View Point

Systematic Reviews and Meta-analyses : Their darker side…

Madhuri S Kurdi[1], Sukhminder Jit Singh Bajwa[2]

Abstract

Background : Systematic reviews and meta-analyses occupy the highest position in the hierarchy of evidence-based medicine and are being increasingly published nowadays. In today's era of evidence-based medicine, medical practitioners are likely to look for evidence in the form of scientific literature to guide them in their clinical decision-making. At such times, a systematic review and meta-analysis on the topic becomes an attractive source of evidence. However, systematic reviews and meta-analyses have their own dark secrets and are associated with limitations about which clinicians should be aware. This article brings to light these limitations and a knowledge of these would go a long way in improving patient safety and outcomes.

Key words : Bias, Meta-analysis, Pitfalls, Publication, Systematic Review.

There has been a surge of Systematic Reviews (SRs) and Meta-analyses (MAs) in the last decade. SRs and MAs have become increasingly popular in healthcare settings and the use of MA in all branches has increased over the years. As the publication of original research articles is increasing, so is the number of SRs and MAs. The brighter side of SRs and MAs is familiar to many; however, understanding their darker side also assumes a lot of significance.

Editor's Comment :

- Systematic reviews and meta-analyses are increasingly published nowadays. It is well known that they provide the highest quality of evidence and provide large amounts of information on a topic. However, they are associated with many pitfalls. It is important that those conducting a systematic review and meta-analysis should follow certain strategies to reduce these lacunae and those reading it should consider all these pitfalls before applying the conclusion in clinical practice.

The Brighter Side :

SRs identify, bring together, evaluate and summarise all relevant individual study findings and available evidence on a specific, clearly defined topic and provide a summary of the available research. Individual researchers, policy/decision makers and clinical practitioners practising evidence-based medicine often do not have time to rummage through individual studies. Nevertheless, the SR and MA will make the evidence of multiple studies easily accessible and available to them in a single study[1]. This will help to reduce time delay in research discoveries to implementation. SRs use explicit, pre-specified and reproducible methods and adhere to strict scientific designs which limit bias and provide more reliable and enhanced precision of effect estimate than individual studies[2]. The results are thus more generisable, consistent and precise which help to draw reliable and accurate conclusions. New hypotheses about the subgroups of the study population can be generated and avenues with less available scientific information and those that deserve further exploration in the form of research are thus opened up. Since they summarise and provide large amounts of information on a topic and identify beneficial or harmful interventions, they can serve as very useful decision-making tools that are given due importance by policy-makers, guideline makers and granting agencies.

The Darker Side :

Though SRs and MAs bask at the top of the hierarchy of evidence, they are associated with several pitfalls. In fact, MAs have been criticised over the years and some authors have referred to them as 'mega silliness' and 'statistical alcherry'[3].

A MA might not have been properly conducted. The protocol of the MA may not have been registered in PROSPERO, the international database registry for the registration of SRs and MAs. The proper steps

[1]MD, Professor, Department of Anaesthesiology, Karnataka Medical College and Research Institute (KMC-RI), Hubballi, Karnataka 580022 and Corresponding Author
[2]MD, Ex Professor & Head, Department of Anaesthesiology and Intensive Care, Gian Sagar Medical College & Hospital, Patiala, Punjab 140601
Received on : 19/01/2024
Accepted on : 09/05/2024

How to cite this article : Systematic Reviews and Meta-analyses : Their darker side… Kurdi MS, Bajwa SJS. *J Indian Med Assoc* 2025; **123(7):** 55-7.

and tools for conduct of the SR, checklists and guidelines for report of the SRs might not have been followed by the authors [eg- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), PRISMA for systematic review protocols (PRISMA P), Quality of Reporting of Meta-analyses (QUOROM), Meta-analysis of Observational Studies in Epidemiology (MOOSE), etc][4]. All this can lead to sub-optimal reporting of the SR. Sometimes, the metaanalysis might have been poorly executed leading to invalid results.That means, the authors of the MA might have been careless in abstracting and summarising appropriate studies, important covariates might have not been considered and there might have been overstatements of the strength and precision of the results. A poorly comprehensive and less sensitive search strategy can lead to bias in study selection for the SR and this bias can further influence the interpretation of findings[5].

The other major problem includes a properly conducted SR and MA plagued with either of the three issues: poor quality of the included studies, heterogeneity between the studies and failure to address publication bias. Poor quality studies could include those with poor study design or insufficient statistical power and erratic results[6]. Nowadays, there is a rising concern for the publication of studies with false research findings. This is possible when the studies are smaller with smaller effect sizes, when there is a greater number and lesser pre-selection of tested relationships, bias and confounding issues of randomisation and blinding of Randomised Controlled Trials (RCTs) and use of faulty statistical analysis[7]. Sometimes, financial and other personal interests of the researchers such as postgraduate students under pressure of completing a dissertation or research grant recipients impatient to get the study published can lead to false and fabricated data collection and erroneous conclusions. The race and pressure to publish for the sake of the academic rules for faculty promotions can also lead to studies getting published in journals with liberal peer review systems[8,9]. Inclusion of such studies in the MA can lead to unreliable conclusions. Many published studies are not replicable and the study conclusion is based on results with formal statistical significance, typically for a p-value less than 0.05. Nonetheless, one has to keep in mind that medical research articles should not be interpreted based only on the p-values[10]. A meta research on published RCTs over the last decade on the potential effects of lowering the threshold of statistical significance in the field of chronic rhinosinusitis concluded that p-value statistic has multiple demerits and limitations. Lowering the p-value threshold from 0.05 to 0.005 would heavily alter the interpretation of RCTs in the last ten years. As is being mentioned in research circles, scientific literature needs to do away with over-reliance on the p-value and there is a requirement for alternate methods of interpretation of results[11]. Non-linear regressions, multivariate rather than univariate effects can also contribute to the lowering of quality of the MA[6].

Heterogeneity, either clinical or statistical between the studies included in the SR or MA is another important cause for concern. The studies included in a MA are like a bunch of grapes; if the grapes are not similar in size, appearance and taste, the homogeneity in the bunch is lost. Combining 'apples and oranges', that means, pooling studies that are dissimilar in some ways is another metaphor commonly accorded for this condition. When the treatment, patients and end-points are not similar or are at least comparable, the data summarised will not be homogeneous. Nonetheless, the effect size summed over heterogeneous data cannot be accorded much validity[6]. Pooling will be effective only if the effects are robust or consistent across the studies[3]. Grouping different causal factors can lead to meaningless estimates of effects[6].

Publication bias is a serious problem in SRs and MAs, which can affect the validity and generalisation of conclusions[12]. It may seriously distort attempts to estimate the effect under investigation.Publication bias can arise from the researcher deciding whether or not to submit results or from the tendency of journals to reject negative studies. Publication bias can arise from unpublished studies relevant to any given hypothesis. As published studies may systematically differ from unpublished ones, reviews or MAs based only on published data may reach misleading conclusions. Publication bias is "an editorial predilection for publishing particular findings, eg, positive results, which leads to the failure of authors to submit negative findings for publication"[13]. There has been supporting evidence to highlight that there is a disproportionate publication of statistically significant results in the journals with high-impact factors (File drawer effect)[14]. A study's source of funding may also unduly influence the probability of subsequent publication of the results[13].

Personal judgement and expertise of the researchers conducting the SR and meta-analysis can also affect the decisions that are made when designing and performing a MA. This can create personal bias that can affect the results of the MA[5].

Preventing and Detecting the Pitfalls :

The loopholes in a MA can be prevented/ corrected by adopting some time-tested strategies. The researchers attempting to conduct a SR and MA should be knowledgeable and well trained in the art and steps of conducting the SR. The Cochrane Collaboration provides training and support for the production of SRs and MA[1]. The inclusion of well-designed, good quality studies in the SR, reporting of heterogeneity statistic, the use of tools such as subgroup analyses and meta-regression tools for exploring the sources of heterogeneity is advocated[3]. Sensitivity analysis can be used to spot bias by exploring the robustness of the findings under different assumptions[5]. Individual Patient Data (IPD) MAs can be conducted; they avoid the biases associated with combining the summary statistics of separate studies and enable adjustment for individual level confounders. However, IPD analysis requires more time and resources.

Approaches such as selection models and funnel-plot-based methods can be used to deal with publication bias. Selection models use weight functions to adjust the overall effect size estimate and are usually employed as sensitivity analyses to assess the potential impact of publication bias. Funnel-plot-based methods include visual examination of a funnel plot, regression and rank tests, and the non-parametric trim and fill method[12]. If the funnel plot projected in the MA appears asymmetrical, one should check if sensitivity analysis has been conducted[3].

One has to remember that every SR may not lead to a MA because at the end of data synthesis, if the studies are not similar enough (homogeneous) in design/population/ outcomes, combining their results and conducting a MA by pooling the data will not lead to meaningful results[1].

As Newton had written in his letter to Oldenburg in 1676: " For it is not the number of experiments, but the weight which is to be regarded; where one will do, what is the need of many?"[6]. This only means that the conclusion of a single, robust RCT or observational study may be more helpful and easier to incorporate into practice than the misleading, unhelpful and harmful results and conclusion of an inappropriately conducted SR or a SR with inappropriately handled data. When one gets to read a MA, one should not get carried away by the numbers, figures and plots. They are like the lights on the floating ship of research. One has to take the results of the SR and MA with a pinch of salt, delve into the depths of the SR and ponder over the reliability of the findings before applying the conclusion in clinical practice. There is no doubt that there is a need for SRs and MAs; but there is an even greater need for high quality SRs and MAs with rigorous research methodology.

Funding : None

Conflict of Interest : None

References

1 Gopalakrishnan S, Ganeshkumar P — Systematic reviews and meta-analysis. Understanding the best evidence in primary healthcare. *J Family Med Prim Care* 2013; **2(1):** 9-14.
2 Yuan Y, Hunt RH — Systematic Reviews:The good, the bad, and the ugly. *Am J Gastroenterol* 2009; **104(5):** 1086-92.
3 Esterhuizen TM, Thabane L — Con: Meta-analysis: some key limitations and potential solutions. *Nephrol Dial Transplant* 2016; **31:** 882-5.
4 Singh S — The systematic review meta-analysis conundrum. *J Conserv Dent* 2022; **25(1):** 1-2.
5 Greco T, Zangrillo A, Biondi-Zoccai G, Landoni G — Meta-analysis: pitfalls and hints. *Heart Lung Vessel* 2013; **5(4):** 219-25.
6 Eysenck HJ — Meta-analysis and its problems. *BMJ* 1994; **309:** 789-92.
7 Dhulkhed VK, Tantry TP, Kurdi MS — Minimising statistical errors in the research domain: Time to work harder and dig deeper! *Indian J Anaesth* 2021; **65:** 567-71.
8 Dhulkhed VK, Kurdi MS, Dhulkhed PV, Ramaswamy AH — Faculty promotions in medical institutions in India: Can we improve the criteria? *Indian J Anaesth* 2016; **60(11):** 796-800.
9 Mehdiratta L, Bajwa SJS, Kurdi MS — A tripartite challenge of orphaned manuscripts, heedless writing and reluctant reviewing..... revamping the editing process! *Indian J Anaesth* 2021; **65:** 777-81.
10 Ionnidis John PA — Why most published research findings are false. *PLoS Med* 2005; **2(8):** e124.
11 Thakur P, Jha V — Potential effects of lowering threshold of statistical significance in the field of chronic rhinosinusitis-A meta-research on published randomized controlled trials over last decade. *Braz J Otorhinolaryngol* 2022; **88(5):** S83-S89.
12 Lin L, Chu H — Quantifying publication bias in meta-analysis. *Biometrics* 2018; **74:** 785-94.
13 Thornton A, Lee P — Publication bias in meta-analysis:its causes and consequences. *J Clin Epidemiol* 2000; **53(2):** 207-16.
14 Rosenthal R — The file drawer problem and tolerance for null results. *Psychol Bull* 1979; **86:** 638-41.