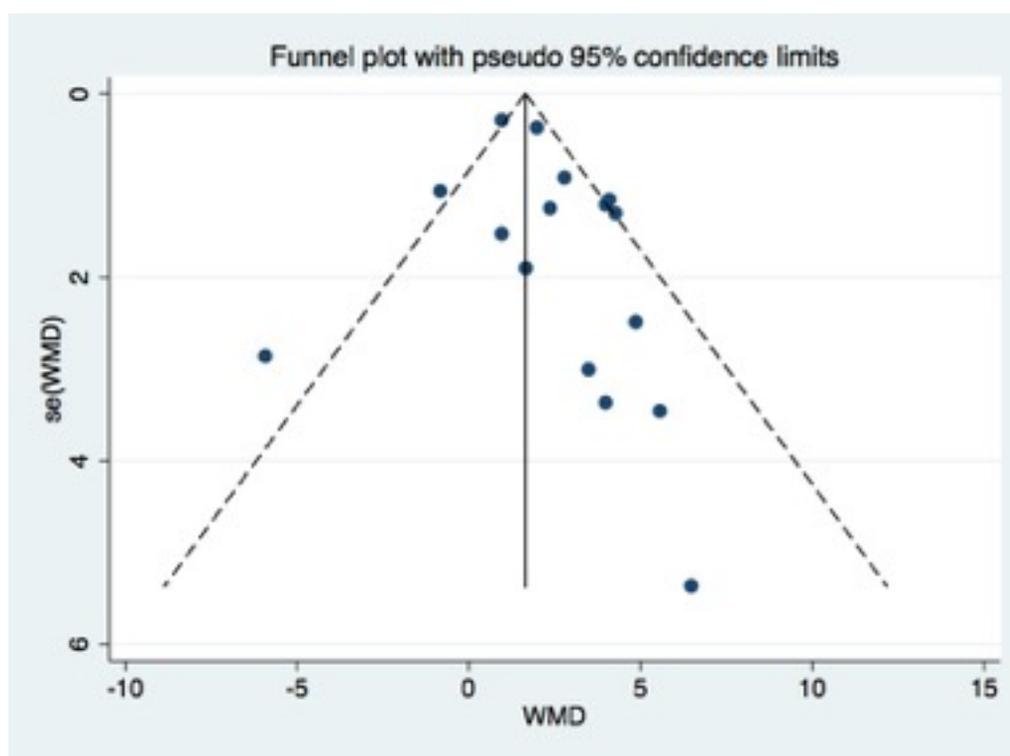


Figure 4. Funnel Plot

Figure 4 shows construction of a Funnel Plot for Publication Bias

The above figure shows a funnel plot of the association between mean differences in diastolic blood pressure in response to ACE inhibitors among Blacks and Whites. Data taken from Peck et.al. (2011) study. Note that the left lower part of the graph is empty indicating publication bias.

To answer whether the meta analysis was based on all relevant studies, evidence of publication bias is tested using a funnel plot (the boundaries of such a plot takes the shape of an upturned funnel, hence the name). A more formal statistical test is not available for further analysis of this graph. The above graph demonstrates a funnel plot. As can be seen in this plot, weighted mean differences in the diastolic pressures of the two groups are plotted on the X-axis and standard error of the mean differences are plotted on the Y-axis. This is done to check visually whether a pattern can emerge such that small or negative studies that are either missed or disproportionately presented in that matrix that would otherwise be present. The mouth of the funnel points downwards where studies that are of low power are presented (they are considered to be of low power as the standard error is quite high and hence they are located to the bottom of the Y axis), but note as well that because of this, we'd expect that the positive and negative studies will be fairly evenly distributed. As the power of the studies will increase, we'd expect that the studies will converge towards the summary estimate that we have seen (the summary estimate line is the dark line). A solid dark line runs through the centre and indicates the pooled effect estimate. Studies that have large sample size and therefore small standard errors are located on the top or tip of the funnel, and studies are arranged according to their effect size but also according to their power or sample size and therefore weights. Note that no studies are located in the left lower quadrant of the funnel plot. This indicates that studies that low powered studies with negative findings were not omitted in this meta analysis. This indicates publication bias in this study.

As in this meta analysis, we noted heterogeneity, therefore a subgroup analysis of the studies is important. While subgroup analyses can be conducted in different ways and indeed, in the study the authors reported subgroup analyses, one common strategy is to conduct a subgroup analysis by conducting a regression analysis. In the linear regression analysis, referred to as “meta regression”, the subgroup can be considered on any study characteristic (ideally measured on a continuous scale) and the y-variable (or the outcome variable) is the outcome variable or a measure of the outcome variable or effect size. The linear model is used to identify whether specific study characteristics can explain why the results might have been different. A statistically non-significant linear model may indicate that the particular explanatory variable did not explain variability in the distribution of the effect size in the studies.

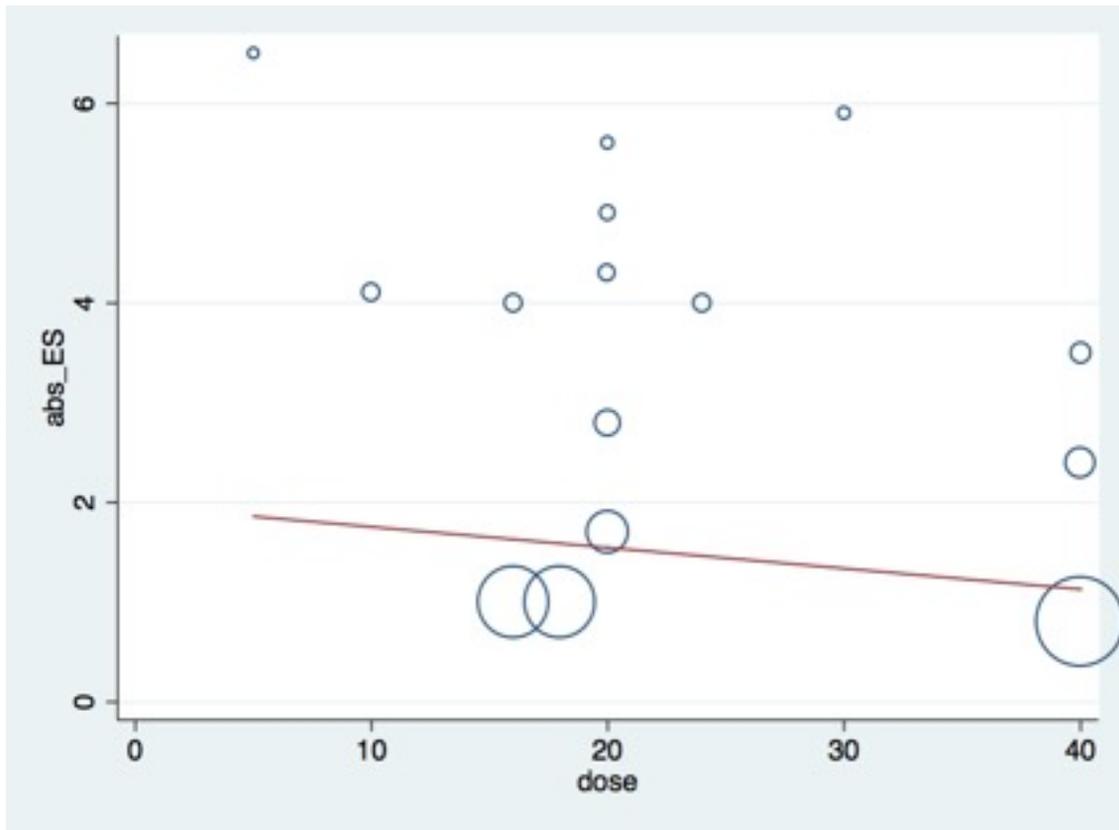


Figure 5. Meta Regression

Figure 5 shows Meta Regression of the Black and White differences in diastolic blood pressure following ACE Inhibitor Therapy

The above figures shows a graph of Meta-Regression of the studies included in the Peck et.al. (2011) meta-analysis, where effect size in terms of reduction in diastolic blood pressure was regressed on the dosage of antihypertensive medication that was administered.

In this meta analysis, given the heterogeneity of the studies in finding the association between ACE inhibitor dosage and response for diastolic blood pressure, a reanalysis was done. In the reanalysis of the, the effect size of the studies was regressed on the

dose of ACE inhibitors administered. It was found that in the regression, that the changes in the diastolic blood pressures decreased as the dosage increased, however, this reduction was not statistically significant (beta coefficient for dose = -0.03, 95% Confidence Interval: -0.11, 0.06, $p = 0.626$)

Thus, to recapitulate the basic principles of data analysis in meta analysis, in the beginning, it is important to decide based on the research question and objective of the meta analysis whether the meta analysis is to answer the larger question of “what is possible” or whether it is reasonable to assume that the studies belong to a larger universe of studies of which these form a sample, and therefore a random effects meta analysis may be attempted. Alternatively, a formal test of statistical heterogeneity of the studies is conducted and one of the several measures are estimated to test statistically, but also clinically and methodologically how similar are the studies. If the studies are similar, then both fixed effects and random effects meta analyses are attempted and the summary estimates are confirmed and discussed. On the other hand, if the studies show considerable heterogeneity, then either a meta analysis is not attempted, or several subgroups are analysed. In all cases, causes of such heterogeneity are explored, using meta regression and other strategies. A search for publication bias is reported as well, using funnel plots or other visual inspection tools such as L’Abbe’ plots.

In conclusion ...

To conclude, a meta analysis is a form of review where the analyst conducts a systematic review but where the scope of the review extends beyond narrative synthesis of information and where statistical data analysis involves comparing two alternative forms of treatment or exposure. One of the two treatments can be a novel or one form of intervention while the other can be an alternative intervention or a placebo. In conducting the meta analysis, the analyst starts with a research team consisting of

clinicians or domain experts (domain experts are those individuals or professionals who are knowledgeable and have experience in the matter under study), information specialists and search experts who can conduct robust searches of literature, statisticians and database experts. The next task for the meta analyst team is to frame a set of research questions using the PICO method, and search comprehensively all available literature on the topic specific to the question. The next steps are close reading of the retrieved studies, search for grey literature, abstraction of data and organisation of the database to prepare for analysis. A set of effect estimates are decided upon, and in general, meta analyses should answer three related questions: whether an evidence exists that the intervention or the exposure is statistically associated with the outcome, whether the results are similar across the studies and whether studies were omitted resulting in publication bias that could be uncovered? Also, at the end of the study subgroup analyses are conducted to indicate robustness of the analyses and cutting the data in various ways to examine if subgroups were to reveal important insights into the data obtained from the primary studies.

In general, in deciding to conduct meta analysis, it is important to keep in mind the comprehensiveness of the search process and the heterogeneity of the studies included in the meta analysis. This is where a decision whether to conduct meta analysis or not at all need to be made. Assessment of study heterogeneity is particularly important. Moher et.al. (2009) have proposed preferred formats of reporting meta analyses (PRISMA) and these in general, these emphasise common elements such as clearly mentioning meta analysis or systematic review on the title, structured abstracts, and clear description of the process of screening articles for the review.

In this chapter, the emphasis was on conducting pairwise meta analyses using a standard approach of identifying studies that compare only two interventions or only two exposure conditions for the same outcome. Newer approaches to meta analyses also

include network meta analyses where more than one intervention or one exposure for a range of outcomes (or a matrix of interventions and outcomes are studied). However, a detailed discussion of network meta analyses is beyond the scope of this review. A place to start while embarking on a meta analysis is Cochrane Collaboration (<http://www.cochrane.org>) which is a rich repository of meta analyses and systematic reviews on a range of topics. Cochrane Collaboration also provides training and offers a free software package to manage systematic reviews and meta analyses easily – the Revman package. While Revman software allows organisation and conduct of meta analysis easy, for additional analyses, statistical software packages such as R and Stata have several packages and routines that enable analysts to conduct meta analyses effectively. It is hoped that this introduction to meta analysis will enable the reader to embark on reading, interpreting, thinking about meta analyses that can be used for their own purposes. When conducted well and appropriately, meta analyses can provide invaluable information on the comparison of different treatment approaches and exposure-outcome associations for Epidemiological studies.

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