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Using Causal Diagrams to Improve the Design and Interpretation of Medical Research

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Causal directed acyclic graphs (cDAGs) have become popular tools for researchers to better examine biases related to causal questions. DAGs comprise a series of arrows connecting nodes that represent variables and in doing so can demonstrate the causal relation between different variables. cDAGs can provide researchers with a blueprint of the exposure and outcome relation and the other variables that play a role in that causal question. cDAGs can be helpful in the design and interpretation of observational studies in pulmonary, critical care, sleep, and cardiovascular medicine. They can also help clinicians and researchers to better identify the structure of different biases that can affect the validity of observational studies. Most of the available literature on cDAGs and their function use language that might be unfamiliar to clinicians. This article explains cDAG terminology and the principles behind how they work. We use cDAGs and clinical examples that are mostly focused in the area of pulmonary medicine to describe the structure of confounding, selection bias, overadjustment bias, and detection bias. These principles are then applied to a more complex published case study on the use of statins and COPD mortality. We also introduce readers to other resources for a more in-depth discussion of causal inference principles.

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KEY WORDS: causal directed acyclic graphs; colliders; confounding; detection bias; overadjustment bias; selection bias

Introduction

Medical research often attempts to ascertain the predictors of a certain outcome or whether a treatment causes a certain outcome. Randomized controlled trials (RCTs) are considered the gold standard for establishing causation. Because RCT data are not available for most causal questions, many research studies that address causal questions use observational designs. At times, results from observational studies can confuse the effect of interest with other variables' effects, leading to an association that is not causal.[1] It would be helpful for clinicians and researchers to be able to visualize the structure of biases in a clinical study to ensure that the study design and analysis considers these kinds of issues. By visualizing these biases, researchers can better identify and control for them.

ABBREVIATIONS: cDAG = causal directed acyclic graph; LABA = long-acting beta$_2$-adrenergic receptor agonist; RCT = randomized controlled trial

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There has been an explosion in recent years of observational studies in the areas of pulmonary, critical care, sleep, and cardiovascular medicine using Big Data. This has led to the identification of different types of biases that might affect the validity of these studies.[2] Causal directed acyclic graphs (cDAGs) are a relatively new framework for visualizing the variables that play a role in causal questions.[3,4] Several reviews and tutorials have been published on the use of cDAGs intended for clinicians and clinician reseachers.[5-8] A review by Lederer et al[8] introduces general concepts, including confounding and selection bias for pulmonary medicine researchers. The current article extends these concepts to include other pertinent terminologies and principles of causal inference that we believe researchers should be familiar with. We also attempt to link principles of causal inference to clinical examples that we believe are critical to the understanding of these concepts for the readers.

The current review expands on the existing literature and provides a more detailed review of how cDAGs can identify four common types of biases in epidemiologic studies (confounding, selection, overadjustment, and detection bias) using, for the most part, examples from the pulmonary, critical care, sleep, and cardiovascular medicine literature. We will also use a published research study on the effect of statin use and COPD mortality as a case study and show, by drawing a cDAG, how to identify and control for potential biases.[9]

Directed Acyclic Graphs

DAGs comprise a series of arrows connecting nodes that represent variables. Any series of adjacent arrows in the graph, regardless of direction, forms a path. The series must be acyclic, meaning it cannot form a feedback loop in which one variable causes itself.

DAGs are based on mathematical graph theory and have historically been used in computer science, particularly in the creation of computer algorithms. They are increasingly used to address causation in areas of science such as epidemiology and medicine.[10] DAGs that show a causal effect between two or more variables are called causal DAGs (cDAGs). Table 1 defines common terms related to cDAGs. The following text discusses application of cDAGs in identifying different types of biases using clinical examples.

Identifying Bias Structures in Epidemiologic Studies Using cDAGs

Confounding Bias

Confounding is perhaps the most prevalent type of bias that can affect the validity of epidemiologic studies. Consider an observational cohort that uses a large health claims database to examine the risk of new COPD exacerbations with current users of a new long-acting beta$_2$-adrenergic receptor agonist (LABA). Suppose the new LABA had previously been shown to reduce COPD

TABLE 1] Common Definitions Used in Causal Directed Acyclic Graphs

Term	Definition
Arrow	Shows direct causal effect
Box	A box around a variable means that variable is conditioned upon
Path	A series of adjacent arrows regardless of their directions
Ancestor/descendent	In a directed path from A to B, A is an ancestor of B and B is a descendent of A
Directed path	A path in which all of the arrows lie tail to head (pointing in the same direction)
Undirected path	A path in which some of the arrows lie tail to head and others head to tail (ie, not all of the arrows point in the same direction)
Collider	A variable that has two arrowheads converging on it within a path
Collider bias	A bias created when a collider variable is conditioned on. Also known as selection bias
Blocked path	A path that contains a noncollider that has been conditioned on or a path that contains a collider, where neither the collider nor its descendant have been conditioned on
Causal path	A directed path from the exposure to the outcome
Biasing path	An open undirected path between the exposure and outcome
Confounding path	An undirected path that contains a common cause of the exposure and outcome
Confounding	Bias created by a confounding path
Confounder	A variable that is on a confounding path and, upon conditioning, blocks that path. A confounder can include but is not required to be common causes of exposure and outcome variables
Mediator	A variable that indirectly mediates the effect of the exposure on the outcome

exacerbations in a large randomized trial but in the observational cohort study, investigators observe the opposite effect (a harmful effect with the drug). One potential reason for this paradoxical effect is confounding by indication.

Figure 1A shows the variables at play in this cohort study. In this graphic, arrows represent a direct effect from one variable to another. There is an arrow or causal path from LABA use to COPD exacerbations because this is the causal question we want to examine. This path can also be called a directed path because it describes a path that starts from LABA use and ends on COPD exacerbations. Thus, all causal paths are directed paths.

COPD severity is an ancestor of COPD exacerbations, whereas COPD exacerbations would be a descendent of COPD severity. There is an arrow from COPD severity to LABA use (patients with more severe COPD are more likely to receive LABAs) and from COPD severity to COPD exacerbations because severe COPD can lead to COPD exacerbations.

The path LABA ← COPD severity → COPD exacerbation is an undirected path because the sequence of arrows is not directional from LABA use to COPD exacerbation. This undirected path through COPD severity is a biasing path. The path on which COPD severity lies is also referred to as a confounding path because it is a path that includes a common cause of LABA use and COPD exacerbations. COPD severity introduces confounding bias[7,11] because it is a common cause of COPD exacerbations and LABA use. This type of confounding is referred to as confounding by indication (also referred to as confounding by disease severity or channeling bias) because it arises due to more patients taking LABAs with more severe COPD developing COPD exacerbations than those taking LABAs with less severe COPD. Biasing paths such as a confounding path need to be blocked to ascertain an unbiased measure of the causal effect (Table 2).

Now that we have acknowledged that COPD severity is a confounder, we can attempt to block the path that it creates to prevent this bias from being transmitted. The most common approach for blocking this path is to statistically adjust for COPD severity. Approaches include stratifying patients according to COPD severity, matching LABA users and nonusers on COPD severity, and restricting or excluding patients on a proxy for this variable. All these methods are examples of conditioning. Once we have conditioned on COPD severity, the only causal path remaining in the cDAG is the path from LABA use to COPD exacerbations.

Selection Bias

Selection bias is another type of bias that can affect the validity of epidemiologic studies. Unlike confounding, selection bias is created by researchers at the study design stage. It occurs when a study conditions on a variable that is a common effect of both the exposure and outcome.[7,10]

Consider a researcher who wants to examine the risk of epilepsy with oral fluoroquinolones, as these drugs have

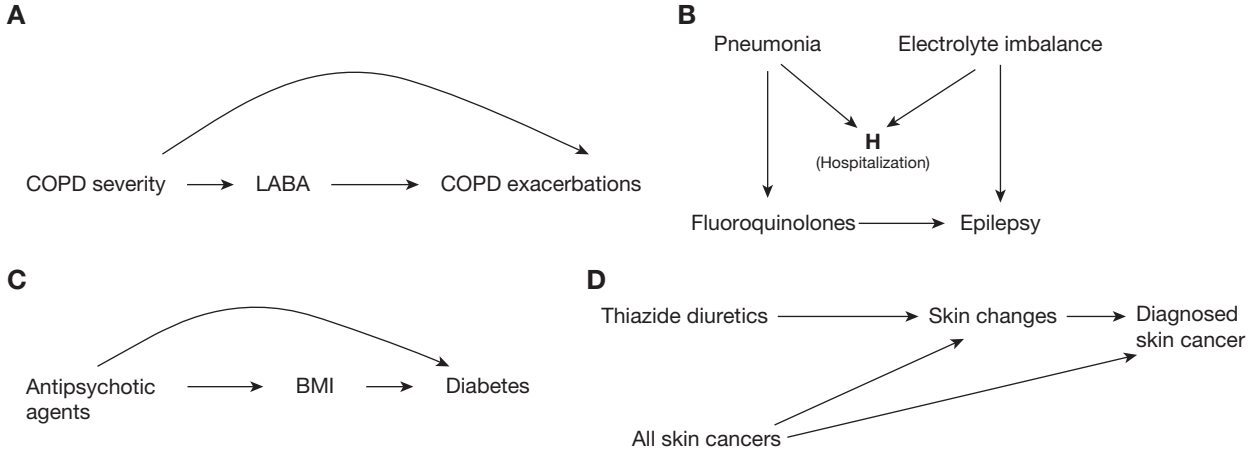
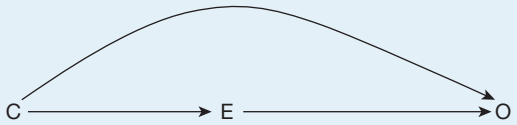
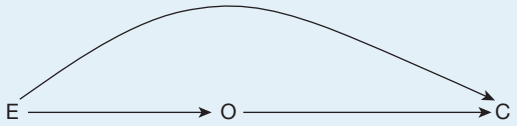
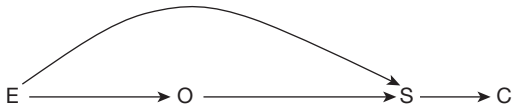
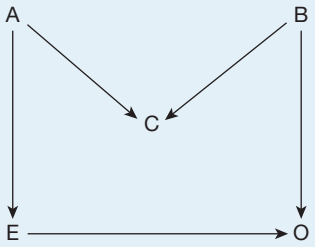
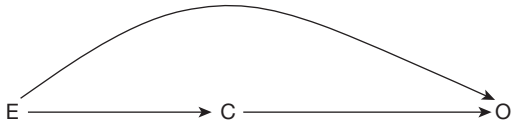


Figure 1 – *A, Example of confounding by indication. The effect of LABAs on COPD exacerbations can be confounded by COPD severity if LABAs are prescribed to patients with more severe COPD who are already at a higher risk of developing exacerbations. B, Example of collider or selection bias. The effect of fluoroquinolones on the risk of epilepsy will be biased if the data are restricted to those who are hospitalized. This restriction creates a selection bias that will spuriously associate fluoroquinolone use with the risk of epilepsy. C, Example of overadjustment bias. The causal effect of antipsychotic use on the risk of diabetes will be biased if BMI, a mediator on the path, is adjusted for. D, Example of detection bias. An otherwise absent causal effect between thiazide diuretics and skin cancer can be spuriously observed if thiazide diuretic users are more likely to be diagnosed with skin cancer than nonusers, as they visit physicians more often due to skin rashes secondary to thiazide use. LABA = long-acting beta$_2$-adrenergic receptor agonist.*

TABLE 2] Description of Different Types of Bias, Their Causal Structure, and the Need for Adjustment

Type of Bias	cDAG	Adjustment, Yes/No	Explanation
Confounding		Yes	Adjustment for **C** is necessary to control for confounding bias
Collider bias			
General structure		No	**C** is a collider, and adjustment for **C** will introduce collider bias
Descendent of a collider		No	**C** is a descendent of collider **S,** and its adjustment will introduce collider bias
M bias		No	**C** is a collider and should not be adjusted for
Overadjustment bias		No	**C** is a mediator between **E** and **O** Its adjustment will bias the total effect of **E** on **O**

Unlike confounding bias, where adjustment for C is necessary, adjustment for C will introduce bias in the case of both collider and overadjustment bias.

recently been linked to adverse events in the CNS by the US Food and Drug Administration.[12] Figure 1B is a cDAG depicting this scenario. There are two causal paths from fluoroquinolone use to epilepsy, one a directed path and the other an undirected path that could lead to bias. Two arrows originate from pneumonia and go to fluoroquinolone use and hospitalization, as pneumonia causes both outcomes. Similarly, two arrows originate from electrolyte imbalance and go to epilepsy and hospitalization. Pneumonia and electrolyte imbalance both cause hospitalization; thus, their effects are said to collide on hospitalization, and hospitalization is called a collider on this path.[7,13] Because the collider sits on the undirected path between the exposure (fluoroquinolone use) and the outcome (epilepsy), it prevents the transmission of any bias through this blocked path. The presence of the collider means that this undirected path is not a biasing path. However, this blocked path can be opened upon conditioning on the variable hospitalization (Table 2).

In our example, imagine a researcher who is not aware of the structure of this cDAG and is curious to know if the risk of epilepsy with fluoroquinolones differs among those who are hospitalized compared with those who are not. The researcher decides to restrict (a form of conditioning) the data to hospitalized patients only. This approach will now open the path that was previously blocked by hospitalization; that is, initially there was no flow of information from fluoroquinolone use to epilepsy due to the path blocked by the variable "hospitalization" and hence no possibility for transmission of bias. Upon conditioning by hospitalization this previously blocked path is now open, creating the path: fluoroquinolones ← pneumonia → hospitalization ← electrolyte imbalance → epilepsy. This new path will introduce a biased, noncausal association referred to as a selection bias or collider

bias.[7,13] Thus, hospitalization should not have been conditioned on. A remedy to this situation would be to block the transmission of this bias by adjusting for pneumonia and/or electrolyte imbalance.

Overadjustment Bias

Investigators are often careful to control for all potential confounding variables, usually using statistical adjustment. Peer reviewers and journal editors also want to be convinced that a submitted study has adjusted for all potential confounding variables. Adjusting for variables that should not be adjusted for leads to overadjustment bias.[14] Overadjustment bias usually occurs when an intermediate variable (also called a mediator) is adjusted for. Mediators are variables that alter the effect of an exposure on the outcome through a specific mechanism.

For example, antipsychotic agents can increase the risk of diabetes.[15] Consider an investigator who wants to look at the total effect of antipsychotic use on the risk of diabetes in a cohort study. Figure 1C shows two causal paths: a direct path from antipsychotic agents to diabetes and an indirect path from antipsychotic agents to diabetes through BMI. The investigator might choose to stratify the antipsychotic users according to their BMI, categorizing this value into a binary variable: > 30 kg/m^2 or < 30 kg/m^2. Conditioning on an intermediate variable will block the flow of information from antipsychotic use to diabetes through an indirect path via BMI (Table 2). The resulting association will be biased due to overadjustment bias.

Intermediate or mediator variables should not be conditioned on when the study question assesses an exposure's overall effect on an outcome. More complex methodologies are needed if an investigator wants to examine how much of the total effect is derived from the intermediate variable.[14]

Detection Bias

Measurement error, also called misclassification of the outcome or exposure, can affect the validity of epidemiologic studies as well. Detection bias is a type of outcome misclassification in which a group of patients are more likely to be diagnosed with a certain condition than another group because of a third variable.

For example, studies have linked the use of thiazide diuretics to skin cancer.[16,17] This increase in risk might be driven by detection bias, as shown by the cDAG in Figure 1D. There is an arrow from thiazides to skin changes (an adverse event with thiazide diuretics) and an arrow from skin changes to all skin cancers. There are also arrows from all skin cancer (diagnosed and undiagnosed) to diagnosed skin cancer and skin changes. The cDAG makes it clear that there is no true effect (arrow) from thiazide diuretics to skin cancer. Notice that although skin changes might appear to be a mediator, they actually are not because we know that thiazides do not cause skin cancer through skin changes. Skin changes are simply an adverse event of thiazides that can lead to a higher number of diagnosed skin cancers. The spurious association is due to detection bias: thiazide users are more likely to go to their physician with skin change-related issues than nonusers, which increases the chance of their skin cancer being spotted, regardless of whether it is related to the thiazide.

We can theoretically control for the detection bias by conditioning on or adjusting for skin changes, blocking the pathway thiazides → skin changes → diagnosed skin cancer. However, the variable "all skin cancer" also has an effect on skin changes. Skin changes is a collider on the remaining undirected path: thiazides → skin changes ← all skin cancer → diagnosed skin cancer. Although conditioning on skin changes removes detection bias, it introduces collider bias. In large database studies, one must often assess the tradeoff between accepting detection bias or collider bias. If a clinical trial design had been used, this problem could have been mitigated by using better screening for skin cancer for both thiazide users and nonusers.

Drawing a cDAG and Addressing Bias: A Case Study

We now present a case study to illustrate how to generate a cDAG and use it to identify biasing paths. A group of researchers investigated the effect of statin medications on lung-related mortality in patients with COPD.[9] Some evidence suggested that statins may lower mortality through their antiinflammatory properties.[18] They examined this question with a cohort study using patients with COPD from a population health database. To control for survival bias (immortal time bias), the investigators started follow-up for statin users and nonusers 1 year following cohort entry. Several potential confounders were controlled for in the Cox regression model, including age, sex, comorbidity, number of physician and hospital visits, geographic location, and income level.

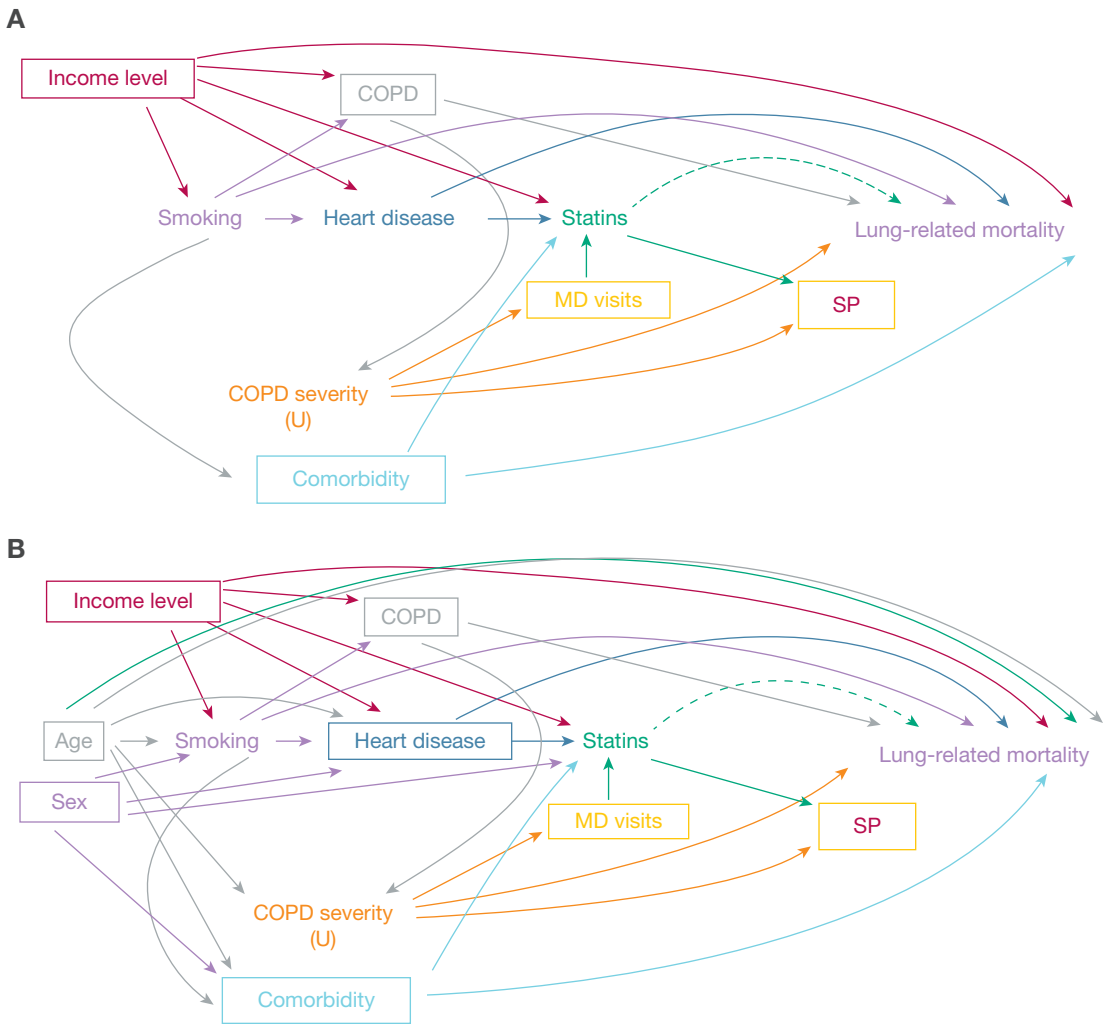


Figure 2 – *A, Causal directed acyclic graph for the statin and lung-related mortality case study. B, Causal directed acyclic graph for the statin and lung-related mortality case study with a complete set of all pertinent variables. Dotted straight arrow indicates causal relation under investigation; solid arrows indicate known relations. MD = physician; SP = survival 1 year following statin prescription; U = unmeasured confounder.*

Figure 2A presents the cDAG for this study. The dotted arrow from statins to total lung mortality shows that this is the causal question under investigation. The variables that were controlled for are indicated with a box. They were adjusted because they lie on biasing paths. "SP" represents survival 1 year following the first statin prescription, which is a condition created by the investigators in the study design. COPD indicates that the cohort was restricted to patients with COPD.

All shared causes (causes shared by statin use and lung mortality) must be included in a cDAG. We have therefore added the variables heart disease and smoking to Figure 2A. However, to avoid overcrowding the cDAG and aid visualization of the biasing paths, we have omitted sex and age from this graphic. All variables are shown in a complete version of the cDAG in Figure 2B.

The aim is to keep all causal paths from statin use to lung-related mortality open and to block all biasing paths that are open undirected paths between the exposure and outcome. For this question, we need to block biasing paths that include a common cause of statins and mortality by adjusting for confounders. We must also avoid adjusting for colliders or descendants of colliders in other undirected paths, which could introduce collider bias[7,13] (Table 2).

Income level and comorbidity are common causes of statin use and lung-related mortality. Age, number of

hospitalizations, number of prescriptions (the variables number of hospitalizations and number of prescriptions were excluded to prevent overcrowding of the cDAG), sex, number of physician visits, and comorbidity are on confounding paths with statin use and mortality. These confounders were correctly adjusted for by the investigators.

Heart disease, smoking (assuming smoking occurred prior to heart disease), and COPD severity are also confounders of statin use and lung-related mortality. Although smoking and COPD severity were not available in the study database, they are shown in the cDAG because they are also on a path that includes a common cause (income level). Heart disease was measured in the database but not adjusted in the study. The cDAG suggests that it should have been adjusted for because it causes both lung-related mortality and statin use. The path statins ← heart disease ← smoking → lung-related mortality is a confounding path. Either smoking or heart disease should have also been adjusted for.

Two additional biasing paths have been created by the conditioning steps in the study design. Restricting the cohort to patients with COPD created the biasing path: statin ← heart disease ←smoking → COPD ← income level → lung-related mortality. The collider bias created by conditioning on COPD can be blocked by conditioning on income level or smoking. Because income level is already adjusted for, collider bias is averted.

Only patients who had been taking statins for 1 year were included in the study. This cohort restriction created the biasing path: statin → SP ← COPD severity → lung-related mortality. This collider bias could not be adjusted for in the analysis because COPD severity is usually not available in most population-based databases.

In summary, the variables adjusted for by the investigators included age, sex, number of physician visits, comorbidity, income level, number of hospitalizations, and number of prescriptions received. Based on our cDAG variables, heart disease and COPD severity should have also been adjusted for. Heart disease could have been adjusted by the investigators because these data were available to them; COPD severity was an unmeasured confounder and could not have been adjusted for. The cDAG also tells us that two collider biases were introduced: (1) COPD, which was controlled for as a result of adjustment for income level; and (2) variable SP, which could not be controlled for because it was introduced at the design stage of the study.

Causal Diagram Resources for Clinicians

Those interested in learning more about the basic principles behind causal diagrams and accessing more detailed discussions of identifying and controlling for confounders and colliders are directed toward reviews and tutorials aimed at clinicians.[5-8] Harvard University offers an excellent introductory online course on casual inference with worked examples for those looking for a more interactive experience.[19]

Several resources are available for drawing causal diagrams. Simple cDAGs can be drawn using Microsoft PowerPoint (Microsoft Corporation). Dagitty (http://www.dagitty.net/) is a freely available software program that has been specifically built for drawing causal diagrams.

Limitations of cDAGs

As with any methodologic or statistical technique, causal diagrams have limitations. They do not convey information about important aspects of causal relations, such as the magnitude of the bias. cDAGs might imply that several sets of variables are sufficient for bias adjustment but offer no further guidance on which to use. The absence of key variables in a cDAG might itself lead to bias, which may be mitigated by researchers proposing different cDAGs to gain a better sense of the effects of different causal assumptions. cDAGs are insensitive to biases that result from small sample sizes, such as bias due to chance confounding[20] or sparse data bias.[21] In practice, one cannot be certain of the temporality between variables because they may be measured simultaneously. Similarly, if a causal relation between two variables is misrepresented, the accuracy of the cDAG will be compromised. Although cDAGs are useful for qualitatively conceptualizing causality, advanced quantitative causal models should be used to estimate causal effects.[2,22-24]

Summary and Conclusion

Judea Pearl, who pioneered the adaptation of cDAGs from quantitative sciences to medical research, said, "Causal analysis without graphs is like medicine without anatomy."[25] Although cDAGs should not be considered a panacea for the proper conduct of high-quality research, they are a useful tool for contending with confounding and selection use. We hope that this primer

will encourage researchers to make use of cDAGs and the resources available to support their use, while also highlighting the limitations of these tools.

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