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# Deficiencies in addressing effect modification in network meta-analyses: a meta-epidemiological survey

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## Abstract

**Objective:** The objectives of this study were to evaluate the current state of reporting and handling of effect modification in network meta-analyses (NMAs) and perform exploratory analyses to identify variables that are potentially associated with incomplete reporting of effect modifiers in NMAs.

**Study Design and Setting:** We conducted a meta-epidemiological survey using a systematic review of NMAs published in 2013 and identified through MEDLINE and Embase databases.

**Results:** The review identified 77 NMAs. The most common type of effect modifiers identified and explored were patient characteristics (50.7% or 39/77), and the most common adjustment method used was sensitivity analysis (51.7% or 30/58). Over 45% (35/77) of studies did not describe a plan, nearly 40% (30/77) did not report the results of analyses, and approximately 47% (36/77) of studies had incomplete reporting. Exploratory univariate regression analyses yielded a statistically significant association for the variables of journal impact factor, ratio of randomized controlled trials to number of comparisons, and total number of randomized controlled trials.

**Conclusion:** Current reporting practices are largely deficient, given that almost half of identified published NMAs do not explore or report effect modification. Journal impact factor and amount of available information in a network were associated with completeness of reporting. 

*Keywords:* Network meta-analysis; Effect modifier; Systematic literature review; Meta-epidemiological survey; Methodology; Indirect treatment comparisons; Heterogeneity

## 1. Introduction

Over the last decade, network meta-analyses (NMAs) of randomized controlled trials (RCTs) have been increasingly used to indirectly analyze the relationship between treatments for which no head-to-head comparisons exist [1,2]. NMAs and indirect treatment comparisons are also playing an increasing role in evidence synthesis to support health technology assessment (HTA) reimbursement submissions, a topic of discussion at the 2014 Canadian Agency for Drugs and Technologies in Health Symposium [3,4]. The increasing role of NMAs is also evident by the extensive NMA technical guidance that has been developed by national HTA agencies [5], such as Technical Support Documents 1, 2, and 7 developed by the National Institute for Health and Care Excellence (NICE) [6], as well as guidance developed by international organizations such as guidance documents and a checklist for conducting and synthesizing NMAs by the International Society of Pharmacoeconomics and Health Outcomes Researchers (ISPOR) [7,8].

Heterogeneity refers to the true variation in treatment effects between different patient characteristics, treatment characteristics, or study characteristics, which may vary between RCTs. The presence of heterogeneity is an indicator of the presence of effect modifiers, which may reflect measured or unmeasured prognostic variables [7–9], such

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**What is new?**

**Key findings**

- Nearly half of identified published network meta-analyses (NMAs) do not explore or report effect modification.
- Journal impact factor and amount of available information in a network were associated with completeness of reporting.

**What this adds to what was known?**

- Current reporting practices of effect modifiers in NMAs are largely deficient, given that almost half of identified published NMAs do not explore or report effect modification.
- Our study identified some variables potentially associated to completeness of reporting, including journal impact factor and those related to amount of available information in a network, although these variables must be further investigated and confirmed through future research.

**What is the implication and what should change now?**

- There is much room for improvement in the current state of how methodological applications are used in the published literature in terms of reporting and methods to handle effect modifiers in NMAs. Readers must be aware of whether statistical analysis plans include steps that report and address potential effect modifiers of NMA studies.

as treatment dosages, disease duration, age, and length of follow-up [7]. The uneven distribution of effect modifiers across treatment comparisons is what causes confounding of indirect estimates, thus attenuating the validity of the indirect comparisons [10]. Guidance from NICE describes several approaches to adjust for effect modifiers in an NMA, including meta-regression [9]. A best practices checklist, prepared by ISPOR, recommends the inclusion of a description of sensitivity analyses, subgroup analyses, and meta-regression to be used in evaluating the NMA [8]. The feasibility of these approaches is largely dependent on the available data in the included RCTs. For example, restricting the network to certain subgroups may lead to excluding RCTs missing these subgroups, which serve as the only link to interventions of interest, thus fragmenting the network and possibly leading to reduced feasibility of the analysis.

To ensure proper dissemination and adoption of these methods, it is important to understand the current state of how methodological applications are reported in the published literature and to identify current practices in the field to guide future research. Our meta-epidemiological survey using a systematic review of NMAs published in 2013 is to our knowledge the first of its kind in the published literature and will be used to evaluate the current state of reporting and handling of effect modification in NMAs.

## 2. Methods

### 2.1. Objectives

The objective of the study was to conduct a systematic literature review to

1. evaluate the reporting of effect modifier(s) addressed in NMA publications.
2. determine the methods used to handle effect modifier(s) in NMAs.
3. identify variables that are potentially associated with incomplete reporting of effect modifiers(s) in NMAs.

Three study outcomes were assessed to answer objective 1 (reporting), and these three outcomes were also evaluated against all 11 independent variables to answer objective 3 (variables of incomplete reporting). The three outcomes were as follows:

1. The presence of a plan to address potential effect modifier(s). This plan was expected to be described in the NMA study as part of the methods of study conduct and would include the study procedures to be followed for handling effect modification, if present.
2. The results on effect modifier(s) analyses being reported. These results were expected to be reported in the results section of the NMA study and would at least reference the general analysis conducted.
3. Complete reporting—a composite outcome defined as an NMA study having both a plan as well as reporting the effect modifier(s) analyses results.

### 2.2. Study design overview

We conducted a meta-epidemiological study through a systematic review of NMA publications comparing the clinical efficacy of three or more interventions with an evidence network composed of only RCTs. No upper limits were placed on NMA complexity, that is, the number of interventions, number of RCTs, or number of comparisons in the evidence network. All NMAs were based on human RCTs that were published in English in 2013, allowing for a more focused review of the latest NMA evidence generalizable to a human clinical setting.

### 2.3. Data sources

We conducted a broad and sensitive literature search for NMAs meeting the aforementioned eligibility criteria using