9-1-2021

The Meta-Analysis in Evidence-Based Medicine: High-Quality Research When Properly Performed

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Recommended Citation

Mahmood S, Nona P, Villablanca P, Nunez-Gil I, and Ramakrishna H. The Meta-Analysis in Evidence-Based Medicine: High-Quality Research When Properly Performed. J Cardiothorac Vasc Anesth 2021; 35(9):2556-2558.

Journal of Cardiothoracic and Vascular Anesthesia 35 (2021) 2556–2558

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Editorial

The Meta-Analysis in Evidence-Based Medicine: High-Quality Research When Properly Performed

The origins of evidence-based medicine (EBM) trace back to the mid-19th century[1] and the gradual evolution from personal journals to textbooks and eventually the advent of the peer-reviewed journal. Evidence-based medicine originally was defined by David Sackett as the "conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[2] Researchers from McMasters University began to introduce the term into the medical litrerature more systematically in the mid 1990s. Further analyzed, its aims include integrating individual clinical expertise (proficiency and judgment that individual clinicians acquire through clinical experience and practice) with the best available external clinical evidence from systematic research and patient's preferences to guide care.[1] Over the years, EBM has become the core guiding principle for those studying patient outcomes.[3] The lower end of this paradigm includes unsystematic observations and narrative reviews, while at the opposite end lie methodologically sound, homogeneous, randomized clinical trials (RCTs). Systematic reviews and metaanalyses of homogeneous RCTS have been given the highest level of evidence. In its strictest definition, a metaanalysis ("analysis of analyses") is a formal, epidemiologic, quantitative statistical technique that analyzes the results of different studies on the same topic and integrates the evidence into a single conclusion.[4,5] By combining individual studies, and thus using more data from a larger sample size, the precision and accuracy of the estimates in the individual studies can be improved upon—essentially improving the strength of the evidence. The key point is that a sound metaanalysis eliminates all bias by employing a strict methodologic/statistical approach and in the process provides evidence of the highest quality—with minimal heterogeneity. Additionally, if the individual studies were underpowered, combining them in a metaanalysis can increase the overall statistical power to detect an effect. When properly performed, meta-analyses can improve precision of effect estimates, generate clinically meaningful answers to questions that individual studies might not be able to accomplish, and even settle controversies from studies that may be conflicted.[4]

The Cochrane Collaboration, an international organization, was developed to aid researchers generate systematic reviews of the highest quality and has become a key point of reference for researchers interested in producing and disseminating accurate data comparing treatment effectiveness.[6] However, in the present day, the metaanalysis arguably has been abused, contributing to misleading conclusions rather than proper evidence-based information. The increasing popularity of metaanalyses can be traced to industrialized nations worldwide, most notably in China. According to PubMed data, 1.3% of publications by Chinese researchers in 2011 were metaanalyses, compared to 0.4% for authors from the rest of the world.[7] This popularity is, in part, due to the pressure to publish on individual researchers for academic achievement and visibility[7] instead of a meaningful contribution to the evidence, and has contributed to this pandemic with flawed and erroneous concepts in design, conduct, statistical analysis, and reporting that have plagued virtually every specialty of medicine.

Redundant, Misleading and Conflicted Data

The incredible popularity of the metaanalysis has led to significant redundancy in data reporting, particularly in outcomes. The extent of redundancy, particularly in meta-analyses of randomized trials, has reached epidemic proportions.[8] Examples of this can be seen in multiple fields, with original meta-analyses showing statistically significant and clinical benefit, followed by subsequent similar meta-analyses, some with identical results and very few actually citing systematically among their references the prior metaanalyses on the same topic. This has led to the current perception of the metaanalysis as inferior research and a possibly diminished role in evidence-based clinical research. More so in cardiovascular medicine, journals are prone to have high levels of hidden biases in accepting manuscripts (articles from prominent researchers or major research institutes) despite significant redundancy of the topic in question in the medical literature. The sine qua non of the metaanalysis is the proper identification of existing literature and the systematic search of existing evidence. For this, a protocol that lists all potential sources and strategies should be

https://doi.org/10.1053/j.jvca.2021.05.025

established first. The authors believe that to help solidify the results and encourage transparency in the metaanalytic process, all metaanalyses should be registered in dedicated international databases of prospectively registered systematic reviews, such as PROSPERO.[9] Registration allows those who are commissioning or planning studies to identify whether there are other metaanalyses already underway that are addressing their topic of interest. This helps provide transparency and avoid unintended and economically wasteful duplication of effort. It also serves as a safeguard against reporting biases by revealing differences between the outcomes reported and those planned in the registered protocol. This will improve the quality and credibility of metaanalyses endpoints and increase confidence behind policy or practice, informed by the findings of a systematic review drawing on the best-quality evidence.

The Search Process Is Critical

A significant factor instrumental in the final results of a metaanalysis lies in the search process; the most commonly used electronic databases may include MEDLINE and EMBASE.[10,11] This can create an inherent bias from inception to find studies published only in English and excluding nonindexed studies in peer-reviewed journals, leading to only a sample of available evidence worldwide.[12] This is referred to as "publication bias", and it is defined properly as the occurrence of studies showing positive effects being published and cited more frequently versus studies that show no significant results.[12,13] This could lead to published data overestimating the actual degree of effect of the therapy or management studied.[12,13] Trends show that larger studies with publication bias tend to get published regardless of their results. Studies that have small positive effects or reject the null hypothesis tend not to materialize in popular databases, whether it be due to publication delay, publications in languages other than English, publications in nonindexed journals, or studies not being published altogether. Therefore, reviewers may not be able to identify them. To minimize bias associated with narrow collection of sources and usage of only the most popular databases, one needs to broaden the scope of databases used. This includes electronic sources such as Cochrane Central,[14] the Federal Drug Administration, and internet websites such as Google Scholar. Examples of search strategies can be found in the Cochrane Collaboration's Reviewers' handbook.[15] The basic search strategy is built based on the research question formulation (ie, PICO or PICOS-Patient/ Problem, Intervention, Comparison and Outcome). Search strategies are constructed to include free-text terms (eg, in the title and abstract) and any appropriate subject indexing (eg, Medical Subject Headings) expected to retrieve eligible studies, with the help of an expert in the topic or an information specialist.

Defining Heterogeneity

Another critical component of the metaanalysis is defining heterogeneity and which cutoff value is defined as heterogeneous. Heterogeneity in metaanalysis refers to the variation in study outcomes between studies. There are three types of heterogeneity: clinical, statistical, and design-related. There is debate among researchers in how one would define heterogeneity—whether just based on a statistical variable using a quantitative test such as the Cochran's Q value or the I^2 value.[4] It has become a common practice to establish an I^2 of 50% (defining the study as heterogeneous) and to disregard the qualitative background of a study due to this cause. Clinical heterogeneity should be defined before quantitative analysis to overcome differences between sample characteristics and properly define the best method of analysis. Qualitative analysis of the heterogeneity due to the characteristics mentioned would provide value over analysis from a statistical test and could shed light over important determinants of treatment effect and increase the scientific and clinical value of the metaanalysis.[16] Exploration of these differences often may yield new insights and hypotheses. Regarding statistical heterogeneity and mixing of studies, the authors' approach to decrease this value includes lowering this threshold to a more rigorous accepted I^2 of 25% or less to improve the inconsistency regarding selection of methods. The examination of all three types of heterogeneity is a crucial methodologic issue in systematic reviews and metaanalyses.

Modeling Effect Sizes

Although a complete discussion of all models available is beyond the scope of this editorial, the authors briefly will discuss two statistical models for a metaanalysis, fixed-effect, and random-effect models. Fixed-effect models assume that the included studies have nonrandom variables and one true effect size, and that variation is caused by sample errors or chance (intrastudy errors).[17] Random-effect models assume the opposite, that the studies exhibit diversity and variability attributed not only to random chance (intrastudy and interstudy errors), with more than one effect size.[18] The authors' belief is that specific selection of a model should be justified based on types of studies, quantitative heterogeneity, and qualitative heterogeneity, and not solely on statistical heterogeneity. When there is discrepancy between models, both should be used as a sensitivity analysis, allowing the reader to interpret the data with more granularity. The flawed data from poor-quality metaanalyses can lead very easily to significant shifts in the delivery of healthcare from flawed guideline recommendations, which use metaanalytical data as the highest-quality evidence. Also, many clinicians, researchers, and editors may not be knowledgeable about how to differentiate between high- and low-quality studies, and some biases may evade the attention of even experienced methodologists and statistical editors

Bias

To address publication bias, methodologists have proposed several statistical and graphic strategies to determine whether a metaanalysis is affected.[12] Although none of these strategies

is accepted widely, the most commonly used is the funnel plot.[19] However, a common problem with usage of the funnel plot to identify evidence of asymmetry and publication bias is that it is subjective and purely visual. It is not a formal statistical test. Presenting a funnel plot in a metaanalysis may be highly misleading, particularly when then are ten or fewer studies in the analysis.[20] Studies using funnel-plot asymmetry to assess publication bias pose several problems, including subjectivity on whether a plot is asymmetric, the amount of asymmetry required to have evidence of bias, likelihood of asymmetry with publication bias, and whether asymmetric plots can occur by chance. A formal statistical test of asymmetry, such as Egger's test, generally should be preferred to funnel plots. Although Egger's test lacks statistical power, it can show appropriate type I error.[21]

Reporting

To maintain the quality and standard of reporting metaanalyses, especially with randomized controlled trials (RCTs), there have been mandates over time to help classify important practices. One such mandate is the Quality of Reporting of Metaanalyses statement, which consists of a checklist and a flow diagram.[5] The checklist is organized into 21 headings and subheadings that encourage the authors to provide information on searches, selection, validity, assessment, data abstraction, study characteristics, quantitative data synthesis, and trial flow.[5] The flow diagram provides information about the number of RCTs identified, included, and excluded and the reasons for doing so.[5] This statement was revised and improved upon later with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement. This template updates the format to consist of a 27-item checklist (inclusive of the Quality of Reporting of Metaanalyses criteria) and four-phase flow diagram, along with expanding its reach from metaanalyses to include other types of research that include RCTs.[22]

The metaanalysis will remain a powerful tool in the research armamentarium, especially in cardiovascular medicine; there is, however, a pressing need for greater attention to the basic principles and crucial issues that the authors briefly have outlined. It will continue to provide high-level evidence for or against a therapy in question, but, as always, the devil is in the details.

Conflict of Interest

None.

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References

1 Freddi G, Romàn-Pumar JL. Evidence-based medicine: What it can and cannot do. Ann Ist Super Sanita 2011;47:22–5.
2 Sackett DL, Rosenberg WM, Gray JA, et al. Evidence based medicine: What it is and what it isn't. BMJ 1996;312:71–2.
3 Masic I, Miokovic M, Muhamedagic B. Evidence based medicine – new approaches and challenges. Acta Inform Med 2008;16:219–25.
4 Lee YH. An overview of meta-analysis for clinicians. Korean J Intern Med 2018;33:277–83.
5 Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: The QUOROM statement. Br J Surg 2000;87:1448–54.
6 Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
7 Ye XF, Yu DH, He J. The rise in meta-analyses from China. Epidemiology 2013;24:335–6.
8 Nunez Gil IJ, Elizondo A, Gradari S, et al. Meta-analysis design and results in real life: Problem solvers or detour to maze. A critical review of meta-analysis of DAPT randomized controlled trials. Cardiovasc Revasc Med 2019;20:897–906.
9 Page MJ, Shamseer L, Tricco AC. Registration of systematic reviews in PROSPERO: 30,000 records and counting. Syst Rev 2018;7:32.
10 Burns CS, Shapiro RM 2nd, Nix T, et al. Search results outliers among MEDLINE platforms. J Med Libr Assoc 2019;107:364–73.
11 Lam MT, De Longhi C, Turnbull J, et al. Has Embase replaced MEDLINE since coverage expansion? J Med Libr Assoc 2018;106:227–34.
12 Montori VM, Smieja M, Guyatt GH. Publication bias: A brief review for clinicians. Mayo Clin Proc 2000;75:1284–8.
13 Dickersin K, Min YI. Publication bias: The problem that won't go away. Ann N Y Acad Sci 1993;703:135–46.
14 Banno M, Tsujimoto Y, Kataoka Y. Using the Cochrane Central Register of Controlled Trials to identify clinical trial registration is insufficient: A cross-sectional study. BMC Med Res Methodol 2020;20:200.
15 Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: A systematic review. J Evid Based Med 2015;8:2–10.
16 Thompson SG. Why sources of heterogeneity in meta-analysis should be investigated. BMJ 1994;309:1351–5.
17 Davey Smith G, Egger M. Meta-analyses of randomised controlled trials. Lancet 1997;350:1182.
18 DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: An update. Contemp Clin Trials 2007;28:105–14.
19 Pham B, Platt R, McAuley L, et al. Is there a "best" way to detect and minimize publication bias? An empirical evaluation. Eval Health Prof 2001;24:109–25.
20 Lau J, Ioannidis JP, Terrin N, et al. The case of the misleading funnel plot. BMJ 2006;333:597–600.
21 Simmonds M. Quantifying the risk of error when interpreting funnel plots. Syst Rev 2015;4:24.
22 Moher D, Liberati A, Tetzlaff J, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009;6.