Review Article

Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare

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Abstract

Healthcare decisions for individual patients and for public health policies should be informed by the best available research evidence. The practice of evidence-based medicine is the integration of individual clinical expertise with the best available external clinical evidence from systematic research and patient's values and expectations. Primary care physicians need evidence for both clinical practice and for public health decision making. The evidence comes from good reviews which is a state-of-the-art synthesis of current evidence on a given research question. Given the explosion of medical literature, and the fact that time is always scarce, review articles play a vital role in decision making in evidence-based medical practice. Given that most clinicians and public health professionals do not have the time to track down all the original articles, critically read them, and obtain the evidence they need for their questions, systematic reviews and clinical practice guidelines may be their best source of evidence. Systematic reviews aim to identify, evaluate, and summarize the findings of all relevant individual studies over a health-related issue, thereby making the available evidence more accessible to decision makers. The objective of this article is to introduce the primary care physicians about the concept of systematic reviews and meta-analysis, outlining why they are important, describing their methods and terminologies used, and thereby helping them with the skills to recognize and understand a reliable review which will be helpful for their day-to-day clinical practice and research activities.

Keywords: Evidence-based medicine, meta-analysis, primary care, systematic review

Introduction

Evidence-based healthcare is the integration of best research evidence with clinical expertise and patient values. Green denotes, "Using evidence from reliable research, to inform healthcare decisions, has the potential to ensure best practice and reduce variations in healthcare delivery." However, incorporating research into practice is time consuming, and so we need methods of facilitating easy access to evidence for busy clinicians.[1] Ganeshkumar *et al.* mentioned that nearly half of the private practitioners in India were consulting more than 4 h per day in a locality,[2] which explains the difficulty of them in spending time in searching evidence during consultation. Ideally, clinical decision making ought to be based on the latest evidence available. However, to keep abreast with the continuously increasing number of publications in health research, a primary healthcare professional would need to read an insurmountable number of articles every day, covered in more than 13 million references and over 4800 biomedical and health journals in Medline alone.

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With the view to address this challenge, the systematic review method was developed. Systematic reviews aim to inform and facilitate this process through research synthesis of multiple studies, enabling increased and efficient access to evidence.[1,3,4]

Systematic reviews and meta-analyses have become increasingly important in healthcare settings. Clinicians read them to keep up-to-date with their field and they are often used as a starting point for developing clinical practice guidelines. Granting agencies may require a systematic review to ensure there is justification for further research and some healthcare journals are moving in this direction.[5]

This article is intended to provide an easy guide to understand the concept of systematic reviews and meta-analysis, which has been prepared with the aim of capacity building for general practitioners and other primary healthcare professionals in research methodology and day-to-day clinical practice.

The purpose of this article is to introduce readers to:

a. The two approaches of evaluating all the available evidence on an issue i.e., systematic reviews and meta-analysis,

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b. Discuss the steps in doing a systematic review,
c. Introduce the terms used in systematic reviews and meta-analysis,
d. Interpret results of a meta-analysis, and
e. The advantages and disadvantages of systematic review and meta-analysis.

Application

What is the effect of antiviral treatment in dengue fever? Most often a primary care physician needs to know convincing answers to questions like this in a primary care setting.

To find out the solutions or answers to a clinical question like this, one has to refer textbooks, ask a colleague, or search electronic database for reports of clinical trials. Doctors need reliable information on such problems and on the effectiveness of large number of therapeutic interventions, but the information sources are too many, i.e., nearly 20,000 journals publishing 2 million articles per year with unclear or confusing results. Because no study, regardless of its type, should be interpreted in isolation, a systematic review is generally the best form of evidence.[6] So, the preferred method is a good summary of research reports, i.e., systematic reviews and meta-analysis, which will give evidence-based answers to clinical situations.

There are two fundamental categories of research: Primary research and secondary research. Primary research is collecting data directly from patients or population, while secondary research is the analysis of data already collected through primary research. A review is an article that summarizes a number of primary studies and may draw conclusions on the topic of interest which can be traditional (unsystematic) or systematic.

Terminologies

Systematic review

A systematic review is a summary of the medical literature that uses explicit and reproducible methods to systematically search, critically appraise, and synthesize on a specific issue. It synthesizes the results of multiple primary studies related to each other by using strategies that reduce biases and random errors.[7] To this end, systematic reviews may or may not include a statistical synthesis called meta-analysis, depending on whether the studies are similar enough so that combining their results is meaningful.[8] Systematic reviews are often called overviews.

The evidence-based practitioner, David Sackett, defines the following terminologies.[3]

- Review: The general term for all attempts to synthesize the results and conclusions of two or more publications on a given topic.
- Overview: When a review strives to comprehensively identify and track down all the literature on a given topic (also called "systematic literature review").
- Meta-analysis: A specific statistical strategy for assembling the results of several studies into a single estimate.

Systematic reviews adhere to a strict scientific design based on explicit, pre-specified, and reproducible methods. Because of this, when carried out well, they provide reliable estimates about the effects of interventions so that conclusions are defensible. Systematic reviews can also demonstrate where knowledge is lacking. This can then be used to guide future research. Systematic reviews are usually carried out in the areas of clinical tests (diagnostic, screening, and prognostic), public health interventions, adverse (harm) effects, economic (cost) evaluations, and how and why interventions work.[9]

Cochrane reviews

Cochrane reviews are systematic reviews undertaken by members of the Cochrane Collaboration which is an international not-for-profit organization that aims to help people to make well-informed decisions about healthcare by preparing, maintaining, and promoting the accessibility of systematic reviews of the effects of healthcare interventions.

Cochrane Primary Health Care Field is a systematic review of primary healthcare research on prevention, treatment, rehabilitation, and diagnostic test accuracy. The overall aim and mission of the Primary Health Care Field is to promote the quality, quantity, dissemination, accessibility, applicability, and impact of Cochrane systematic reviews relevant to people who work in primary care and to ensure proper representation in the interests of primary care clinicians and consumers in Cochrane reviews and review groups, and in other entities. This field would serve to coordinate and promote the mission of the Cochrane Collaboration within the primary healthcare disciplines, as well as ensuring that primary care perspectives are adequately represented within the Collaboration.[10]

Meta-analysis

A meta-analysis is the combination of data from several independent primary studies that address the same question to produce a single estimate like the effect of treatment or risk factor. It is the statistical analysis of a large collection of analysis and results from individual studies for the purpose of integrating the findings.[11] The term meta-analysis has been used to denote the full range of quantitative methods for research reviews.[12] Meta-analyses are studies of studies.[13] Meta-analysis provides a logical framework to a research review where similar measures from comparable studies are listed systematically and the available effect measures are combined wherever possible.[14]

The fundamental rationale of meta-analysis is that it reduces the quantity of data by summarizing data from multiple resources and helps to plan research as well as to frame guidelines. It also helps to make efficient use of existing data, ensuring generalizability, helping to check consistency of relationships, explaining data inconsistency, and quantifies the data. It helps to improve the precision in estimating the risk by using explicit methods.

Therefore, "systematic review" will refer to the entire process of collecting, reviewing, and presenting all available evidence, while the term "meta-analysis" will refer to the statistical technique involved in extracting and combining data to produce a summary result.[15]

Steps in doing systematic reviews/meta-analysis

Following are the six fundamental essential steps while doing systematic review and meta-analysis.[16]

Define the question

This is the most important part of systematic reviews/meta-analysis. The research question for the systematic reviews may be related to a major public health problem or a controversial clinical situation which requires acceptable intervention as a possible solution to the present healthcare need of the community. This step is most important since the remaining steps will be based on this.

Reviewing the literature

This can be done by going through scientific resources such as electronic database, controlled clinical trials registers, other biomedical databases, non-English literatures, "gray literatures" (thesis, internal reports, non–peer-reviewed journals, pharmaceutical industry files), references listed in primary sources, raw data from published trials and other unpublished sources known to experts in the field. Among the available electronic scientific database, the popular ones are PUBMED, MEDLINE, and EMBASE.

Sift the studies to select relevant ones

To select the relevant studies from the searches, we need to sift through the studies thus identified. The first sift is pre-screening, i.e., to decide which studies to retrieve in full, and the second sift is selection which is to look again at these studies and decide which are to be included in the review. The next step is selecting the eligible studies based on similar study designs, year of publication, language, choice among multiple articles, sample size or follow-up issues, similarity of exposure, and or treatment and completeness of information.

It is necessary to ensure that the sifting includes all relevant studies like the unpublished studies (desk drawer problem), studies which came with negative conclusions or were published in non-English journals, and studies with small sample size.

Assess the quality of studies

The steps undertaken in evaluating the study quality are early definition of study quality and criteria, setting up a good scoring system, developing a standard form for assessment, calculating quality for each study, and finally using this for sensitivity analysis.

For example, the quality of a randomized controlled trial can be assessed by finding out the answers to the following questions:

1. Was the assignment to the treatment groups really random?
2. Was the treatment allocation concealed?
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were the assessors, the care provider, and the patient blinded?
6. Were the point estimates and measure of variability presented for the primary outcome measure?
7. Did the analyses include intention-to-treat analysis?

Calculate the outcome measures of each study and combine them

We need a standard measure of outcome which can be applied to each study on the basis of its effect size. Based on their type of outcome, following are the measures of outcome: Studies with binary outcomes (cured/not cured) have odds ratio, risk ratio; studies with continuous outcomes (blood pressure) have means, difference in means, standardized difference in means (effect sizes); and survival or time-to-event data have hazard ratios.

Combining studies

Homogeneity of different studies can be estimated at a glance from a forest plot (explained below). For example, if the lower confidence interval of every trial is below the upper of all the others, i.e., the lines all overlap to some extent, then the trials are homogeneous. If some lines do not overlap at all, these trials may be said to be heterogeneous.

The definitive test for assessing the heterogeneity of studies is a variant of Chi-square test (Mantel–Haenszel test). The final step is calculating the common estimate and its confidence interval with the original data or with the summary statistics from all the studies. The best estimate of treatment effect can be derived from the weighted summary statistics of all studies which will be based on weighting to sample size, standard errors, and other summary statistics. Log scale is used to combine the data to estimate the weighting.

Interpret results: Graph

The results of a meta-analysis are usually presented as a graph called forest plot because the typical forest plots appear as forest of lines. It provides a simple visual presentation of individual studies that went into the meta-analysis at a glance. It shows the variation between the studies and an estimate of the overall result of all the studies together.

Forest plot

Meta-analysis graphs can principally be divided into six columns [Figure 1]. Individual study results are displayed in rows. The first column ("study") lists the individual study IDs included in the meta-analysis; usually the first author and year are displayed. The second column relates to the intervention groups and the third column to the control groups. The fourth column visually displays the study results. The line in the middle is called "the line of no effect." The weight (in %) in the fifth column indicates the weighting or influence of the study on the overall results of the meta-analysis of all included studies. The higher

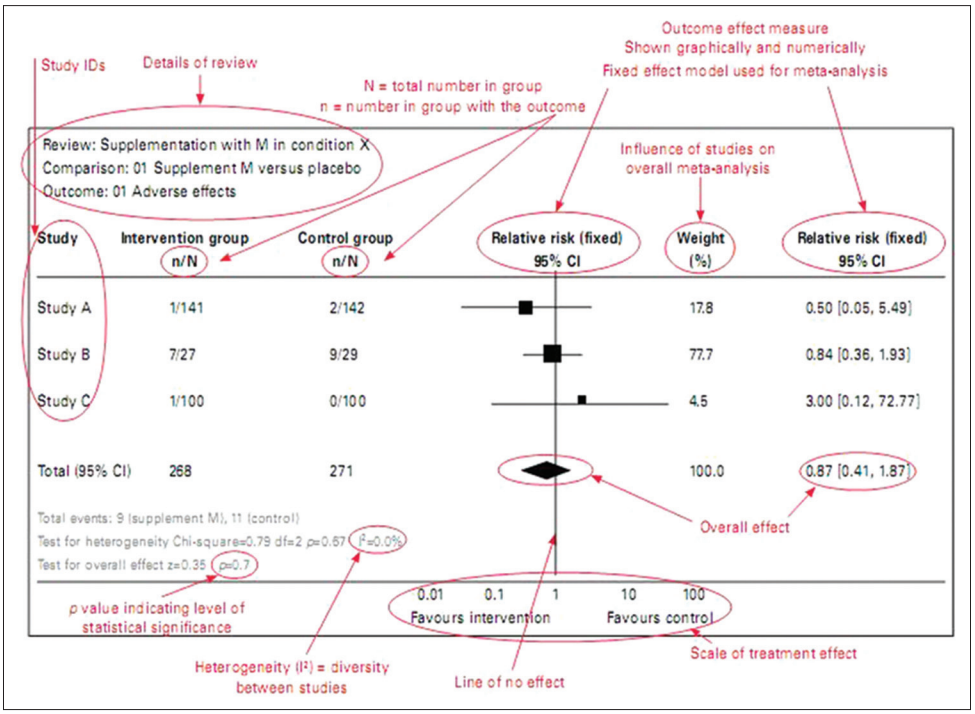

Figure 1: Interpretation of meta-analysis[4]

the percentage weight, the bigger the box, the more influence the study has on the overall results. The sixth column gives the numerical results for each study (e.g., odds ratio or relative risk and 95% confidence interval), which are identical to the graphical display in the fourth column. The diamond in the last row of the graph illustrates the overall result of the meta-analysis.[4]

Thus, the horizontal lines represent individual studies. Length of line is the confidence interval (usually 95%), squares on the line represent effect size (risk ratio) for the study, with area of the square being the study size (proportional to weight given) and position as point estimate (relative risk) of the study.[7]

For example, the forest plot of the effectiveness of dexamethasone compared with placebo in preventing the recurrence of acute severe migraine headache in adults is shown in Figure 2.[17]

The overall effect is shown as diamond where the position toward the center represents pooled point estimate, the width represents estimated 95% confidence interval for all studies, and the black plain line vertically in the middle of plot is the "line of no effect" (e.g., relative risk = 1).

Therefore, when examining the results of a systematic reviews/meta-analysis, the following questions should be kept in mind:

1. Were apples combined with oranges?
   - Heterogeneity among studies may make any pooled estimate meaningless.
2. Were all of the apples rotten?
   - The quality of a meta-analysis cannot be any better than the quality of the studies it is summarizing.
3. Were some apples left on the tree?
   - An incomplete search of the literature can bias the findings of a meta-analysis.
4. Did the pile of apples amount to more than just a hill of beans?
   - Make sure that the meta-analysis quantifies the size of the effect in units that you can understand.

Subgroup analysis and sensitivity analysis

Subgroup analysis looks at the results of different subgroups of trials, e.g., by considering trials on adults and children separately. This should be planned at the protocol stage itself which is based on good scientific reasoning and is to be kept to a minimum.

Sensitivity analysis is used to determine how results of a systematic review/meta-analysis change by fiddling with data, for example, what is the implication if the exclusion criteria or excluded unpublished studies or weightings are assigned differently. Thus, after the analysis, if changing makes little or no difference to the overall results, the reviewer's conclusions are robust. If the key findings disappear, then the conclusions need to be expressed more cautiously.

Advantages of Systematic Reviews

Systematic reviews have specific advantages because of using explicit methods which limit bias, draw reliable and accurate conclusions, easily deliver required information to healthcare providers, researchers, and policymakers, help to reduce the time delay in the research discoveries to implementation, improve the generalizability and consistency of results, generation of new hypotheses about subgroups of

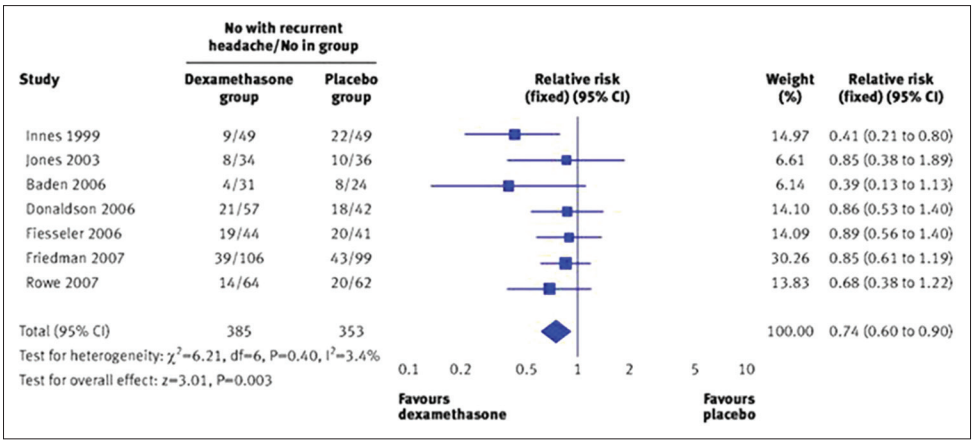

Figure 2: Forest plot of the effectiveness of dexamethasone compared with placebo in preventing the recurrence of acute severe migraine headache in adults[17]

the study population, and overall they increase precision of the results.[18]

Limitations in Systematic Reviews/ Meta-analysis

As with all research, the value of a systematic review depends on what was done, what was found, and the clarity of reporting. As with other publications, the reporting quality of systematic reviews varies, limiting readers' ability to assess the strengths and weaknesses of those reviews.[5]

Even though systematic review and meta-analysis are considered the best evidence for getting a definitive answer to a research question, there are certain inherent flaws associated with it, such as the location and selection of studies, heterogeneity, loss of information on important outcomes, inappropriate subgroup analyses, conflict with new experimental data, and duplication of publication.

Publication Bias

Publication bias results in it being easier to find studies with a "positive" result.[19] This occurs particularly due to inappropriate sifting of the studies where there is always a tendency towards the studies with positive (significant) outcomes. This effect occurs more commonly in systematic reviews/meta-analysis which need to be eliminated.

The quality of reporting of systematic reviews is still not optimal. In a recent review of 300 systematic reviews, few authors reported assessing possible publication bias even though there is overwhelming evidence both for its existence and its impact on the results of systematic reviews. Even when the possibility of publication bias is assessed, there is no guarantee that systematic reviewers have assessed or interpreted it appropriately.[20]

To overcome certain limitations mentioned above, the Cochrane reviews are currently reported in a format where at the end of every review, findings are summarized in the author's point of view and also give an overall picture of the outcome by means of plain language summary. This is found to be much helpful to understand the existing evidence about the topic more easily by the reader.

Summary

A systematic review is an overview of primary studies which contains an explicit statement of objectives, materials, and methods, and has been conducted according to explicit and reproducible methodology. A meta-analysis is a mathematical synthesis of the results of two or more primary studies that addressed the same hypothesis in the same way. Although meta-analysis can increase the precision of a result, it is important to ensure that the methods used for the reviews were valid and reliable.

High-quality systematic reviews and meta-analyses take great care to find all relevant studies, critically assess each study, synthesize the findings from individual studies in an unbiased manner, and present balanced important summary of findings with due consideration of any flaws in the evidence. Systematic review and meta-analysis is a way of summarizing research evidence, which is generally the best form of evidence, and hence positioned at the top of the hierarchy of evidence.

Systematic reviews can be very useful decision-making tools for primary care/family physicians. They objectively summarize large amounts of information, identifying gaps in medical research, and identifying beneficial or harmful interventions which will be useful for clinicians, researchers, and even for public and policymakers.

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