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VIEWPOINT

Understanding Meta-Epidemiological Studies

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Abstract

The concept of meta-epidemiology has been introduced because of the methodological limitations of the systematic review of clinical trials of intervention. Meta-epidemiology has moved from a statistical method to a new methodology to close gaps between evidence and practice, controlling the potential biases in quantitative systematic review and drawing appropriate evidence to establish evidence-based guidelines. Network meta-epidemiology has been suggested to overcome some limitations of meta-epidemiology. This review aims to clarify the concept and major methods to conduct a meta-epidemiological study.

Introduction

Owing to the recent advances to overcome the limitations of systematic review (SR), 'meta-epidemiology' has been proposed as a new methodology aimed at investigating the conflicting results of a SR with the same hypothesis, as well as the problems inherent in the research process, such as heterogeneity, publication bias, allocation concealment or post-allocation patient blinding, which make it difficult to provide a rationale for the results of a SR and drawing of appropriate conclusions.[1-2]

The term 'meta-epidemiology' can be defined as a 'statistical method' to analyze the influence of qualitative problems in randomized clinical trials and their confounding variables. In randomized clinical trials, the topics of traditional epidemiological studies are the individuals, while the topics of meta-epidemiological studies are the original articles of randomized clinical trials and observational studies.[3-5] Table 1 shows the characteristics of meta-epidemiological studies.

Meta-epidemiology is based on the combination of two concepts: epidemiology and metaanalysis. To adjust the purposes of those two concepts, meta-epidemiology strains to: (A) describe the distribution of the research evidence for a specific question; (B) examine heterogeneity and risk factors associated; and (C) control the biases between studies and summarize the research evidence. Considering such model, several methods, such as meta-regression, imputation, lack of informational odds ratio, double statistical models, have been tested, the term 'meta-epidemiology' being thus introduced.[3,6,7] Meta-epidemiological studies analyze the articles of randomized clinical trials and observational studies, meta-meta-epidemiologic studies analyze the meta-epidemiologic studies, and network meta-epidemiology analyzes the metaanalyses of published randomized clinical trials, whose data were analyzed with a statistical method valid for indirect comparisons or network metaanalysis, also called multiple-treatment or mixed-treatment comparison metaanalysis. Table 2 shows the major characteristics of meta-epidemiological, meta-meta-epidemiological and network meta-epidemiological studies.[3]

Recently there was a trend towards the application of the potentials of confounding meta-variables, such as genotype, study design, number of participants, generation of allocation sequence, allocation, concealment, blinding, placebo-control vs. no treatment control, exclusion of patients, randomization, effect size, single-center vs. multicenter study, and experimental vs. observational study.[8]

Keywords

Evidence-Based Practice / statistics & numeric data; Evidence-Based Medicine; Epidemiology.

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Table 1
Characteristics of meta-epidemiological studies

Unit of analysis	Metaanalysis
Statistics	Mainly metaanalysis or logistic regression
Comparison of interventions	Assess the effects of the research design, not the interventions
Assessment of quality	Not necessarily part of the design
Viability	Requires statistics for its definition
Target public	Researchers, professors and scientists

Table 2
Characteristics of meta-epidemiology, meta-meta-epidemiology and network meta-epidemiology

	Meta-epidemiology	Meta-meta-epidemiology	Network meta-epidemiology
Data sources	• MA studies of RCT	• M-epi studies combined into a harmonized dataset without overlap between MAs	• Network MA
Restrictions	• Informative MAs must include at least one trial with and without the risk factor of interest	• Different M-epi studies should investigate several sets of risk factors, potentially assessed with different methods	• Eligible networks should include more trials than interventions
Assessment of risk factors related to the trial level	• Re-assessment from individual trial reports or reliance on assessment from each selected MA	• Assessment from each M-epi study	• Re-assessment from individual trial reports or reliance on assessment from each selected network MA
Assumption regarding direction of bias	• In active-inactive comparisons, a risk factor is not expected to favor the inactive comparator • In active-active comparisons, an assumption regarding direction of bias is required		• In star-shaped networks, a risk factor is expected not to favor the common comparator • In networks with closed-loops, an assumption regarding direction of bias is necessary
Estimation of the impact of risk factors on intervention effect estimates	• Effect estimates are compared between trials with and without the risk factor within each MA; the significant impact of the risk factor is estimated across all MAs		• Effect estimates are compared between trials with and without the risk factor within each network; the mean impact of the risk factor is estimated across all networks
Assumption regarding exchangeability of the impact of risk factors on intervention effect estimates	• Between trials within MAs, and between MAs		• Between trials within networks, and between network MAs

** MA: metaanalysis; RCT: randomized clinical trial; M-epi: meta-epidemiological.*

Meta-epidemiological studies have limitations: study results allow for a dichotomous analysis and continuous results cannot be managed; if the number of study subjects is reduced, the statistical power is limited; and indirect comparisons cannot be applied. Aiming at overcoming such limitations, the term 'network meta-epidemiology' has been proposed to emphasize how to make direct comparisons when several types of interventions are assessed. Therefore, developing research tools, Copas parametric model, graphs presented and published items are paramount for their conduction.[9]

In a study assessing 31 metaanalyses on cardiovascular biomarkers (C-reactive protein, non-HDL-cholesterol, lipoprotein(a), post-load glucose, fibrinogen, B-type natriuretic peptide and troponins), the prognostic effect was significantly stronger in observational studies than in randomized clinical trials. Cardiovascular biomarkers often have less promising results in the evidence derived from randomized clinical trials than from observational studies.[10]

Conclusion

This topic is extremely new, generating new questions that fill the gaps in this type of investigation. In addition, this challenging topic requires new methodologies for science advance.

Author contributions

Conception and design of the research:Borges LSR. Acquisition of data: Borges LSR. Analysis and interpretation of the data: Borges LSR. Writing of the manuscript: Borges LSR. Critical revision of the manuscript for intellectual content: Borges LSR.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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