

Bibliographic study showed improving statistical methodology of network meta-analyses published between 1999 and 2015

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Abstract

Objectives: To assess the characteristics and core statistical methodology specific to network meta-analyses (NMAs) in clinical research articles.

Study Design and Setting: We searched MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews from inception until April 14, 2015, for NMAs of randomized controlled trials including at least four different interventions. Two reviewers independently screened potential studies, whereas data abstraction was performed by a single reviewer and verified by a second.

Results: A total of 456 NMAs, which included a median (interquartile range) of 21 (13–40) studies and 7 (5–9) treatment nodes, were assessed. A total of 125 NMAs (27%) were star networks; this proportion declined from 100% in 2005 to 19% in 2015 ($P = 0.01$ by test of trend). An increasing number of NMAs discussed transitivity or inconsistency (0% in 2005, 86% in 2015, $P < 0.01$) and 150 (45%) used appropriate methods to test for inconsistency (14% in 2006, 74% in 2015, $P < 0.01$). Heterogeneity was explored in 256 NMAs (56%), with no change over time ($P = 0.10$). All pairwise effects were reported in 234 NMAs (51%), with some increase over time ($P = 0.02$). The hierarchy of treatments was presented in 195 NMAs (43%), the probability of being best was most commonly reported (137 NMAs, 70%), but use of surface under the cumulative ranking curves increased steeply (0% in 2005, 33% in 2015, $P < 0.01$).

Conclusion: Many NMAs published in the medical literature have significant limitations in both the conduct and reporting of the statistical analysis and numerical results. The situation has, however, improved in recent years, in particular with respect to the evaluation of the underlying assumptions, but considerable room for further improvements remains. © 2016 Elsevier Inc. All rights reserved.

Keywords: Multiple interventions; Meta-epidemiology; Mixed-treatment comparisons; Inconsistency; Reporting; Indirect evidence

1. Introduction

Network meta-analysis (NMA) is becoming increasingly popular for evidence synthesis [1–4] with enthusiasts considering NMA as the “new norm” for comparative effectiveness research [5]. However, empirical studies exploring the characteristics of published NMAs of interventions have raised the need for improving the quality of the application of NMA methods [1,2,6–9]. Concerns about inappropriate applications of NMA methods and inadequate and nontransparent reporting of methods and results have been identified as major issues [10–12]. For instance, Nikolakopoulou et al. [1] found that 68% of the

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What is new?**Key findings**

- Although the amount of evidence (the number of treatments and studies) included in published network meta-analyses (NMAs) remains stable, the undertaking and reporting of statistical methods have significantly improved over the years. The assumptions underlying NMA are increasingly discussed and evaluated using appropriate methods. Less than 10% of NMAs published in 2014 and 2015 failed to evaluate the assumptions of the joint synthesis.

What this adds to what was known?

- This meta-epidemiological study presents the largest collection of published NMAs over the past 16 years. It provides an overview of the structural characteristics and statistical methodology of 456 published networks of interventions. It shows that the statistical methods in NMA have considerably improved in all aspects and some, such as the use of appropriate methods to evaluate the plausibility of the assumptions, are now routinely performed. We conclude that the increasingly populous community of NMA methodologists is quickly advancing through the learning curve of statistical methods employed in NMA.

What is the implication and what should change now?

- The updated description of the structural characteristics of the published NMAs can be used to inform pragmatic simulation studies and the development of methods that are relevant to the type of networks typically found in the medical literature.
- Future tutorials and training should be focused on improving the methodology and reporting on items that, although they have improved, their prevalence remains low, such as the formal exploration of heterogeneity and inconsistency and the presentation of all pairwise treatment effects.

NMAs published by the end of 2012 used either inappropriate or unspecified methods to assess inconsistency, whereas Bafeta et al. [6] concluded that reporting guidelines are necessary to reduce heterogeneity in presentation of NMA results.

The importance of empirical evidence in a novel, rapidly evolving methodological field is illustrated by the role such studies played in shaping the methodology for conventional pairwise meta-analysis. The assessment of risk of bias in

the included studies [13–15], the magnitude and determinants of heterogeneity [16–18], the relative advantages of different methods to evaluate publication bias and small-study effects [19–21], and the importance of a comprehensive search for relevant studies [22] are examples of meta-epidemiological studies that have guided the choice of optimal methods. We are aware of only three such meta-epidemiological studies in NMA: Song et al. [23,24] evaluated the prevalence of inconsistency in networks with three treatments, Veroniki et al. [25] studied the prevalence of inconsistency in complex NMAs that included at least four treatments using two alternative methods, whereas Chaimani et al. [26] have provided empirical evidence about the impact of risk of bias and small-study effects.

In recent years, the methodology of NMA has been further refined and many tutorials and guidance papers have been published [12,27–31]. Efthimiou et al., [32] in a recent review of methodological articles published until March 2014, found a steep increase after 2011 in the number of relevant publications. In 2012 and 2013, 83 methodological articles were published compared to 58 articles between 2005 and 2011. For example, until recently, most networks were fitted within a Bayesian framework as hierarchical models [1], but new NMA methods include publications by White et al. [33] suggesting NMAs can be viewed as a specific case of multivariate meta-regression and by Higgins et al. [34] presenting a new test for inconsistency. Their work enables researchers to fit models using frequentist software. Stata routines were made available by White et al. and Chaimani et al. that simplified NMA implementation by nonstatisticians [35–39].

In this paper, we aim to describe how methodologies specific to NMA and reporting quality of results has evolved over time, monitor the rate of adoption for the new methodological developments, and provide an updated overview of the characteristics of published networks.

2. Methods*2.1. Inclusion criteria*

Networks of randomized controlled trials were eligible if they included at least four different interventions (defined as different drugs or other medical treatments, or different schedules, doses or formulations of the same treatment) including placebo, no treatment, waiting list, or other control interventions. We excluded networks that included observational or diagnostic test accuracy studies, NMAs in which the number of trials was smaller than the number of interventions, and articles that performed naive indirect comparisons by pooling data across study arms.

2.2. Literature search

An expert librarian compiled the literature search, which was peer reviewed by a second librarian using the Peer

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