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Directed acyclic graphs can help understand bias in indirect and mixed treatment comparisons

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Abstract

Objective: To introduce and advocate directed acyclic graphs (DAGs) as a useful tool to understand when indirect and mixed treatment comparisons are invalid and guide strategies that limit bias.

Study Design and Setting: By means of DAGs, it is heuristically explained when indirect and mixed treatment comparisons are biased, and whether statistical adjustment of imbalances in study and patient characteristics across different comparisons in the network of RCTs is appropriate.

Results: A major threat to the validity of indirect and mixed treatment comparisons is a difference in modifiers of the relative treatment effect across comparisons, and statistically adjusting for these differences can improve comparability and remove bias. However, adjustment for differences in covariates across comparisons that are not effect modifiers is not necessary and can even introduce bias. As a special case, we outline that adjustment for the baseline risk might be useful to improve similarity and consistency, but may also bias findings.

Conclusion: DAGs are useful to evaluate conceptually the assumptions underlying indirect and mixed treatment comparison, to identify sources of bias and guide the implementation of analytical methods used for network meta-analysis of RCTs. © 2012 Elsevier Inc. All rights reserved.

Keywords: Indirect treatment comparisons; Multiple-treatment meta-analysis; Network meta-analysis; Bias; Directed acyclic graphs; Randomized controlled trials

1. Introduction

In the absence of a randomized controlled trial (RCT) comparing all interventions of interest, an indirect treatment comparison of different RCTs can provide useful evidence to inform healthcare decision making [1−8]. Even when the results of the direct comparisons are conclusive, combining them with indirect estimates in a mixed treatment comparison may yield more refined estimates [1−4]. If the available evidence base consists of a network of RCTs involving treatments compared directly or indirectly or both, it can be synthesized by means of a network meta-analysis [9].

In indirect and mixed treatment comparisons, the randomization holds within but not across trials. Accordingly, covariates that affect treatment effects may be imbalanced across comparisons, resulting in violations of the similarity assumption [6]. When the network of RCTs consists of both direct and indirect evidence for some comparisons, the imbalance in these treatment-by-covariate interactions results in consistency violations. Regression-based techniques have been used to account for such differences across comparisons [6,10−14].

The objective of this article was to advocate directed acyclic graphs (DAGs) as a useful tool to understand bias in indirect and mixed treatment comparisons and guide the implementation of analytical methods.

2. DAGs, effect modification, confounding bias, and collider stratification bias

2.1. DAGs

A DAG is a graphical structure consisting of a set of relevant *nodes*, each associated with a random variable and corresponding *arrows* connecting the nodes representing dependence [15−19]. In Fig. 1, three DAGs include the

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What is new?

- It is known that the assumptions of similarity and consistency underlie indirect and mixed treatment comparisons. These assumptions are violated if effect modifiers of the relative treatment effect differ across comparisons.
- This article uses directed acyclic graphs (DAGs) to conceptually evaluate the assumption of similarity and consistency, and to explain heuristically when analyses of indirect and mixed treatment comparisons of randomized controlled trials are biased.
- Although statistically adjusting for differences in effect modifier across comparisons can improve comparability, by means of DAGs it is demonstrated that adjusting for differences that are not effect modifiers is not necessary and can even introduce bias.
- Furthermore, it is shown that adjustment for the baseline risk to explain heterogeneity can introduce bias in indirect and mixed treatment comparisons as well.
- This article suggests the use of DAGs to identify sources of bias in indirect and mixed treatment comparisons and guide the implementation of analytical methods used for network meta-analysis of RCTs.

nodes treatment T, outcome O along with co-variables severity of disease C1, adverse events C2, and biomarker status C3. A node pointing to another is called a *parent*; a node pointed to is a *child* (e.g., C1 is a parent node of T, Fig. 1B). A *path* between two variables is an unbroken sequence of arrows (in any direction). A graph is acyclic if no directed path (following the arrows) forms a closed loop [15–18]. If we are interested in estimating the effect of T on O, the path between T and O reflects the *target path*.

A DAG is a causal DAG when all common causes of any pair of variables in the graph are included [15–18]. A causal DAG does not need to include variables that are not of interest for the analysis, and that are not common causes of other variables in the DAG [15–18]. In a causal DAG, the arrows reflect causal effects. A complete DAG does not exclude any possible causal effects. Incomplete DAGs reflect expert knowledge with missing arrows; the absence of an arrow between two variables reflects no dependency between these [15–18]. A causal effect implies an association (i.e., correlation) between the two variables [15–18]. In Fig. 1A, T has a causal effect on O, and as such there is an association between T and O.

2.2. Effect modification

A variable can be considered an *effect modifier* when the causal relative treatment effect (i.e., causal risk difference or relative risk or odds ratio) of one variable on another is different for different levels of a covariate [20]. In Fig. 1A, B, C1 is an effect modifier for the causal effect of treatment T on outcome O if the effect is different for severe disease than for nonsevere disease [21]. In general, a variable C is said to be an effect modifier of the relative effect of T on outcome O if: 1) C is *not* affected by T; 2) there exist multiple levels of T; and 3) the difference between outcome O for the levels of T (i.e., the relative effect size) varies across strata of C [20,21].

2.3. Confounding bias

In addition to a causal effect, two variables that share a common cause will also be marginally associated (i.e., correlated) even if neither is a cause of the other [15–19]. In Fig. 1B, T and O share a common cause C1. The path from T via C1 to O is called a *backdoor path* because it has an arrowhead pointing to T [15–19]. The *backdoor criterion* defines that *confounding bias* would be present if and only if treatment T would remain associated with outcome O even if all exposure effects (i.e., the direct association of T on O) were removed [15–17,19–24]. If in Fig. 1B the arrow between T and O were removed, there would still be an association between T and O given the presence of common cause C1; C1 is a confounder here. Conditioning on C1 (through stratification or regression) will remove this bias. Note that the variable C1 in the second DAG can act both as confounder and effect modifier.

2.4. Collider stratification bias

A *blocked path* between the two variables is a path that passes from a parent to child and then back to another parent in the opposite direction. In Fig. 1C, the variable C2 is called a *collider* on the blocked path T → C2 ← C3 (e.g., two arrowheads are pointing toward each other) [15–19,23,25]. Despite the path from T to C3, the presence of a collider on this path implies no marginal association between these two variables. However, because two variables that have a common effect will be conditionally associated if a measure of association is computed within levels of this common effect, conditioning on a collider on a path between two variables creates an *unblocked* or *open* path and a marginal association [25]. In Fig. 1C, new treatment B (node T) and the presence of a certain biomarker (node C3) makes it more likely that a patient experiences an adverse event C2. Now, only knowing that a patient is positive for biomarker C3 provides no information about whether a patient has received the new treatment B (node T). There is no association between T and C3. But, if we also know that the patient has experienced an adverse event (node C2), then it is more likely that the patient with C3 has received new treatment B. Alternatively, if that same patient has not experienced an adverse event (C2), then the patient would be more likely to have received the standard

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