Using a Systematic Review and Meta-analysis for Clinical Decision

Nenacia Ranali Nirena P. Mendoza, MD, FPAFP and Cherry Bernardo-Lazaro, MD, FPAFP

A systematic review summarizes the results of a number of individual studies that address a focused clinical question. It may be accompanied by a meta-analysis, which is a quantitative method of combining the results of all these studies in order to come up with a summary statistic of the overall effect of an intervention. Single studies may be unrepresentative of the total body of evidence, that is why combining the results of several studies in a systematic review increases precision, provides better estimates of effect, and includes a greater range of patients thus facilitating better clinical decision making. This must be done in a systematic and reproducible manner.

Critical Appraisal

Relevance

1. Is the objective of the article on systematic review and meta-analysis similar to your clinical dilemma?

Validity

1. Were the criteria for searching and selecting articles for inclusion and exclusion explicit and reproducible?
2. Was there an objective and standard data extraction method applied to all included studies?
3. Did the review address possible explanations of between-study differences in results?

Results

1. What are the overall results of the systematic review?
2. Were the results similar from study to study?
3. Are the results clinically and statistically significant?

Applicability

1. Are the study patients in the main or subgroup analysis similar to my own?
2. Are the intervention and results of the review acceptable and applicable in my practice?

Key words: Evidence-based family practice, systematic review, meta-analysis

Introduction

A systematic review summarizes the results of a number of individual studies that address a focused clinical question. This is done in a systematic and reproducible manner.[1] It may be accompanied by a meta-analysis, which is a quantitative method of combining the results of all these studies in order to come up with a summary statistic of the overall effect, or what is known as a pooled estimate. It typically focuses on summary measures of relative benefit, such as odds ratio or relative risk. A systematic review with meta-analysis is the highest among the hierarchy of studies ("study among studies").[2] Single studies may be unrepresentative of the total body of evidence, that is why combining the results of several studies in a systematic review increases precision, provides better estimates of effect, and includes a greater range of patients thus facilitating better clinical decision making.1 Systematic reviews of articles on diagnosis and prognosis are also done, but the focus of this chapter is on therapeutic interventions.

Clinical Scenario

Obesity in children and adolescents has important consequences, including psychosocial disorders and increased risk of lifestyle disease during adulthood, and children who are overweight are more likely to be obese during adulthood.[3] Unfortunately, many parents of obese children do not perceive that their child is overweight. Treatment of obesity is often difficult and complex. Interventions will predominantly be behavioral and will require time.[4] A primary care level prevention and management approach is very important to stop this rising

prevalence. However, in a busy practice, physicians can only afford to give brief health education and counseling intervention. Unfortunately, clinical trials on brief health education and counseling have shown mixed results. Thus, a systematic review with meta-analysis on this topic may provide better evidence.

Consider a case of a 16-year-old girl, obese with weight of 65 kg, height of 5'0", and BMI of 28 who was accompanied by her mother for consultation due to ankle pain. It was a simple musculoskeletal pain and she was given an NSAID. The physician also considered addressing the problem of obesity but was unsure if brief counseling will be effective.

"How effective is brief counseling in a primary care setting in weight reduction among obese adolescents" is the question that should be addressed. After identifying the key terms "adolescent" "obesity" "counseling" "weight reduction" and "primary care" the physician searched PubMed and was able to obtain the meta-analysis of Sim LA, et al. Brief Primary Care Obesity Interventions: A Meta-analysis. Pediatrics 2016 Oct; 138(4): e20160149.5

Critical Appraisal

Relevance

1. Is the objective of the article on systematic review and meta-analysis similar to your clinical dilemma?

The formulated clinical question must be addressed by the objective of the systematic review or meta-analysis. The objective of an appropriately done meta-analysis is often a focused clinical objective with PIO and the method being clearly defined. In some cases, the review may specify several outcomes that are relevant to the effect of the intervention. The title, abstract or final paragraph of the introduction section should clearly state the objective. If you still cannot ascertain what the focused question of the systematic review or meta-analysis is after reading these sections, consider searching for another paper.

In Sim, et al., the objective was "to determine the effect of typical primary care, office-based, weight management interventions (eg, motivational interviewing, lifestyle modification education) compared with any control intervention (eg, usual care, no intervention, BMI feedback only, active control treatment) on BMI in children and adolescents aged 2 to 18 years. Thus, the objective of the article is relevant to the PIO in the physician's clinical question.

Validity

1. Were the criteria for searching and selecting articles for inclusion and exclusion explicit and reproducible?

A systematic search and appraisal of the literature is done in order to ensure that no relevant articles are missed, studies are included because they are relevant and are of good quality regardless of their results and excluded because they are not relevant. The criteria for inclusion and exclusion of studies in a systematic review should be clearly defined. These should specify the patients, interventions or exposures and outcomes of interest. In many cases the type of study design will also be a key component of the eligibility criteria.

From the focused clinical question, MESH terms and free text are used to search for studies. The search should not be limited to English language only. The starting point of a comprehensive search for all relevant studies is the major bibliographic databases (eg Medline, Cochrane, EMBASE, etc). A search from reference lists of relevant studies may also be done, and experts on the topic may be contacted to inquire about unpublished studies. Searching the grey literature (outside of traditional publishing and distribution channels) is also important to decrease the risk of publication bias, which may occur because studies with favorable results have a higher chance of being published compared to those with negative results.

The authors should describe the method of searching the medical literature. Statements like "an electronic search of published articles in the MEDLINE using the terms . . . from 1966 to present date was done" must be found in the methodology section. This assures the readers that the findings of the study were based on a wide range of literature source and represent the most current and complete information about the clinical problem.

Evaluation and appraisal methods used for study inclusion must be explicit. It is recommended that this should be done by at least two members of the research team. A third member may be included when the 2 reviewers cannot agree after discussion of differences in the selection and appraisal of studies. This assures the readers that the studies in the review were objectively chosen.

The article should describe how the quality of each study was assessed using predetermined criteria appropriate to the type of clinical question (e.g., randomization, blinding and completeness of follow-up for questions on therapy). Studies included in a systematic review and meta-analysis are subjected to critical appraisal using a set of criteria for quality similar to what are asked in critical appraisal tools. While there are available standards to evaluate validity (risk of bias tools), the reviewers may use their own criteria, in which case they should develop a checklist of criteria that focused on the methodology of the study being appraised and specify this in the methods section.

In summary, the methods section should include the search strategy, including the terms used, and describe in detail the inclusion and exclusion criteria as well as the assessment of quality of included studies and the criteria used. The results section should provide information on the quality of the individual studies and risk of bias assessments. It should also outline the number of titles and abstracts reviewed, the number of full text studies retrieved, and the number of studies excluded together with the reasons for exclusion. This information may be presented in a figure or flow chart, eg PRISMA flow diagram.[6] This meticulous process of formulating the clinical question, performing a valid sensible, and exhaustive search for evidence, and appraising the individual studies for inclusion is what makes a systematic review systematic, and differentiates it from a traditional narrative review.

In Sim, et al., they searched Medline, CENTRAL, Embase, PsycInfo, and CINAHL for relevant publications from January 1976 to March 2016 and cross-referenced with published studies. Then two reviewers

independently screened the studies, extracted data on participant, intervention, and study characteristics, and quality using the Cochrane and Newcastle-Ottawa risk of bias tools. In the study, eligible studies were randomized controlled trials (RCTs), quasi-experimental trials, non-randomized trials and prospective cohort studies published in any language that compared the effect of office-based primary care weight management interventions. They excluded studies that included patients presenting for targeted weight management services at non-primary care/specialty clinics and studies of interventions representative of specialty weight management services. A PRISMA flow chart was presented where from an initial 845 studies, 12 studies were selected.

2. Was there an objective and standard data extraction method applied to all included studies?

Extraction of patient characteristics, interventions and outcome data from included studies must be objective and standardized. This can be done by utilizing a standard data collection form used and applied independently by at least 2 reviewers. After individual data extraction, the panel summarizes the data extracted. Disagreement is resolved by discussion or involvement of a third party if agreement is not reached. There should also be a process on how to deal with missing data.

In Sim, et al., two reviewers/researchers used a pilot-tested computerized extraction form independently. In case of disagreements, the same 2 researchers met to review and resolve discrepancies for final data extraction. For missing data, the authors of the primary studies were contacted to request for missing data and to verify the data as abstracted.

3. Did the review address possible explanations of between-study differences in results?

In a systematic review and meta-analysis, there is the possibility of variability in the results across individual studies (heterogeneity) despite a standardized search, appraisal, inclusion and exclusion criteria. This can happen when there are differences in population characteristics, the manner or duration of application of the intervention, the method of outcome assessment or in the risk of bias.

Possible explanations for heterogeneity must be hypothesized and tested through subgroup analysis.[1] This can be done by grouping studies with similar characteristics in terms of population, intervention (including duration), outcomes or study design. Subgroups must be determined a priori (during the planning stage), and the criteria for subgroups must be scientifically plausible. If there is considerable variability in the results, random effects model must be employed during data analysis.

Sim, et al., conducted subgroup analysis based on several parameters including age above or below 6 years old, duration of interventions and study quality to name a few. This did not have an effect on the overall results.

Results

1. What are the overall results of the systematic review?

Results of systematic reviews and meta-analysis should present the effect of intervention on relevant outcomes. A systematic review without meta-analysis presents the summary of the results of included studies in text or table formats. On the other hand, a meta-analyis uses a forest plot in presenting the individual and pooled estimates of the effect of the intervention.

A forest plot (Figure 1) is composed of trees or individual studies in the leftmost column, depicted by the author's name and year of publication (A), the point estimate of the effect in individual studies shown as squares with sizes proportional to the weight of the study and the confidence interval depicted as a horizontal line passing through each square (B), a solid vertical line signifying no effect which is 1.0 for dichotomous variables reported as relative risk or odds ratio, and 0 for continuous variables usually reported as mean difference (C), the pooled estimate or combined summary effect depicted as a diamond with its width representing the confidence interval (D), and the tests for heterogeneity (E).

It is very important to review the interpretation of outcomes like Risk Ratios or Odds Ratios (discussed in previous chapters). In some cases meta-analysis will measure outcomes like blood pressure or quality of life score and will be presented as weighted mean difference. Table 1 is a guide in interpreting the horizontal confidence interval lines in a forest plot, for relative risk and mean difference.

In Sim, et al., compared with usual care or control treatment, brief interventions in primary care for overweight or obese children showed a statistically significant but minimal reduction in BMI z-score with mean difference of –0.04, p value = 0.02 (95% CI -0.08, -0.01). Below is the forest plot, with reduction in z-BMI presented as mean difference between groups (Figure 3).

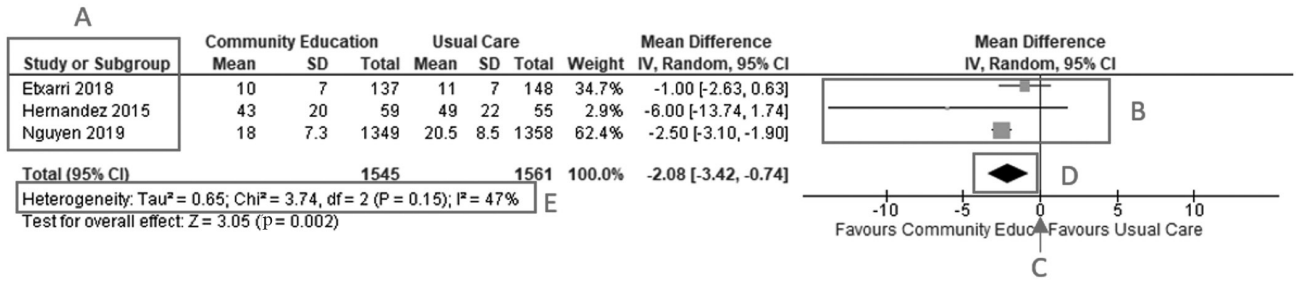


Figure 1. Sample forest plot

Table 1. Guide to interpretation of confidence interval lines in a forest plot.

	Relative Risk[7]	Mean Difference	
entire line or width of confidence interval is to the left of 1.0 or 0	Statistically significant benefit	Statistically significant reduction	A
entire line or width of confidence interval is to the right of 1.0 or 0	Statistically significant harm	Statistically significant increase	B
confidence interval line straddles 1.0 or 0 and extends far to the left and to the right	Inconclusive		C
point estimate is to the left of 1.0 or 0, and CI line also to the left but slightly touching 1.0 or 0	Trend towards benefit, inconclusive	Trend towards reduction, inconclusive	D
point estimate is to the right of 1.0 or 0, and CI line also to the right but slightly touching 1.0 or 0	Trend towards harm, inconclusive	Trend towards increase, inconclusive	E
line straddles 1.0 or 0 and does not go far to the left or right	Two interventions are equal		F

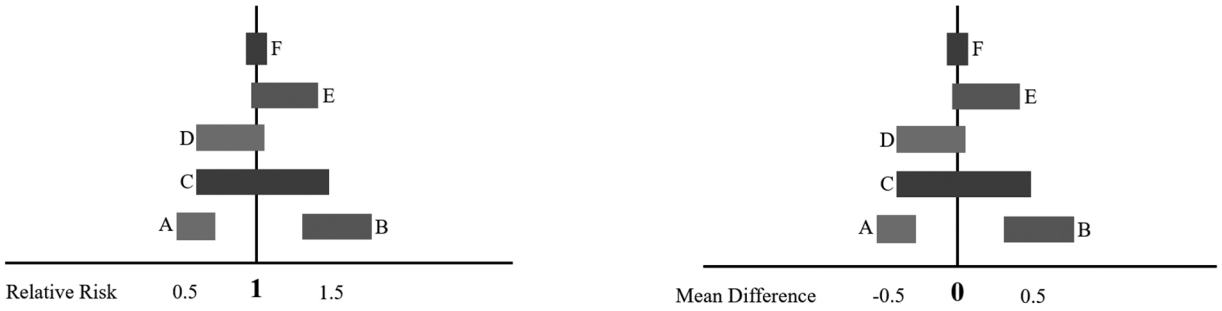
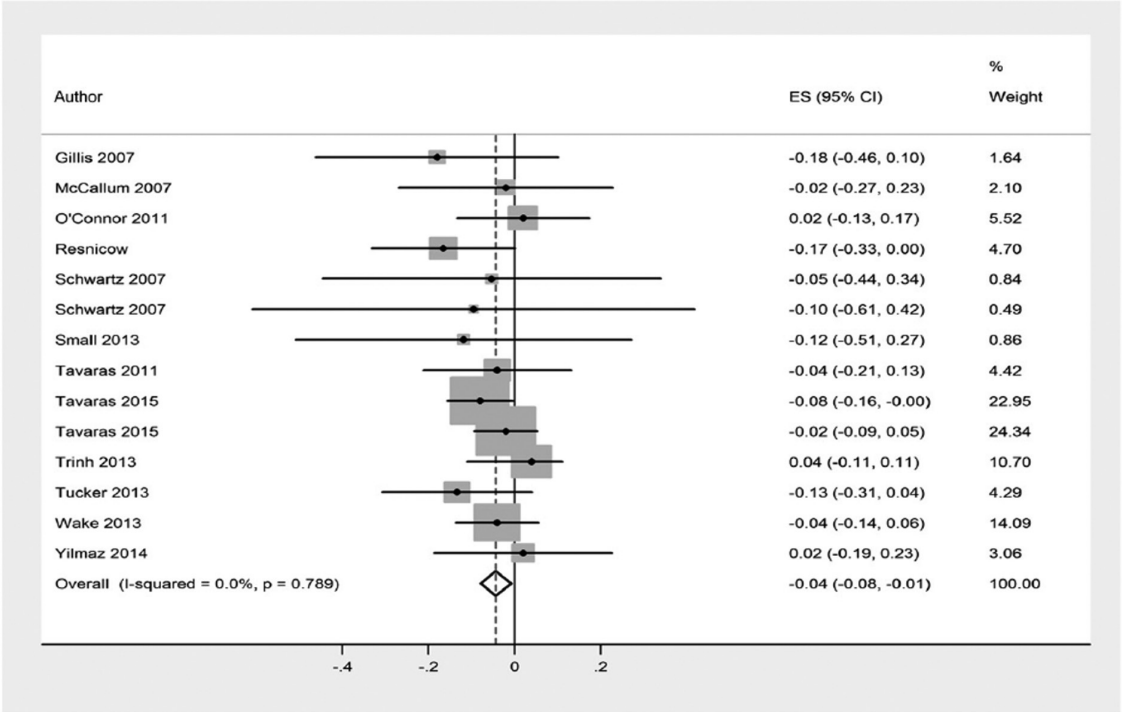


Figure 2. Possible position of confidence interval lines in a forest plot.



Random effect meta-analysis (the effect of brief primary care interventions vs usual care or active control on *z*-BMI). Central vertical line represents no treatment effect. Squares and horizontal lines represent the point estimates and associated confidence interval (CI) for each study, respectively. Point estimates to the right of the central vertical line reflect increase in *z*-BMI. Weights are from random effects analysis.

Figure 3. Mean difference in z-BMI (Sim, et al).

2. Were the results similar from study to study?

Aside from the actual summary or pooled estimate of the result, it is important to look at whether the results are consistent across studies. This is known as heterogeneity. Caution must be taken against statistically combining the results of diverse studies, as this may "lead to spurious conclusions (for instance, that the same estimate of effect applies to different patient groups or different ways of administering an intervention, when it in fact does not)".[1]

Heterogeneity can be observed visually in a forest plot by looking at the degree to which confidence intervals of individual studies overlap. Overlapping CI's imply that random error or chance is a plausible explanation for differences in point estimates. Another way is looking at statistical tests of heterogeneity. A p-value of less than 0.05 indicates significant heterogeneity. The degree of heterogeneity is also reported as the I^2 statistic, which may be interpreted as:[8]

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

The authors of the meta-analysis must investigate possible sources of heterogeneity. This can be addressed by doing subgroup analysis (described above). If after doing subgroup analysis, there is still significant heterogeneity, it is prudent NOT to combine the results in a meta-analysis.

In the Sim, et al. study, I^2 on the effect brief primary care intervention on BMI was 0% (p value 0.524), indicating that the results are similar or consistent across studies.

3. Are the results clinically and statistically significant?

Statistical significance indicates the reliability of the results while clinical significance reflects its impact on clinical practice. Statistical significance is largely dependent on the sample size and is reported as a "p value <0.05" (at 95% confidence level). This indicates the probability that the results are not due to chance and is a real treatment effect.

Clinical significance is dependent on its implications on clinical practice i.e., magnitude of the effect of treatment. More often clinical significance is based on the judgment of the family physician and the patient.[9]

In Sim, et al., there was a significant but small reduction in z-BMI i.e., decrease by 0.04 when brief primary care intervention is done in addition to standard of care. This amount is roughly equivalent to a 1 kg decrease in body weight. This reduction in z-score was achieved through a series of 2-4 meetings with brief interventions over a period of 1-12 months (based on characteristics of included studies). Although statistically significant, the relatively small clinical impact or significance must be discussed and evaluated by both the physician and patient.

Applicability

1. Are the study patients in the main or subgroup analysis similar to my own?

In a systematic review, patient characteristics may be varied because they came from different studies. Application to patients therefore becomes wider. When variation in patient inclusion may influence the effect, subgroup analysis between different patient characteristics may help decide what kind of patient will benefit from the intervention or will be affected by the exposure. This information can be seen in the methodology section where the researchers describe the type of patients in the literature search and inclusion criteria of the studies.

In Sim, et al., all but one of the studies included children who were in the overweight to mildly obese weight range. Two studies recruited both children and adolescents (ages 4–18 and 7–16 years). The patient in the scenario is included in these groups.

2. Are the intervention and results of the review acceptable and applicable in my practice?

Individual clinic family practice setting in the Philippines is limited in terms of implementing complex interventions and drugs requiring close monitoring. Before deciding to prescribe the intervention to the patient, the family physician must make sure there is capacity to implement it and monitor the outcome and manage the potential side effects.

In Sim, et al., the intervention was given in 2-4 sessions which included motivational therapy approaches and nutrition education. Treatments were delivered either by primary care providers i.e., physicians, physicians-in-training, nurse practitioners, physician assistants and health educator. This is well within the expertise and capacity of family practice.

SHARE: Patient-Centered Communication and Shared Decision Making

While critical appraisal of articles on systematic reviews and meta-analysis is an important skill every family physician must possess, the greater burden lies in effectively communicating the results to patients in order to agree on the best management options through shared decision-making with the patient and family. Let us apply the SHARE approach described in a previous chapter to the clinical scenario.

References

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S	Seek patient's participation	Use active listening skills to engage the patient in the discussion. Involve also the parent or caregiver, since the patient is a minor. But consider the option of having time to talk with her without her companion, being an adolescent who may be willing to share some things with a professional like you but is not yet comfortable sharing with her parent or guardian. Make sure the discussion takes place in an area which allows privacy, since overweight/obesity is still associated with stigma. Explore the patient's current knowledge and insights about being obese, and its possible consequences. Elicit her perceived benefits of losing weight.
H	Help patient explore treatment options	Offer the patient the option of doing a series of brief interventions (motivational counselling, health education) with you as the physician. Relay to her and her parent/guardian/caregiver that each session will be brief. This will not entail additional cost aside from the usual cost of consultation. Inform her of the meta-analysis result showing 1 kg decrease in body weight with brief counseling/health education sessions in a primary care setting like your clinic. Give information also about more intensive treatment options which may be available in the area, given the relatively small weight reduction that the brief intervention provides.
A	Assess patient's values and preferences	Explore what outcomes are valuable to the patient. Aside from actual weight reduction, she may value overall health both in the short and long term, body satisfaction, and self-esteem. Explore patient's interests, and how she can be connected to other resources through her preferences. Screen for and caution against against potential risky behaviors like crash dieting, eating disorders, etc.
R	Reach a decision with patient	Ask the patient if she is ready to make a decision regarding undertaking these sessions with you as her family physician. Set realistic goals. Set a schedule for the next meeting.
E	Evaluate patient's decision	On follow-up visits, evaluate if the patient wishes to maintain her decision to undergo sessions. Determine her level of satisfaction with the current management. Check if goals are being met. Evaluate the effect of the intervention and re-consider other options if warranted.

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