JAMA Guide to Statistics and Methods

Causal Directed Acyclic Graphs

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The design and interpretation of clinical studies requires consideration of variables beyond the exposure or treatment of interest and patient outcomes, including decisions about which variables to capture and, of those, which to control for in statistical analyses to minimize bias in estimating treatment effects. Causal directed acyclic graphs (DAGs) are a useful tool for communicating researchers' understanding of the potential interplay among variables and are commonly used for mediation analysis.[1,2] Assumptions are presented visually in a causal DAG and, based on this visual representation, researchers can deduce which variables require control to minimize bias and which variables could introduce bias if controlled in the analysis.[3-5]

In a 2019 article in *JAMA Pediatrics*, Ramirez et al[6] studied the association between atopic dermatitis and sleep duration and quality among children. The authors used a causal DAG (Figure 1 in their article) to illustrate potential relationships among demographic and socioeconomic factors, smoking exposure, comorbid asthma, and allergic rhinitis.

What Are Causal DAGs and Why Are They Important?

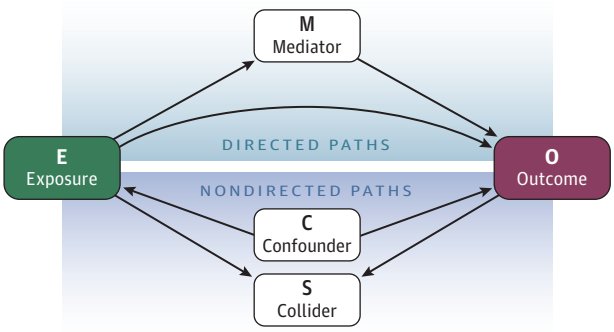
A causal DAG is a graph with arrows that show the direction of hypothesized causal effects (eg, from atopic dermatitis to sleep quality). Because causality implies ordering in time from cause to effect, cycles are not possible (eg, atopic dermatitis at a given time may affect sleep quality, but sleep quality cannot then affect atopic dermatitis at or before that time). Hence, causal DAGs are directed and acyclic. The lack of an arrow between any 2 variables represents an assumption that there is no direct causal relationship between those variables. The presence of an arrow between 2 variables does not guarantee that a relationship will be observed in the data because, for example, the effect it represents may be negligible.

A complete causal DAG includes, for each possible pair of variables along the paths from cause to effect, any variable that has a causal effect on both members of the pair. Often these additional variables cannot be measured. The causal DAG should also include a variable representing selection of patients included in the study. By providing a visual representation of potential causal pathways that may influence the relationship between patient exposures or treatments and clinical outcomes, causal DAGs help identify sources of bias and ways to adjust for them.

How Do Causal DAGs Work?

The **Figure** shows a causal DAG with study exposure or treatment E and study outcome O (for example, atopic dermatitis E and sleep quality O). The arrow from E to O implies that the value of O may be affected by the value of E. A path in a causal DAG is a sequence of variables connected by arrows. There are 2 types of paths, directed paths and nondirected paths. Directed paths are those that follow the arrow direction from cause to effect, eg, E → O and E → M → O (where M is an intermediate or mediator). All other paths from E to O are considered nondirected

Figure. Example of Directed and Nondirected Paths



The directed paths represent the effect of E on O that is being estimated. Bias can be reduced by adjusting or controlling for C to close that nondirected path. Conversely, the nondirected path that includes S is closed if it is uncontrolled and thus is not a biasing path; controlling for S opens that path and may introduce bias.

(eg, E ← C → O and E → S ← O). If the causal DAG is an accurate representation of the potential causal pathways, and the sources of association can be limited to the directed paths from E to O, the observed association will accurately measure a causal relationship. In other words, the observed association between E and O will provide an unbiased estimate of the effect of E on the outcome O. Conversely, nondirected paths are potential sources of bias.

A nondirected path, such as E ← C → O that exits the exposure against the direction of an arrow, is called a *backdoor path*. Associations transmitted by backdoor paths produce the bias known as confounding; here, C is the confounding variable or confounder.[3-5] A nondirected path contains a *collider* if there is a variable on the path with 2 arrows entering it (ie, the collision), eg, the path E → S ← O, where S is the collider on the path. To obtain unbiased effect estimates, it is necessary to ensure that the nondirected paths linking exposure and outcome cannot transmit associations and influence the observed effect; this is called closing a path. Methods for ensuring a nondirected path is closed are different depending on whether the source of potential bias is a confounder or a collider.

Statistical adjustment or control of a variable (eg, by regression or stratification) is an example of conditioning on a variable. Conditioning on a confounder closes that backdoor path, thus eliminating it as a bias source. Unlike a confounder, conditioning on a collider (or one of its effects) actually opens the path at that collider; not conditioning on the collider leaves the path closed and avoids bias. In the Figure, before statistical adjustment, the path E ← C → O is open and E → S ← O is closed. If the analysis conditions on C, the biasing confounding path becomes closed. However, if the analysis conditions on S, that path becomes opened, making it a biasing collider path.[4,5] This means that analyses should avoid controlling for colliders or their potential effects.

Unlike controlling for a variable, however, conditioning is not always intentional. For example, if S represents loss of patients before study completion, the analysis is forced to condition on the resulting selection of patients (as only patients who complete the study are likely to have the measured outcome) and use appropriate analysis methods.

Mediators are part of a directed path, and thus, controlling for them in the analysis removes part of the effect of exposure. While researchers may wish to control for M to try to estimate the effects of E that are not mediated through M, doing so may induce bias if M is a collider along another path.[4]

There are often additional confounders that cannot be controlled because they are either not known to the researchers or because they cannot be accurately measured. For instance, there may be an unmeasured variable U (eg, parent atopy), such that there is a confounding path E ← C ← U → O. In this case, if C were measured, the path could still be closed by controlling for C even though the path contains the unknown U.

Measurement error or misclassification can also be included by drawing arrows from each included variable to its recorded value (eg, C → C*, where C* is the measured value of C). If C is a confounder, the weaker the relationship between C and C*, the less well C will have been controlled for when adjusted for C*, and the more residual confounding by C will be left. With additional variables, other bias sources (such as biased recall) can be depicted in the causal DAG.

Limitations of Causal DAGs

Causal DAGs illustrate a particular set of assumptions that may not be correct; however, they afford readers the opportunity to decide which potential effects need to be considered. Causal DAGs do not indicate the magnitude of biases or their interplay with random errors. Additionally, causal DAGs can become complex, especially if there are repeated measures, making their interpretation more cumbersome. This complexity, however, reflects real-world concerns about potential sources of bias.

Application of a Causal DAG in Ramirez et al

Ramirez et al[6] used their causal DAG to identify a minimal set of variables that required statistical control to help ensure an unbiased estimate. For instance, they controlled for Child Race and Ethnicity, a variable along the Atopic Dermatitis ← Child Race and Ethnicity → Sleep nondirected (backdoor) path. They noted Child Asthma or Allergic Rhinitis (CAAR) was a collider and did not control for it; they thus avoided opening nondirected paths such as Atopic Dermatitis ← Child Race and Ethnicity → CAAR ← Maternal Age at Delivery → Sleep. However, CAAR is not a collider on the Atopic Dermatitis ← Parent Atopy → CAAR → Sleep path. Because Parent Atopy is unmeasured (and thus cannot be controlled), and CAAR remained uncontrolled, this nondirected path is a potential source of bias. The amount of bias left depends on the aggregate strength of association transmitted by any remaining biasing paths (including those not included in the graph).[4,5]

Interpretation of Ramirez et al

By providing a detailed causal DAG, Ramirez et al[6] made the assumptions of their analysis more explicit and transparent, revealing potential sources of bias that were not controlled in their analysis. Judgements about the validity of their results should depend on how much bias is left by that control, which in turn depends on how well that control reduced bias sources (eg, poor measurement of a variable limits its control).[4]

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