How to do Systematic Review and Meta-analysis

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Objectives

By reading this paper students and readers are expected to be able to: Differentiate narrative review, systematic review, and meta-analysis; Know the steps of conducting a systematic review and meta-analysis; Appraise a systematic review article; Interpret the forest plot and pooled result; and Understand, explore, and deal with heterogeneity.

Clinical Scenario

In May 2007, Steven Nissen and Wolski published a systematic review in the New England Journal of Medicine entitled, "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes".(1) Rosiglitazone (Avandia) belongs to the Thiazolidinedion group that was approved by FDA in 1999 as an antidiabetic drug that increases insulin sensitivity. Physicians prescribed this drug for patients as an adjunctive therapy for those who have an uncontrolled HbA1c level (indicative of poor management of hyperglycemia) and/or for diabetics who refuse insulin injections. The result of Nissen's systematic review was shocking to all physicians who used Avandia, especially when around 7 million people were using it with sales exceeding US$3 billion. Nissen and Wolski combined data from 42 clinical trials with a total of approximately 15,000 patients on Avandia and 12,000 on controlled treatments. Odds Ratios (OR) for acute myocardial infarction and cardiovascular death were 1.43 and 1.64, respectively. On appraising Nissen's systematic review, many flaws have been found in the methodology including: exclusion of studies with no cardiovascular events, unclear outcome definitions, problems with inclusion and exclusion criteria, study selection problems, and problems in the quality of the included studies. These caused many not to believe the results of Nissen and Wolski's systematic review.

Following Nissen and Wolski's review, other systematic reviews (with accepted quality) were published during 2007, and all supported its main conclusion of serious side-effects of Avandia. Avandia was withdrawn from the market based on the results of these systematic reviews.

What is a Review?

A 'review' is the generic term for any attempt to synthesize the results and conclusions of two or more publications on a given topic.

If the review is synthesized using systematic methods for searching, selecting, and appraising articles, it is called Systematic Review; while, if such methods were not implemented in full, it is called Narrative Review. Combining the results of studies to produce one pooled result is called Meta-analysis.

Most of the time systematic review has a pooled result (meta-analysis). The names of systematic review and meta-analysis are exchangeable because results of both methods are frequently presented together in the same report.

Narrative review:
It is a report or a detailed commentary written by an expert to consider the critical points of current knowledge including substantive findings of a particular topic. It may be part of a thesis and usually precedes a research proposal and results section.

Strengths:
• It offers broad overview of a topic, similar to a textbook chapter.
• It serves as a scientific resource by providing a bridge between the scattered articles on a topic and the reader who does not have time or access to track them down.
• It provides conclusions related to the scope and theory that individual empirical reports cannot normally address.

• It usually covers multiple background aspects of a disease such as natural history, etiology, epidemiology, signs and symptoms, diagnosis, treatment, and prognosis.
• It provides a comprehensive summary of results from a pool of primary studies.

Limitations:
• The summarized studies are chosen at the discretion of the author.
• Usually conducted with no explicit methodology procedures reported or vote counting.

Systematic Review
A systematic review combines all available research in order to answer a specific question that fits pre-defined eligibility criteria.

A systematic review can be considered a review report characterized by the following features:

1. A rigorous review of specific clinical question;
2. A systematic methodology and literature search; and
3. Explicit regarding information provided

Meta-analysis
Many systematic reviews contain meta-analyses. Meta-analysis is the use of statistical methods to integrate the results of independent studies into one pooled result.

Table 1: Differences between a narrative and systematic reviews

Item	Narrative Review	Systematic Review
The question	Many broad questions, more background type	One clinical foreground question
Search Methods	None	Explicit, comprehensive search strategy
Selection of studies	No inclusion or exclusion criteria	Explicit eligibility criteria for inclusion or exclusion of studies
Combining of results	None	The results are pooled together (meta-analysis)

Why do we perform Systematic Reviews?

Systematic reviews and meta-analyses use systematic method of searching and locating studies to minimize bias. This is achieved by combining high quality studies by searching electronic databases preferably with no restriction to language and including both published and unpublished articles. Combining studies together increases the sample size and minimizes the effect of random error in the overall appreciation of evidence. In addition, systematic reviews also can save the costs of conducting additional randomized controlled trials (RCT) to answer the same research question.

Six steps for conducting systematic review
1. A well formulated question
2. Finding studies
3. Selecting studies
4. Data extraction
5. Appraising studies
6. Combining results

Step 1: A well formulated question
A well formulated question is the first step in any research. Well-formulated questions will guide many aspects of the review process, including determining eligibility criteria, searching for studies, collecting data from included studies, and presenting findings. Converting the question into PICOT format is essential to define each component well. PICO was discussed in a previous chapter and T stands for type of study and time.

PICOT defines well the Population, the Intervention, the Comparison, the Outcome, and the Type of study, its duration and time it was conducted.

The question may be broad or narrow. A broad question for example is: antibiotics for treatment of UTI; while a narrow question is like: third generation cephalosporin for treatment of childhood cystitis.

Review authors will decide about the scope of their review, bearing in mind that a too narrow question may affect the generalizability of the results, while a too broad question, may affect the manageability of the project (i.e., authors may not be able to do the review due to resources consumption).

Step 2: Finding studies
A comprehensive search strategy that includes most relevant electronic databases (e.g., Pubmed, Embase and Cochrane library) in addition to non-electronic resources is necessary to retrieve all relevant studies. The choice of keywords (based on PICOT) is critical for the search. A good search is one with no language restriction, no date restriction, up-to-date, and includes both published and unpublished literature.

The bottom line is not to miss any relevant study until the date of manuscript submission.

Following are the resources to be searched:
1. Electronic databases
2. Hand or manual search
3. Full text journals and table of contents (TOC)
4. Conference abstracts and proceedings
5. Reference lists
6. Unpublished studies
7. Clinical trial registries
8. Grey literature
9. Pharmaceutical industry trial registers

1. Electronic databases: The aim of thorough search is to locate, as many as possible, relevant studies and not to miss an important study. A minimum of three essential databases must be searched, which are: The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE. Both free-text and subject headings should be used (e.g., Medical Subject Headings (MeSH). Searching MEDLINE alone is not sufficient to detect all RCT.
2. Hand search: Hand searching is complementing electronic database search because not all journals are indexed in electronic databases.
3. Full text journal search and table of contents: Many journals have an electronic full text either free of charge or with subscription.

Examples of free of charge websites:
• BioMed Central: www.biomedcentral.com/browse/journals/
• Public Library of Science (PLoS): www.plos.org/journals/
• PubMed Central (PMC): www.pubmedcentral.nih.gov/

Web sites listing journals offering free full-text access includes:
• Free Medical Journals: freemedicaljournals.com/
• HighWire Press: highwire.stanford.edu/lists/freeart.dtl

There are also a number of international initiatives to provide free or low-cost online access to full-text journals (and databases) over the internet, including:
• The Health InterNetwork Access to Research Initiative (HINARI) www.who.int/hinari/en/
• The International Network for the Availability of Scientific Publications (INASP) www.inasp.info/file/68/about-inasp.html, and
• Electronic Information for Libraries (EIFL) www.eifl.net/cps/sections/about

Table of Contents (TOC): Several organizations and journals, offer Table of Contents (TOC) services free of charge, normally through e-mail alerts or RSS feeds.

Examples of organizations offering TOC services
• British Library Direct (free): direct.bl.uk/bld/Home.do
• British Library Direct Plus (subscription): www.bl.uk/reshelp/atyourdesk/docsupply/roductsservices/bldplus/
• British Library Inside (to be replaced by British Library Direct Plus) (subscription): www.bl.uk/inside
• Current Contents Connect (subscription): scientific.thomson.com/products/ccc/
• Scientific Electronic Library Online (SciELO) - Brazil (free): www.scielo.br/

4. Conference abstracts and proceedings: More than 50% of clinical trials presented in conferences failed to be published. Those that are eventually published in full have shown to be systematically different from those that are never published in full (Scherer, 2007). Conference abstracts are identified by hand search and proceedings in CD Rom. A number of websites publish these abstracts:

• The BIOSIS databases (http://www.biosis.org/)
• The American Society of Clinical Oncology (ASCO): www.asco.org/ASCO/Meetings
• Biological Abstracts/RRM (Reports, Reviews, Meetings): scientific.thomson.com/products/barrm/
• British Library Inside (to be replaced by British Library Direct Plus): www.bl.uk/inside
• British Library Direct Plus: www.bl.uk/reshelp/tyourdesk/docsupply/productsservices/bldplus
• ISI Proceedings: scientific.thomson.com/products/proceedings/

5. Reference list: Reference lists of published systematic reviews, studies, or guidelines are convenient resources of studies. Useful resources are the Cochrane library, Trip database, NICE guidelines, SIGN guidelines and guideline.gov.

6. Unpublished studies: Not all completed studies are published. Finding and including unpublished studies minimizes bias. Publication bias occurs when the decision to publish is based on study results and not how the study was conducted (the method). Are Published studies enough? Studies with positive results are submitted and get published 2.5 times more than negative ones. Negative studies are less likely to be published.(11)

Publication Bias
Studies with positive results are more likely to be published, published rapidly, in English, have more than one source (duplication), and are cited more than negative studies.

All trials should be registered as early as possible even at protocol stage for example:
• Clinical trial registry: www.clinicaltrial.gov
• The National Clinical Trials Registry: Cancer trials
• National Institutes of Health Inventory of Clinical Trials and Studies
• International Registry of Perinatal Trials
• Meta-registry of Trial Registries: www.controlled-trials.com

Publication bias may be presented visually by plotting and reviewing the funnel plot, which is a graph with (Y) axis representing the sample size, starting from the bottom with small sample size studies and ends at the top with large studies. The (X) axis represents effect measures of

individual studies. The line at the middle is the line of point estimate (not the line of no effect). Usually effect measures of studies will be distributed equally on both sides of the point estimate line with effect measures of small sized studies that are more in number and situated at the bottom of the curve. If publication bias is not a major issue, then an inverted funnel shaped, symmetrical curve is usually produced.

In case of publication bias, there is asymmetry of the funnel plot due to unpublished small and negative studies.

7. Clinical trials registries were established to prevent reporting bias including publication bias (i.e., ClinicalTrials.gov register: clinicaltrials.gov/)

8. Grey literature: Hirtle has defined Grey Literature as: Unpublished printed reports, but circulated papers, unpublished proceedings of conferences, printed programs from conferences, and the other non-unique material which seems to constitute the bulk of our modern manuscript collections (Hirtle, 1991). Conference abstracts and other grey literature have been shown to be sources of approximately 10% of the studies referenced in Cochrane reviews (Mallett, 2002). In a recently updated Cochrane

Figure 1: Forest plot with dotted line of pooled estimate and studies distributed equally

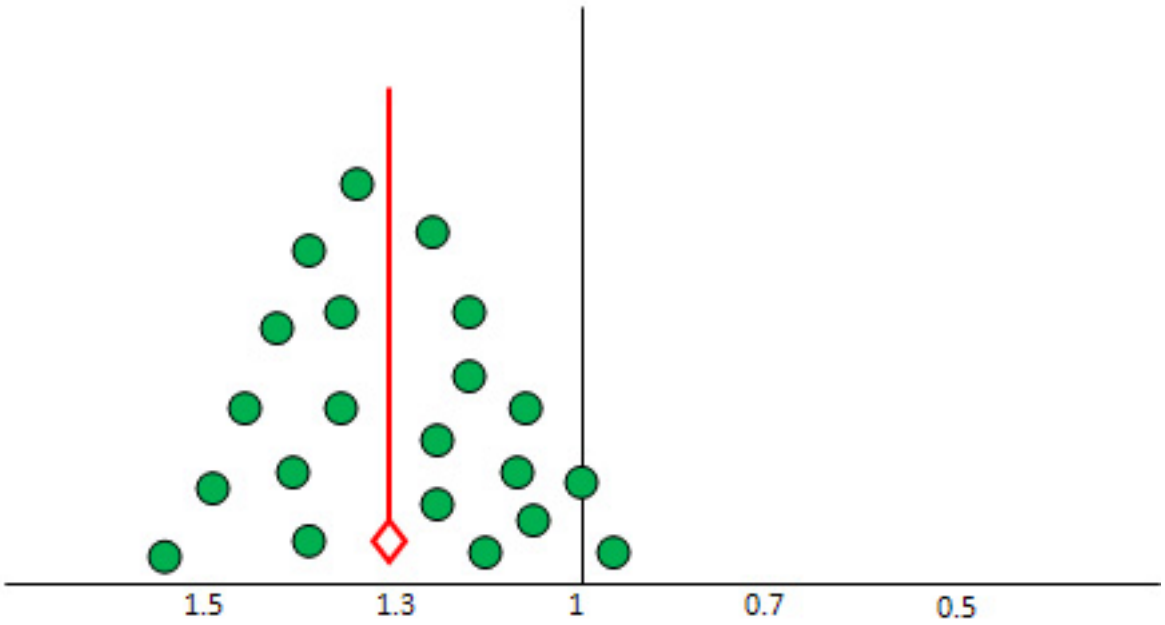


Figure 2: Funnel plot Y=100-1000, x= 1 no effect line, 1.2 1.1.6 the other side 0.8, 0.6, 0.4 with symmetrical distribution of studies

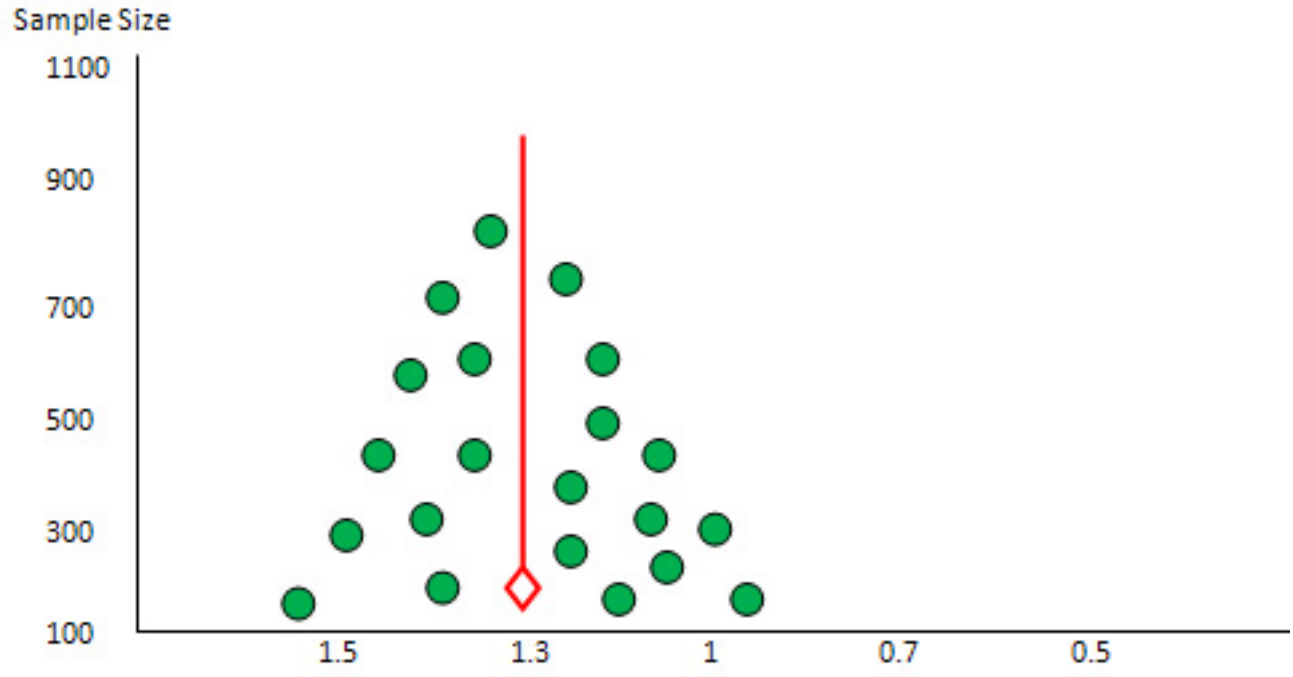
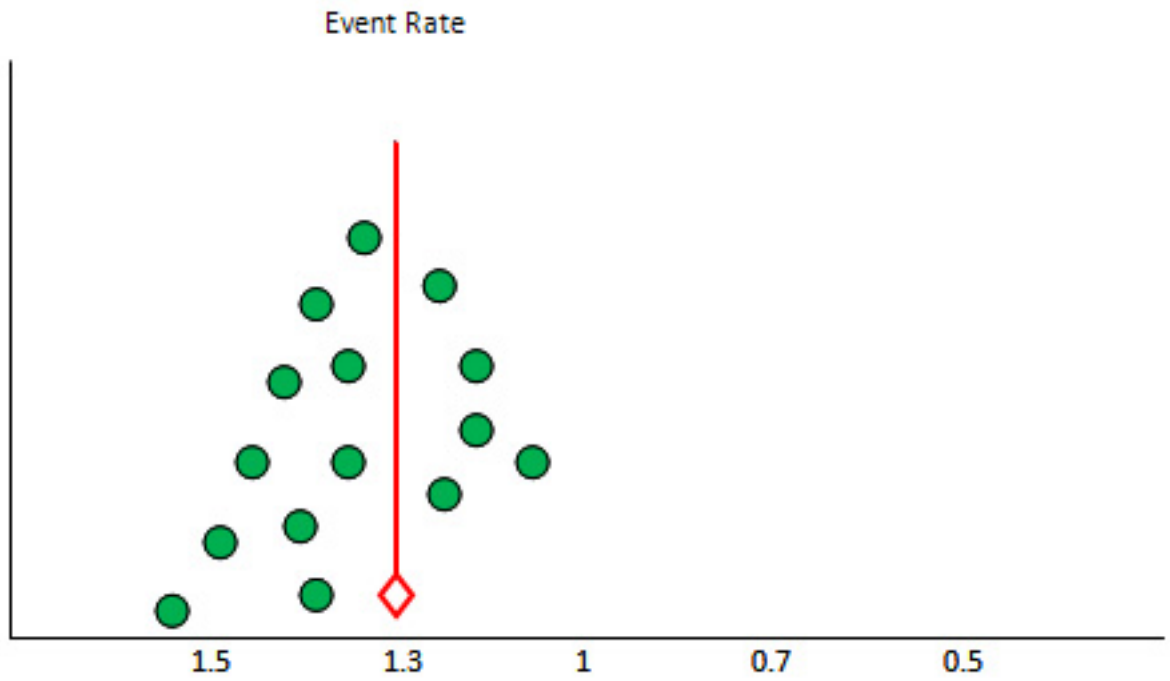


Figure 3: Funnel plot with asymmetry due to missing studies



methodology review, all five studies reviewed showed that published trials presented an overall greater treatment effect than grey literature trials (Hopewell 2007b). Grey literature may be found in the internet from the following resources:

• **ALA Internet Resources:** Gray Literature
• **GreyNet:** The Grey Literature Network Service
• **Science.gov** is a gateway to over 50 million pages of authoritative selected science information provided by U.S. government agencies, including research and development results.
• http://www.scienceaccelerator.gov/ Science Accelerator searches science, including R&D results, project descriptions, accomplishments, and more, via resources made available by the Office of Scientific and Technical Information (OSTI), U.S. Department of Energy.
• **The GrayLIT network:** A science portal of technical reports. From the Office of Scientific & Technical Information at the United States Department of Energy.
• Grey Literature Library for UK Archaeology.
• The International Journal on Grey Literature published one volume in 2000. The content may be limited to subscribers.
• **CiteSeerX** indexes some of the gray literature such as technical reports in computer and information science.
• **Open Grey Repository**, formerly OpenSIGLE.

9. Pharmaceutical industry trial registers: Most pharmaceutical industries keep registry for all clinical trials funded by them.

Step 3: Study selection

Researchers should apply the pre-specified inclusion and exclusion criteria in order to select the relevant studies. At least two reviewers are doing the selection of relevant studies independently.

A disagreement about whether certain studies should be included is resolved by discussion. The following steps are useful to do so:

1. Merge search results using reference management software (e.g., endnote) and remove duplicate records of the same report.
2. Examine titles and abstracts to remove obviously irrelevant reports (i.e., authors should generally be over-inclusive at this stage).
3. Retrieve full text of the potentially relevant reports.
4. Examine full-text reports for compliance of studies with eligibility criteria.
5. Correspond with investigators, where appropriate, to clarify study eligibility (it may be appropriate to request further information, such as missing results, at the same time).
6. Make final decisions on study inclusion and proceed to data collection.

Step 4: Data extraction

The systematic review process of obtaining necessary information from retrieved articles in specific forms is called data extraction. The nature of information extracted should be tailored to the review question. Details of the data extraction process and the data extraction form should be included in the review protocol. The latter should be piloted, refined, and linked to the future assessment of the study quality prior to the start of the systematic review. The use of electronic data extraction forms can facilitate obtaining relevant information from an article in a standardized way and can reduce the time for data analysis and production of tables.

Piloting of data extraction:

Ideally, data extraction forms should be piloted on a sample of included articles to ensure that the process will

be conducted in a comprehensive and standardized way. The process of data extraction should be assessed for both accuracy and consistency. The latter is usually evaluated by quantifying the inter-rater agreement beyond chance (Kappa) and is of particular importance in reviews where coding data will be employed.

Process of data extraction:
The primary aim of the data extraction process is to avoid human errors and subjective decisions, and hence the form should be valid and reliable as much as possible. In an ideal data extraction process, two researchers should independently perform the task; while a third researcher should be checking the forms for accuracy, completeness and consistency. The number and reasons of disagreements among data extractors should be reported and resolved by consensus among researchers first, or by arbitration in case a consensus could not be reached. If time and resources constraints limit the number of researchers involved in data extraction, the minimum acceptable process would be that one researcher should extract the data with a second researcher checking for accuracy and completeness. Blinding researchers to the journal and author details can be time-consuming but has been recommended to avoid observer bias in terms of selecting and extracting evidence from individual studies. However other investigators have reported a limited benefit of blinding in improving the accuracy of results.

Nature of extracted data:
The type of data extracted in the predefined extraction forms depends on the research question posed and the types of study designs included. The box below includes data that are most commonly extracted in systematic reviews for clinical trial.

Step 5: Assess Risk of Bias (ROB)
A bias is defined as a systematic error, or deviation from the truth, in results or inferences. Biases are not the same. Some have a minor effect on the validity of any study; while some can pose a substantial effect. Biases can lead to underestimation or overestimation of the true intervention effect. To what extent biases have affected the results of a study is difficult to answer. Studies included in systematic reviews should be classified into studies with low risk of bias, unclear, or high risk of bias.

In 1995, Moher and colleagues identified 25 scales and 9 checklists that had been used to assess the validity or 'quality' of randomized trials (Moher, 1995 and 1996).(14,15)

One commonly-used scale was developed by Jadad and colleagues for randomized trials in pain research (Jadad, 1996).(14) Cochrane collaboration discourage the use of this scale as it does not cover one of the most important potential biases in randomized trials, namely allocation concealment.

The Cochrane Collaboration's recommended tool for assessing risk of bias is neither a scale nor a checklist. It is a domain-based evaluation, in which critical assessments are made separately for different domains.

There are 5 possible sources of biases in individual studies:

1. Selection bias: What differentiates RCT from other types of studies is that it starts with balanced groups, i.e., the baseline characteristics of the groups is similar. This balance is due to two processes: (1) generation of randomization list by computer then the (2) distribution of subjects to the intervention and control groups by secret methods (concealment); by using serially numbered, opaque and sealed envelopes; or, by remote telephone call. Failure to do so can affect the validity of the study and lead to selection bias.
2. Performance bias: The intervention and control groups must maintain balance by blinding which should be masked until the end of the study. Everyone who is dealing with a patient or his data must be blind to who is taking what. The care provided to both groups must be the same. Failure to do so, can lead to what is so called performance bias.
3. Detection bias: If outcome assessors know who is taking what, they may deviate from the truth, and create bias in the evaluation of outcomes. Outcome assessors must be blind especially when the outcome is subjective (e.g., assessment of pain). Failure to do so can lead to "detection" bias.
4. Attrition bias: Attrition refers to any situation in which the outcome data of a particular subject is not complete or corrupted. It may be due to drop-out, cross-over, or the outcome data is not complete. When any of these situations happen, an attrition bias should be suspected.
5. Reporting bias: There are many types of reporting biases. Publication bias was described before. Within-study publication bias describes a condition when positive findings are reported more than negative ones.

Step 6: Meta-analysis
Meta-analysis is the statistical combination of results across the combined studies. There are many statistical packages to do so, mainly RevMan (The Review Manager), produced by Cochrane collaboration. It is free of charge for Cochrane reviewers or anyone doing systematic review. Another one is the comprehensive meta-analysis software (CMA); which is a commercial software that needs to be purchased. Another software for diagnostic meta-analysis is the Metadisc software, which is also free of charge.

The principle concept of pooling results together in meta-analysis is weighted average principle.

Example:
In class A, the average score of the 20 students is 50, while in class B the average score for the 10 students is 60. What is the average of the 2 classes?

(50 X 20) + (60 X 10)/ (20 + 10) = 48 (not 55)

To interpret the meta-analysis, one needs to answer 4 questions:

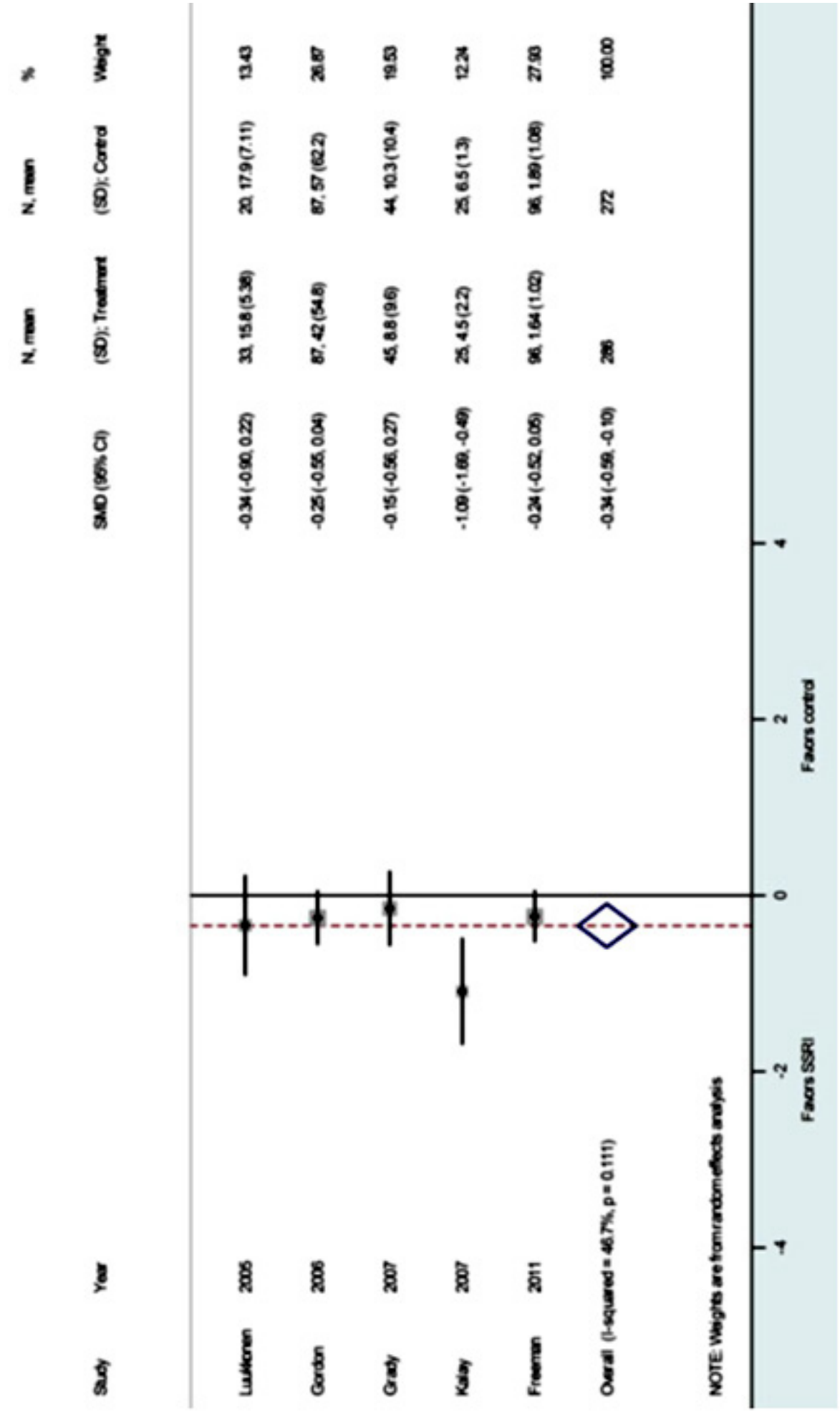


Figure 4: SSRI for hot flashes meta-analysis, improvement in standardized hot flashes

1. What is the direction of effect?
2. What is the size of effect?
3. Is the effect consistent across studies?
4. What is the strength of evidence for the effect?

Q1. What is the direction of effect? Is the pooled effect (point of estimate) at the site of control (favors control); or at the site of intervention (favors intervention); or crosses the no effect line (no difference of the effect between the intervention and the control). The line of no effect is (1) for dichotomous data, or (0) for continuous data.

Q2. What is the size of effect? The effect measure may be a relative value (RR, OR or HR) or absolute mean difference (MD) or standardized mean difference (SMD). The effect is presented as the effect measure (size) and the confidence interval (CI) or P value.

Q3. Is the effect consistent across studies? Inconsistency or heterogeneity across studies is the amount of variation of the results across studies. (This will be discussed later under heterogeneity.)

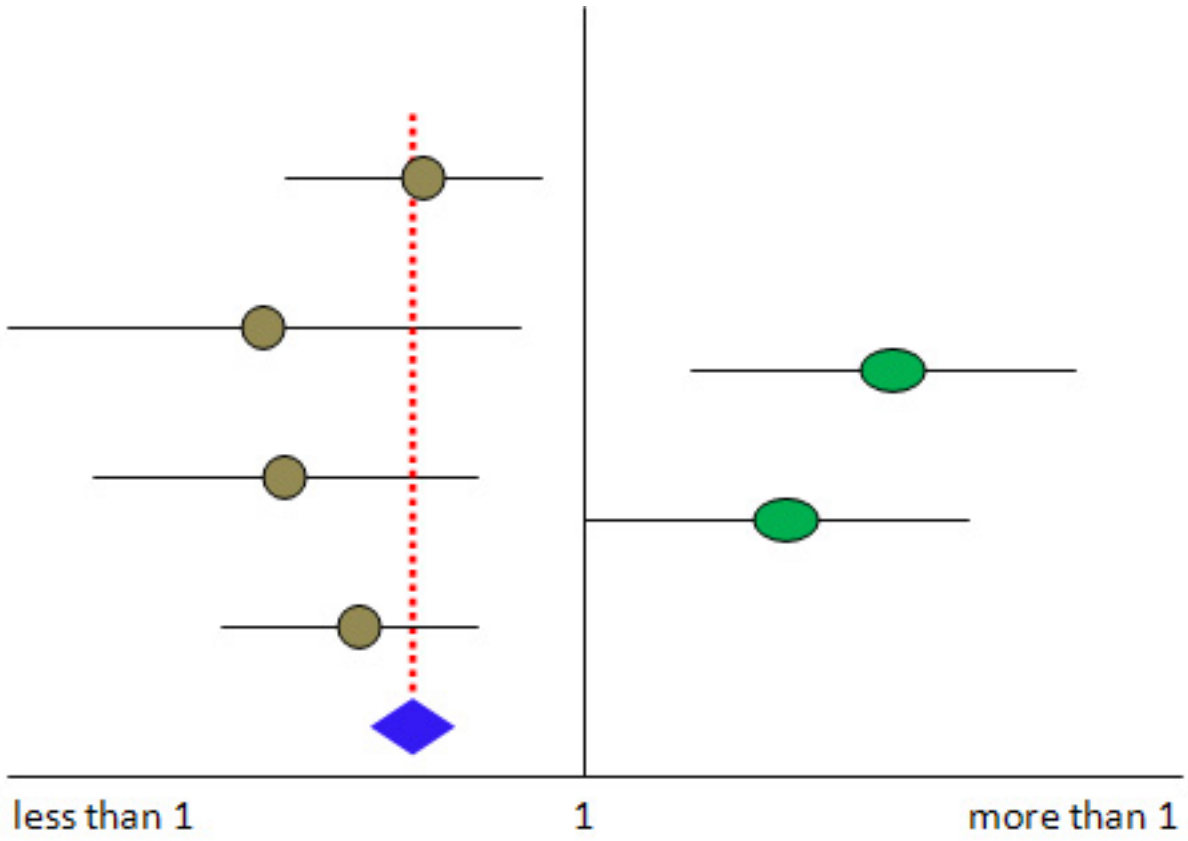
Q4. What is the strength of evidence for the effect? This needs judgment in addition to the effect measure. It depends on the study design and risk of bias.

Heterogeneity (Inconsistency)

1. What is heterogeneity? Variation of results across studies that may be due to random effect (no statistical significance) or due to heterogeneity (statistical significance). It may be due to diversity in PICO elements, differences in population, intervention or outcome measures (called clinical heterogeneity); or may be due to bias, e.g., variation in study design, conduct or attrition between individual studies (called methodological heterogeneity).

2. Identifying and measuring heterogeneity
There are 3 methods to identify heterogeneity:

a. Eye ball or visual overlap: The extent of overlap of the CI in the included studies determine its consistency. Draw an imaginary line from the pooled effect result. If there is one study or more that are not crossed by this line, it means that there is heterogeneity.



b. P value: The chi square test of heterogeneity, when it is less than or equal to 0.05 it indicates presence of heterogeneity.
c. I^2 test: The I^2 test is a modified chi square test, but it is a quantitative test, that represents the percentage of heterogeneity. It is the proportion of total variability explained by heterogeneity. How much is too much heterogeneity? Low heterogeneity, when I2 is 25%, moderate when I2 is 50% and high when I2 is 75%.

3. Strategies for addressing heterogeneity: How to deal with heterogeneity
a. Recheck the data of individual studies.
b. Do not do meta-analysis in case of considerable heterogeneity, especially when the result is in favor of intervention.
c. Do subgroup analysis: it is the splitting of all participants' data into subgroups, based on any of the PICOT elements. Subgroup analysis must be pre-specified, because ad-hoc subgroup analysis of multiple outcomes may be misleading

due to false positive and false negative results.
d. Ignore heterogeneity: Fixed effect-model (FEM) ignores heterogeneity.

Fixed Effect Model:
In non-heterogeneous studies, there is one true treatment effect.
Results are combined with the studies weighted according to the inverse of within-study variance. The statistical tests used are:

- Mantel-Haenszel method for relative risk (RR)
- Peto's method for odds ratio (OR)

Assumptions:
1. Only a single true value underlies all the study results;
2. If all studies were infinitely large, they would yield identical estimate of the effect; and
3. Each study estimates a difference underlying true effect and the distribution of these effects follows a normal curve.

The combined effect size is given by a weighted average of the effect from each individual study and the weight for each study is the inverse of its variance.

e. Perform Random-effect model (REM).

Random Effect Model:
While in heterogeneous studies, there are multiple true treatment effects.
Results are combined with the study weighted according to the inverse of the sum of within-study variance and among-study variance, the statistical test used is DerSimonian and Laird method.

Assumptions:
1. Individual studies are estimating different treatment effects;
2. The treatment of different studies has a distribution with some central value and some degree of variability.

The excess variation should be taken into consideration in computing the combined estimate.

The procedures to obtain a combined estimate is the same as a fixed-effects model, i.e., weighted average, which is the inverse variance in FEM while in REM is the inverse "variance plus the excess variation."

e. Do Sensitivity analysis: Heterogeneity may be due to outliers that are totally different than the rest of the studies. It is not logical to exclude them, but in a few occasions, if the outlier is blamed as the cause of the variability, it may be excluded.

If the result after excluding the study is within the CI of the result before exclusion, then the study could be excluded without affecting the result. But if the result after exclusion is changed, i.e., not included within CI of the result before exclusion, in this case you cannot exclude it.

Figure 5-A: Hypothetical forest plot that includes 4 studies favoring one intervention while 1 study (outlier) favors another intervention; this study may be the cause of heterogeneity.

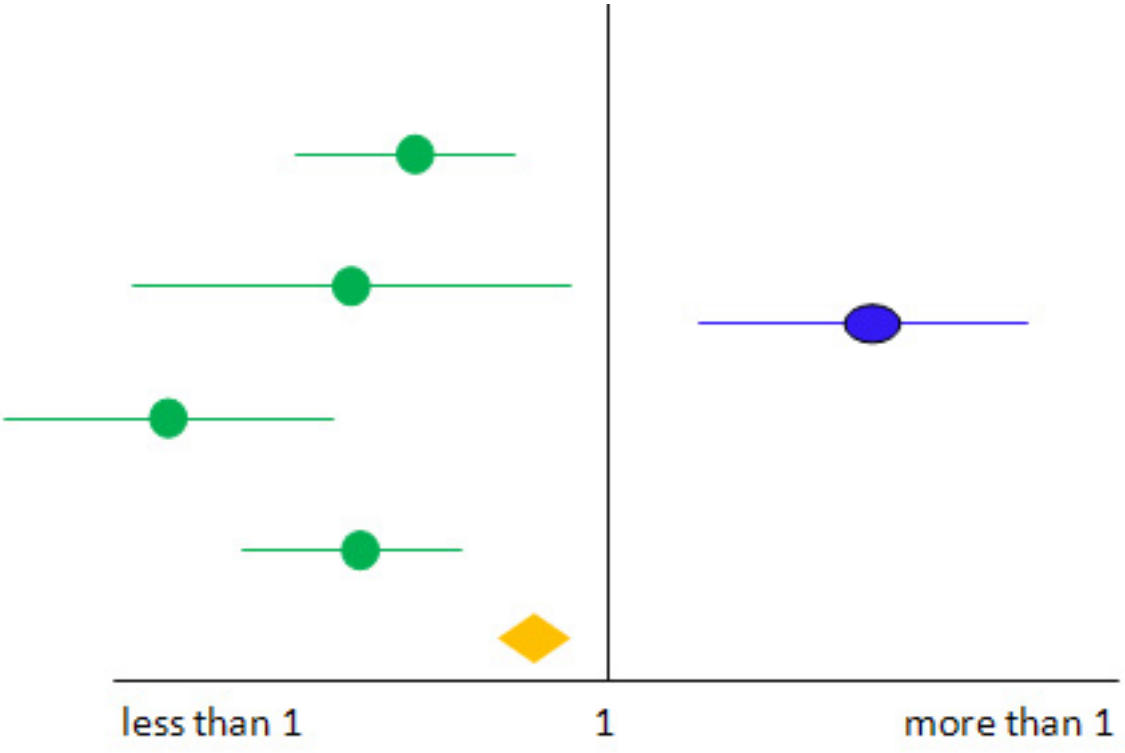


Figure 5-B: In case the outlier study is removed and the pooled result is significantly changed (the darker diamond shape), then one can't remove it

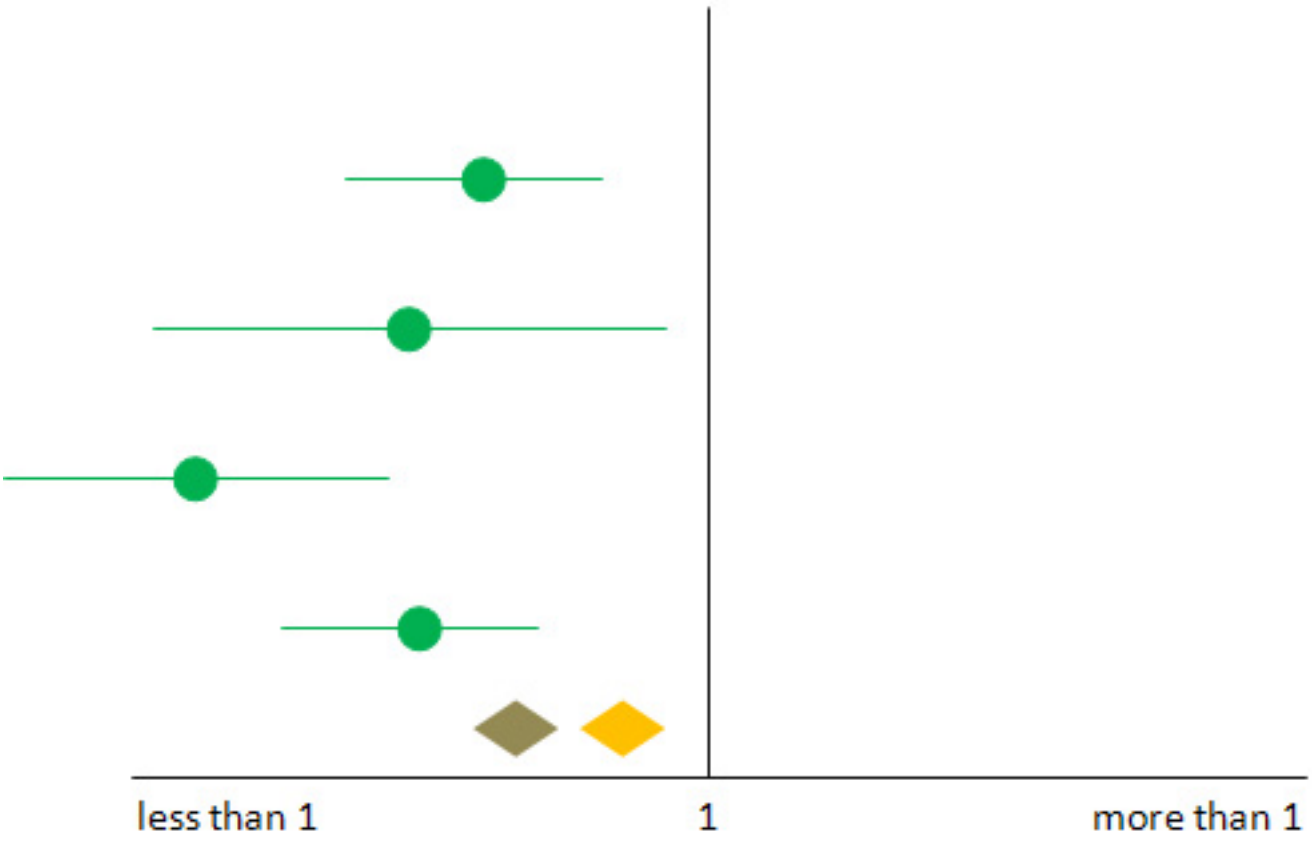
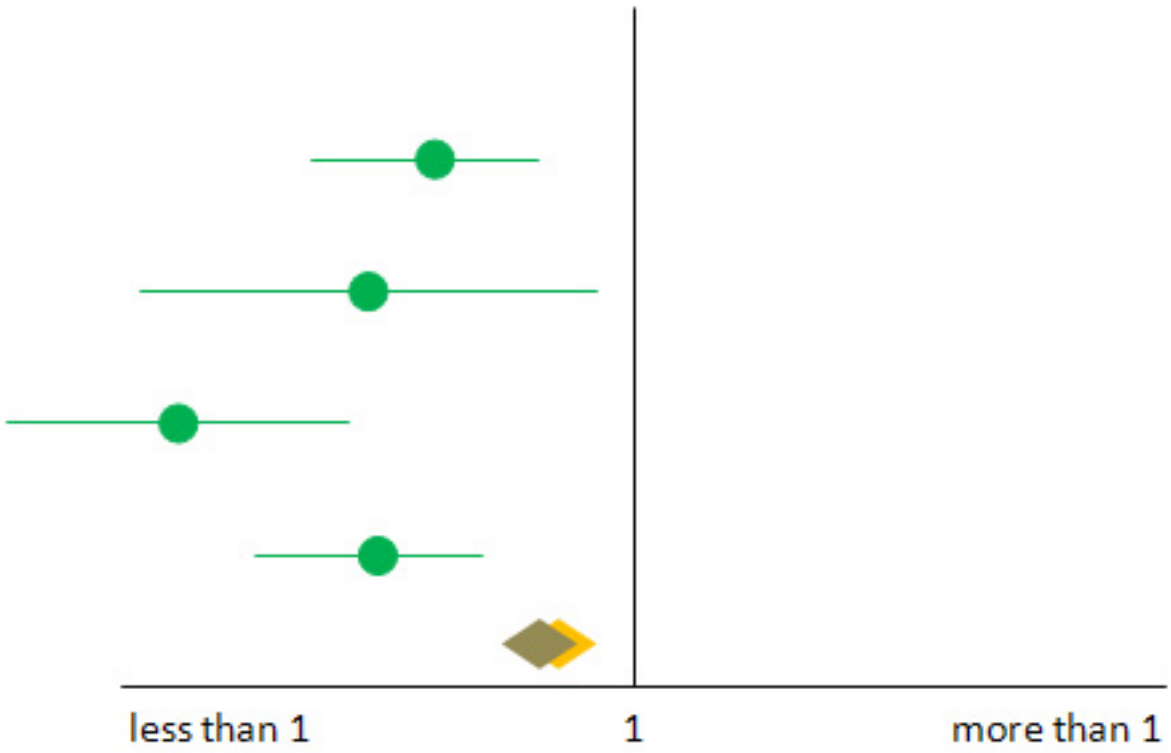


Figure 5-C: However, if the result doesn't change significantly, then one may remove the outlier safely



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