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Causal Diagrams for Epidemiologic Research

Sander Greenland,[1] *Judea Pearl,*[2] *and James M. Robins*[3]

Causal diagrams have a long history of informal use and, more recently, have undergone formal development for applications in expert systems and robotics. We provide an introduction to these developments and their use in epidemiologic research. Causal diagrams can provide a starting point for identifying variables that must be measured and controlled to obtain unconfounded effect estimates. They also provide a method for critical evaluation of traditional epidemiologic criteria for confounding. In particular, they reveal certain heretofore unnoticed shortcomings of those criteria when used in considering multiple potential confounders. We show how to modify the traditional criteria to correct those shortcomings. (Epidemiology 1999;10:37–48)

Keywords: bias, causation, confounding, epidemiologic methods, graphical methods, observational studies.

Summarization of causal links via graphs or diagrams has long been used as an informal aid to causal analysis. Causal graphs in the form of path diagrams are an integral component of path analysis[1] and structural equations modeling.[2] In more recent times, the theory of directed acyclic graphs (DAGs) has been extended to application in expert-systems research.[3,4] In these applications, there is a pressing need for valid formal rules that allow an automated system or robot to deduce correctly the presence or absence of causal links given correct background information and new data. The outgrowth of this research has been the development of a formal theory for evaluating causal effects using the language of causal diagrams.[5,6] Unlike path analysis and structural-equations modeling, this theory does not require parametric assumptions such as linearity.

The theory of causal graphs is equivalent to the G-computation theory of Robins.[7–9] It has a benefit, however, of providing a compact graphical as well as algebraic formulation of assumptions and results, which may be easier for the general reader to comprehend. In addition, it provides a novel perspective on traditional epidemiologic criteria for confounder identification. This perspective reveals how traditional criteria can be inadequate when multiple confounders must be considered simultaneously. We describe the modifications required of traditional criteria that enable their valid extension to situations involving multiple confounders.

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We here provide a brief introduction to the theory of causal diagrams based on DAGs.[5,6] We pay special attention to its relation to nongraphical epidemiologic treatments of confounding.[10–13] We show how diagrams can serve as a visual yet logically rigorous aid for summarizing assumptions about a problem and for identifying variables that must be measured and controlled to obtain unconfounded effect estimates given those assumptions. Thus, use of such graphs can aid in planning of data collection and analysis, in communication of results, and in avoiding subtle pitfalls of confounder selection.

Except where noted otherwise, the present paper will deal only with relations among variables in a given source population; that is, we will deal only with structural (systematic) relations among the underlying variables of interest, so that issues of measurement error and random variation will not arise. We will also not present proofs of results, but we will give references in which proofs can be found.

A Rationale for Graphs

Any deduction about a causal relation must start from some set of assumptions, which we call the analysis model.[14] For example, such a deduction may assume that uncontrolled confounding is negligible; this assumption usually corresponds to a set of assumptions that various uncontrolled factors have negligible associations with the study factor or study disease, given what has been controlled. The subsets of these assumptions pertaining to causation, measurement, and selection correspond to the causal, measurement, and selection models, whereas the subset of assumptions pertaining to the probability distribution of the observations corresponds to the statistical model. These subsets of assumptions may overlap. For example, the assumption that vaginal bleeding increases the chance of diagnosis of endometrial cancer and hence selection for a case-control study is common

to all four subsets; it is a probabilistic assumption about causation of diagnosis, measurement of disease, and selection for study.[15]

Sometimes the assumptions of an analysis model are so obviously correct that they sound silly to explicate; an example is the assumption that the apparent deadliness of botulism in humans in not attributable to confounding factors. In such situations it is rarely recognized that a model is present. But most epidemiologic research is plagued by uncertainty about assumptions, in which case it is important to recognize and explicate fully the analysis model.

A serious drawback of common statistical models is that they embody many parametric assumptions that are not known to be correct and may well be incorrect. Consider, for example, a conventional correlated-outcome logistic regression analysis of data on daily air pollution exposure and respiratory illness in schoolchildren, with sex entered as a covariate. The analysis model assumes (among other things) that the odds ratios relating pollution to the illness do not vary by sex and that the relation of the illness odds to pollution is exponential. Neither of these assumptions is known to be correct, and tests of them often have little power to detect important violations.

Another drawback of common statistical models is that they cannot capture all types of assumptions. Continuing the example, a conventional logistic-regression model for illness cannot represent or impose the assumption that the sexes of the children are not affected by pollution exposure, even though this assumption is correct and may be useful in an analysis of pollution effects.

Causal diagrams are graphical models for causal relations that can serve a role complementary to conventional models; they are also called influence diagrams, relevance diagrams, or causal networks.[4] Such diagrams do not incorporate the strong parametric assumptions of conventional models; instead, they display assumptions about the web of causation that are not captured by conventional models. As with conventional models, some of the assumptions may be of unknown validity; some may be untestable, but others may be tested (albeit with limited power) and may be varied to examine the sensitivity of inferences to reasonable variations.

Basics of Graph Construction

A causal diagram can be constructed by abstracting the causal assumptions embedded in a narrative description of the hypothesized relations among the study variables. To illustrate the idea, consider a proposed study of the relation of antihistamine treatment to asthma incidence among first-grade children attending various public schools. Suppose our narrative asserts that pollution levels and sex are independent among first-grade public-school children; that sex influences administration of antihistamines only through its relation to bronchial reactivity but directly influences asthma risks; that industrial air pollution leads to asthma attacks only through its influence on antihistamine use and bronchial reactivity; and that there is no important confounder beyond air pollution, bronchial reactivity, and sex. For this example, let A represent air pollution level, and let B, C, E, and D represent indicators for sex (B = 1 for boy, 0 for girl), bronchial reactivity, antihistamine treatment, and asthma, respectively. The assertions of the narrative are incorporated into Figure 1, which we will use to illustrate terminology.

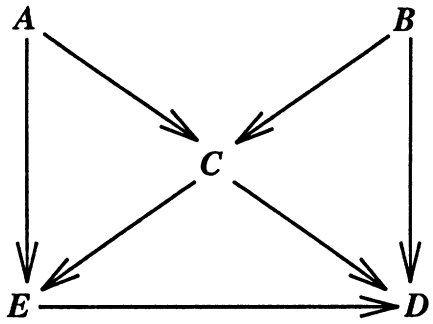

FIGURE 1.

Any line or arrow connecting two variables in the graph is called an *arc* or an *edge*. Two variables in a graph are *adjacent* if they are directly connected by an arc; in Figure 1, A and C are adjacent, but A and D are not. Single-headed arrows represent direct links from causes to effects; in Figure 1, the arrow linking A to C represents a direct effect of A on C (that is, an effect not mediated by another variable in the diagram). In the example, the assertion that pollution affects asthma only through bronchial reactivity and antihistamine use corresponds to the absence of an arrow from A to D; likewise, the assertion that sex affects antihistamine administration only through bronchial reactivity corresponds to the absence of an arrow from B to E.

The points on the graph representing the variables are called *nodes* or *vertices*. A *path* through the graph is any unbroken route traced out along or against arrows or lines connecting adjacent nodes; an example is the E-C-D path between E and D, which passes only through C. A *directed path* from one node to another in the graph is one that can be traced through a sequence of single-headed arrows, always entering an arrow through the tail and leaving through the head; such a path is also called a *causal path* in causal graphs. In Figure 1, the path A-C-D is directed, but E-C-D is not. A node within a path is said to *intercept* the path; in Figure 1, C intercepts the paths A-C-D and E-C-D.

A variable X is an *ancestor* or *cause* of another variable Y if there is a directed path of arrows leading out of X into Y; in such a case, Y is said to be a *descendant of* X or *affected by* X. In Figure 1, A, B, and C are ancestors of E and D, and E and D are descendants of A, B, and C. A variable X is a *parent* of Y in a graph if there is a single-headed arrow from X to Y; in such a case, Y is said to be a *child of* X or *directly affected by* X. In Figure 1, A and C are parents of E, whereas C and E are children of A.

Note that the "parent-child" relation and the corresponding notion of "direct effect" are not inherent bio-

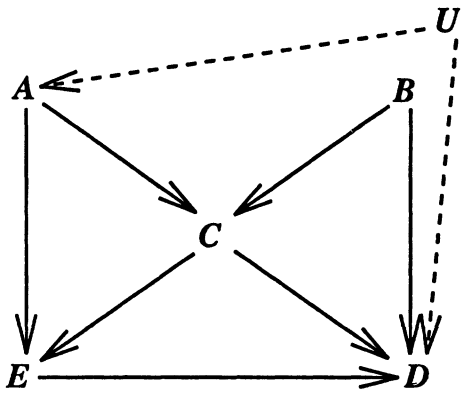

FIGURE 2.

logic properties, but merely express the limits of detail represented in the causal model. For example, to say that "antihistamine use E directly affects asthma occurrence D" means only that the intermediate steps through which antihistamine may alter asthma occurrence (for example, by decreasing capture and elimination of antigens in the upper airways) are not elaborated in the model. In contrast, the more general concepts of ancestor and descendant correspond to the basic concepts of cause and effect.

A bidirectional (two-headed) arrow connecting two variables in a graph is often used to indicate that the two variables share one or more ancestors (that is, have a cause in common), but the ancestors and their interrelations are not shown in the graph.[6] We will instead represent such unspecified common ancestors by the letter U, with dashed arrows. U may represent more than one variable. For example, if we suspected actions taken at high-pollution-area schools reduced pollution exposure and also independently reduced asthma risk, we would use Figure 2 instead of Figure 1; these conditions would be satisfied if children were kept indoors on high-pollution days, with consequent reduced exposure to particulate emissions and allergens.

A nondirectional arc (an arc without arrowheads) is sometimes used to indicate that two variables are associated for reasons other than sharing an ancestor or affecting one another; Figure 3 gives an example, which we will discuss below. Here, we use dashed nondirectional arcs to represent relations whose source is not

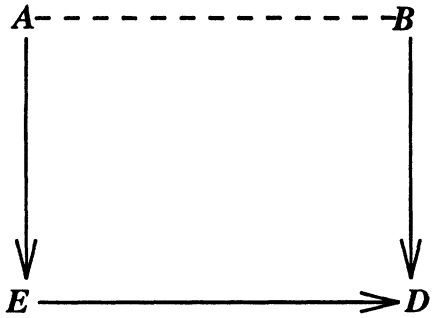

FIGURE 3.

specified by the graph. In the example of Figure 1, the assertion that pollution exposure and sex are marginally unassociated follows from the absence of arcs or common ancestors connecting A and B in Figure 1.

A graph is *directed* if all arcs between variables are arrows (single or double headed), that is, if it contains no nondirectional arc. A graph is *acyclic* (or recursive) if no directed path in the graph forms a closed loop. Figures 1 and 2 are examples of graphs that are directed and acyclic. In the present paper we will deal primarily with DAGs; we will also discuss other acyclic graphs arising from DAGs, such as Figure 3.

We will also need the following terms. A path that connects X to Y is a *backdoor path from* X *to* Y if it has an arrowhead pointing to X.[6] In Figure 1, all paths from E to D except the direct path are backdoor paths. A path *collides at* a variable X if the path enters and exits X through arrowheads, in which case X is called a *collider* on the path.[5] A path is *blocked* if it has one or more colliders; otherwise it is *unblocked*. The backdoor path E-A-C-B-D in Figure 1 is blocked because it collides at C; C is the only collider on the path. In contrast, the backdoor path E-A-C-D is unblocked because neither A nor C are colliders on this path. Either kind of path may include nondirectional arcs; for example, the backdoor path E-A-B-D in Figure 3 is unblocked.

Causation and Association in Graphs

Graphical assumptions are qualitative and nonparametric, in that they imply nothing about the specific functional form of the relations or distributions among the variables. In particular, the variables may be discrete or continuous, and dose-response relations may have any shape. Production of an effect by a cause requires a causal path from the cause to the effect, however; such paths are represented by directed paths in a graph. Thus, absence of a directed path from X to Y represents the assumption that there is no effect of X on Y.

Every absence of a single-headed arrow represents a basic null (no-direct-effect) assumption encoded by the graph and implies absence of every causal effect that would be transmitted through that arrow. For example, Figure 1 has no single-headed arrows from A to B, B to A, A to D, and B to E (these single-headed arrows are the only ones that could be put back in without disrupting the acyclic nature of the graph). Thus, the figure encodes the basic causal assumptions that A does not directly affect B, B does not directly affect A, A does not directly affect D, and B does not directly affect E; the first assumption also implies that there is no effect of A on D that is transmitted through B, and so on.

In some situations, one may wish to assume that two variables have no marginal (crude) association. Although this assumption would rarely be exactly correct, it is often a reasonable working hypothesis; for example, it is a common assumption in studies of genetic and environmental factors.[16] This assumption follows from the absence of an unblocked path between the variables;[3–6] for example, Figure 1 implies that A and B have

no marginal association. Put another way, a marginal association between two variables in a graph requires that there be an unblocked path between them.

In a DAG, there are only two possible kinds of unblocked paths between variables: directed paths and backdoor paths through a shared ancestor. Thus, a marginal association between two variables in a DAG requires that the DAG exhibit a causal pathway from one to the other or a common cause of both variables. The first condition holds when the association between the variables is at least partly causal, and the second condition holds when the association is at least partly confounded. Of course, both conditions may hold; that is, the marginal association may be partly causal and partly confounded, as with E and D in Figure 1.

The fact that every association between two variables X and Y in a DAG is due to either a direct causal connection or a common cause may appear to conflict with the usual epidemiologic intuitions. For example, associations may appear in a study population because of biases in selection into the population; Berkson's bias is a well-known example.[17] The conflict may be resolved by noting that the associations generated by selection bias are represented by nondirectional arcs, as in Figure 3; graphs with such arcs are *by definition* not directed graphs. Directed graphs represent only causal relations in unselected populations; nonetheless, we will show how such graphs can be used to deduce nondirected graphs for selected populations, such as Figure 3.

The independence implied by the absence of unblocked paths between two variables applies regardless of the magnitude of any effect or association shown in the graph. On the other hand, the presence of an unblocked path between two variables allows but does not automatically imply that the two variables are marginally associated. For example, in Figure 1 there is a direct path and four backdoor paths between E and D. Although each path can induce an association, these associations might cancel one another out to yield no marginal E-D association. Standard epidemiologic examples occur when an effect is hidden by confounding, so that one observes no crude association of exposure and disease, even though exposure affects disease risk.

The presence or absence of a blocked path between two variables is irrelevant to their marginal association. This irrelevance corresponds to the fact that the marginal association between two causes of an effect (that is, two ancestors of a collider) is fixed by the time both causes have occurred, and the association cannot be changed by the fact that these causes may trigger a later event. For example, if the *BRCA1* gene and intrauterine diethylstilbestrol (DES) exposure are marginally independent of one another, this independence is not changed by the fact that later outcomes (such as breast cancer) may be affected by both variables. In other words, a blocked path cannot contribute to a marginal association, because an event cannot alter conditions that were determined before the event occurred; in particular, breast cancer cannot induce a marginal association between *BRCA1* and DES exposure.

Confounding and Causal Graphs

There are many different definitions of *confounding* and *confounder*. Our concern here is with confounding for the net (total) effect of exposure, defined as a situation in which the study exposure groups (the study groups at levels of E) differ in their probability distribution for the outcome (D) for reasons other than effects of exposure.[10–12] Inevitably, such differences are attributable to effects of extraneous variables (variables other than exposure) on the distribution of the outcome. The latter variables are often called *confounders* (although the term "confounder" is often used more broadly to include proxies for such variables). A variable that is a hypothetical candidate to be a confounder is sometimes called a *potential confounder*.

Assuming that exposure precedes disease, confounding will be present if and only if exposure would remain associated with disease even if all exposure effects were removed, prevented, or blocked.[10] This condition is easy to check in a DAG that represents the relations among exposure, disease, and potential confounders, using the following algorithm:

1. Delete all single-headed arrows emanating from the exposure (that is, remove all exposure effects).
2. In the new graph without exposure effects, see whether there is any unblocked path from exposure to disease (that is, see whether exposure and disease may remain associated even if exposure effects are removed).

If there is no unblocked path from exposure to disease once all the exposure effects are removed, then (according to the graph) there is no confounding of the net exposure effect. In a DAG, the task of checking condition 2 reduces to that of checking whether the graph indicates that exposure and disease share a common ancestor.

Note that effects of disease play no role in the above definition. Such effects can only occur after the exposure and the disease have occurred. Their irrelevance corresponds to the fact that, in a DAG, paths from exposure to subsequent disease that pass through a descendant of disease must also pass through a collider and so are blocked.

Criteria for Control of Confounding

We wish to present some general criteria that will not only allow us to check for confounding, but also give us qualitative guidance for confounding control. To do so, we will first consider some traditional criteria in a graphical context, note their shortcomings, and introduce new graphical criteria that rectify these shortcomings.

One conventional set of criteria often considered necessary although not sufficient for a variable to be a confounder can be phrased as follows: (1) the variable is an ancestor (cause) of the outcome, and (2) the variable is associated with exposure, but (3) the variable is *not* a descendant (effect) of the exposure or outcome.[12,13] With these criteria in mind, we presented Figure 1 to various colleagues and students, with the question, "Assuming the graph is correct for our study population—

TABLE 1. Numerical Example of How Independent Variables (A and B) Can Appear Associated within Strata of a Variable That They Both Affect (C)

	A = 1		A = 0	
	B = 1	B = 0	B = 1	B = 0
C = 1	800	600	400	200
C = 0	200	400	600	800
Total	1,000	1,000	1,000	1,000

that is, that there is no direct effect of A on D or B on E, that A and B are independent, and that there is no other confounder—what is the smallest subset from the covariates A, B, and C that would be sufficient for adjustment to estimate the effect of E on D without bias?" By far, the most common response we encountered was that A alone or B would not be sufficient, but that C alone would be sufficient.

Typically, the reasoning about Figure 1 went as follows: "Adjustment for A and B would leave C as a confounder. But because C intercepts the path from A to D, its control would render A unassociated with D given E. Similarly, because C intercepts the path from B to E, its control would render B unassociated with E. Therefore, once we adjust for C, A and B would fail to satisfy one of the necessary criteria required of confounders, and so adjustment for C would control confounding by A and B as well as C." Although this reasoning contains a core of wisdom, it turns out that adjustment for C alone is *not* sufficient for control of confounding in Figure 1. This insufficiency indicates that a naive reading of the graph is inadequate.

There is, however, a chain of reasoning that would have allowed us to answer the question correctly. First, A and B have no marginal (crude) association under Figure 1, because A and B share no common ancestor that would produce covariation between them. Second, A would have to be associated with C given B because A affects C; similarly, B would have to be associated with C given A. Thus, when we stratify on C, the association of A and B within at least one stratum of C will almost certainly differ from the crude A-B association; in particular, it will almost certainly not be null in all strata of C, or in an overall summary across strata of C. (By "almost certainly," we mean that exceptions can occur in special examples involving perfect cancellations across strata of a polytomous C.[18])

Table 1 provides a numerical example. Here, we assume that A = 1 and B = 1 each occur in 50% of a population of size 4,000 in which Figure 1 holds, and that A and B are marginally unassociated (that is, they are unassociated in the bottom margin of the table). We also assume that having A = 1 always adds 40% to the risk of C = 1, while having B = 1 always adds 20% to the risk of C = 1, so that the effects of A and B exhibit no interaction on an additive-risk scale. If we now look within strata of C (that is, within rows C = 1 and C = 0), we see that A and B *are* associated; for example, the odds ratio for the A-B association is 2/3 within strata of C.

One may view the preceding example as a variation on Berkson's bias.[17] In Berkson's original example, A and B were indicators of lung cancer and tuberculosis, whereas C was an indicator of hospital admission. Berkson showed that, if A and B were independent in the general population and had probabilistically independent effects on admission C, then A and B would be associated among the hospital admittees, who compose the C = 1 stratum.[17] Note that recognition of this bias requires consideration of the original DAG for the entire population; one could not recognize the in-hospital association of A and B as biased if one considered only the hospital data.

The preceding example corresponds to a general rule about causal relations: Suppose two variables A and B both affect a third variable C (that is, C is a descendant of A and B). Then the association of A and B within strata of C will almost certainly differ from the marginal association of A and B. This rule has long been recognized in epidemiologic problems in which the effect of A on B is of interest[7,13,15]; it is known as the "explaining away" effect in artificial-intelligence research.[19] Applying the rule to Figure 1, in which the effect of E on D is of interest, we see that adjustment for C can create an unblocked backdoor path from E to D that circumvents C: the association of A and B within strata of C can create an association of A with D indirectly, through B; it can also create an association of B with E indirectly, through A.

Figure 3 illustrates the situation within strata of C. By creating an association between A and B, adjustment for C has generated a new unblocked backdoor path from E to D (the path E-A-B-D). Because B is now associated with E, B now satisfies the earlier (conventional) confounder definition, so that control of B appears necessary once C is controlled. We will see below, however, that control of B is not necessary given Figure 1; instead, B and C are *sufficient* to control confounding, but A and C would do as well. We will also present an algorithm that will allow us to identify sufficient confounder sets using simple manipulations of the original graph (Figure 1).

We may generalize what we have illustrated so far. Suppose each of several variables satisfies the conventional definition of a confounder, such as A, B, and C in Figure 1. By controlling a subset of these variables, we may alter the associations among the remaining variables; in particular, we may create new associations among the remaining variables, the exposure, and the disease. These new associations can produce new unblocked paths between E and D and thus can create (as well as control) confounding. Consequently, intuitions based on situations involving only one confounder can be an inadequate guide in situations involving multiple confounders.

Stratification under a Multiplicative Model

A striking contrast of the parametric focus of conventional methods *vs* the nonparametric focus of graphical

methods arises in considering case-only studies of "gene-environment interactions."[20,21] Suppose two factors are marginally independent, as in the *BRCA1*-DES example above; then, if their effects are multiplicative, there will be no association of the factors among the cases. As a consequence, if biases are absent and the factors are independent in the source population giving rise to the cases, an association of the factors among the cases has to be attributed to a departure from multiplicativity of the factor effects.[20,21]

The rationale for a case-only study is that, under a multiplicative model, unbiased selection into the case-only study should yield a population (comprising only cases) with no association of the factors. Nonetheless, in keeping with the earlier graphical results, the noncases left behind *will* exhibit an association of the factors (albeit a weak one if the disease is rare). That is, the association induced by stratifying on the outcome will be entirely concentrated among the noncases if the factors are marginally independent and have multiplicative effects on disease.

In a real application of the case-only design, one should consider whether there is any scientific basis for focusing on a multiplicative model form, which is after all just one of an infinitude of possible model forms. As Table 1 shows, marginally independent factors may be strongly associated among cases under other reasonable "no-interaction" models.

Physical vs Analytic Control of Confounding

The failure of intuitions in the above examples may arise because common intuitions about confounding control arise from experiments, in which "control" may mean direct physical control (manipulation) of a variable. In a structure such as that in Figure 1, successful experimental control of C could mean that the investigator physically prevents C from varying in response to variations in A, B, or any other variables. As a result, A and B would no longer have effects on E or D that are mediated through C. For example, if A were weight, B were apolipoprotein E genotype, C were serum cholesterol, E were blood pressure, and D were cardiovascular disease, then effective medical control of cholesterol would block those effects of weight and genotype that are mediated through serum cholesterol. The result of such medical control would be a diagram like that in Figure 4, in which the arrows from A to C and B to C are erased or cut. In this new diagram, with C controlled by intervention, there is no confounding by A or B, hence, the common intuition that control of C is sufficient to control confounding, given Figure 1. (Of course, in reality the available interventions would weaken but not eliminate the effects of A and B on C.)

By definition, physical blocking of a path is not an option in observational studies. Instead, we can only "control" C in a data-analytic sense of *adjustment*; that is, we restrict our analyses (and perhaps our data collection) to a stratum of C; we may then combine results across different strata or employ some regression ana-

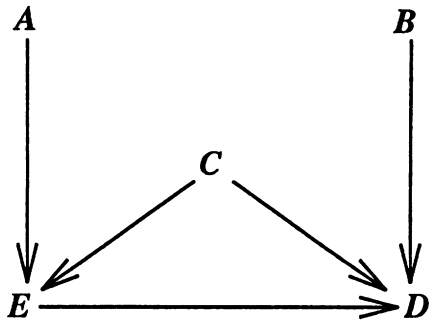

FIGURE 4.

logue of this process. Unfortunately, analytic adjustment for C has consequences quite different from those of physical control. With adjustment for C, we must shift our attention from the crude A-B association to the A-B associations within strata of C. In doing so, we descend into strata of C, in which A and B can be associated (as in Figure 3), even though they have no cause (ancestor) in common and hence have no association in the original directed graph.

Unnecessary Adjustment and Harmful Adjustment

Improper adjustment for a third variable can create confounding even when exposure and disease share no common cause. Figure 5 gives an example; here, A and C have no effect on D other than through E, and B and C have no effect on E. As in Figure 1, however, A and B would be associated within strata of C; hence, if one adjusted for C, one would have to adjust for A or B to ensure that there is no confounding within the strata.

There is a broader lesson in Figure 5. Given that diagram, there is no confounding and hence no need to adjust for C, because there is no unblocked backdoor path from E to D. We can nonetheless make A and B into confounders by adjusting for C. Thus, given Figure 5, unconfounded answers can be obtained by adjusting for nothing *or* by adjusting for anything other than C alone. More generally, adjustment for variables (such as C in Figure 5) that are not necessary to control may necessitate adjustment for even more variables.

Now consider Figure 6, in which we observe a variable F that is affected by E and D. There is no confounding of the effect of E on D in this diagram. Thus, given the

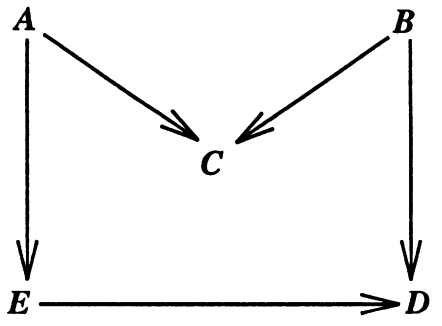

FIGURE 5.

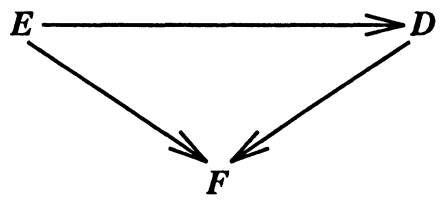

FIGURE 6.

diagram, the crude association of E and D should represent the effect of E on D without bias, and adjustment for F is unnecessary. Furthermore, because F is associated with both E and D, the associations of E and D with strata of F would differ from the crude association and hence differ from the true effect; that is, they would be biased. This situation is similar to that of adjustment for C in Figure 5, except that there is no other variable to control that would remove the bias. Thus, adjustment for F is not only unnecessary but irremediably harmful (biasing).

A classic example of adjustment-induced bias occurred when, in studies of estrogen (E) and endometrial cancer (D), some researchers attempted to control for detection bias by stratifying on uterine bleeding (F), which could be caused by either estrogen or cancer, as in Figure 6. The association between estrogen and cancer within levels of bleeding was drastically reduced by this stratification; unfortunately, the reduction was more plausibly attributable to bias produced by stratification than to removal of detection bias.[15]

Another important example of adjustment-induced bias can occur in attempts to adjust for the "healthy-worker survivor effect."[7] This effect is the bias that occurs when unmeasured health conditions (U) influence decisions to leave work (for example, quit, take disability leave, or retire) and also influence mortality (D); when this happens, leaving work may become associated with mortality, even if it has no effect on mortality. Suppose the study exposure (E) is job-site assignment, which influences worker decisions about when to leave work (L). Figure 7 illustrates such a scenario. In this figure, there is no confounding of the E-D association, so that the crude association is unbiased. Because L is associated with E and D, however, control of L would most likely yield an E-D association different from the crude and therefore would be harmful.

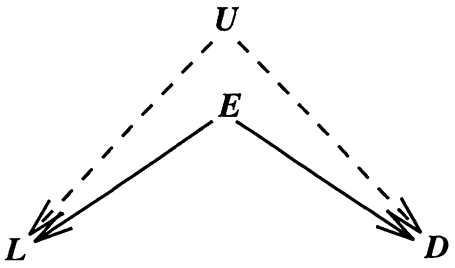

FIGURE 7.

Sufficient Sets of Adjustment Variables

Suppose now that we have laid out our working assumptions about causal relations in a DAG, and we wish to estimate the effect of E on D, where E and D are variables in the graph and E temporally precedes D. We know that adjustment for a variable can produce bias if the variable is a descendant of E. We have also seen that adjustment for a variable along a backdoor path from E and D can produce bias if that variable is a collider along the path, as C was in Figure 5. This finding is a subtle insight about analytic control added by causal graph theory, and we must account for it in revising conventional criteria for adjustment.

Suppose we have a set S of variables that we are considering for use in adjustment. We will refer to the strata defined by cross-classification on all of the variables in S as "strata of S". We define a set of variables S as *sufficient for confounding adjustment* of the E-D relation if there is no confounding of the E-D relationship in any stratum of S. Our usage of "sufficient" will thus refer only to control of confounding. Concerns about possible heterogeneity of effect measures (effect-measure modification) may dictate finer stratification than that sufficient for confounding adjustment. For example, in a large randomized trial, one may have no concern about confounding, in that the unadjusted (crude) estimates may be unconfounded summary effect estimates; nonetheless, one may wish to look for possible differences in effects among men and women, young and old patients, etc.

Graphical Criteria

Given a DAG and a set S of variables in the graph that are not descendants (effects) of E or D, it can be shown that S is sufficient for adjustment if, upon adjustment for S, there is no unblocked backdoor path from E to D.[6] This condition is equivalent to the following pair of graphical criteria:

G1. Every unblocked backdoor path from E to D is intercepted by a variable in S, and

G2. Every unblocked path from E to D induced by adjustment for the variables in S is intercepted by a variable in S.

Criterion G2 is the key addition to conventional wisdom. At first glance, it might seem difficult to verify that this criterion is satisfied; fortunately, it is equivalent to the following operational criterion:

G2*. If every collider on a backdoor path from E to D is either in S or has a descendant in S, then S must also contain a noncollider along that path.[6]

In Figures 1 and 5, the set containing only C does not satisfy this criterion, whereas the sets {A, C} and {B, C} do.

The above criteria lead to a graphical (and hence visual) algorithm for checking whether a set of variables is sufficient for adjustment given a particular DAG. This algorithm is known as the *backdoor test* for sufficiency.[22] This test may be performed as follows. Given a subset $S = \{S_1, \ldots, S_n\}$ of variables that contains no descendant of E or D, perform the following series of manipulations (steps) on the original graph:

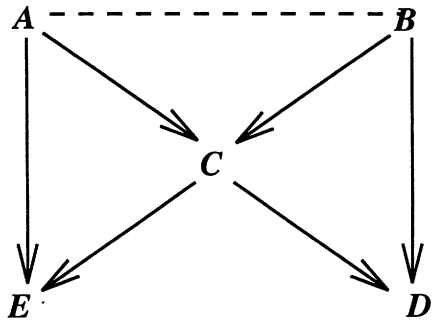

FIGURE 8.

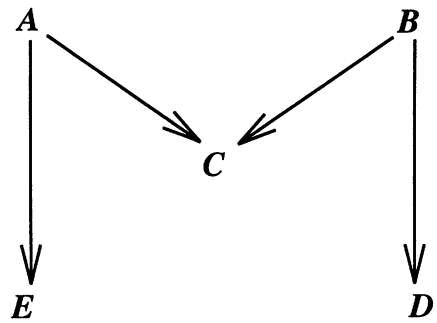

FIGURE 10.

M1. Delete all arrows emanating from E (that is, remove all exposure effects);

M2. Draw undirected arcs to connect every pair of variables that share a child that is either in S or has a descendant in S (that is, put in all arcs generated by control of S); and

M3. In the new graph derived from steps M1 and M2, see whether there is any unblocked path from E to D that does not pass through S.

S is sufficient if the answer to M3 is negative, that is, if every unblocked path from E to D in the graph resulting from M1 and M2 passes through S.

Applying M1 and M2 to Figure 1 with S = {A, C}, S = {B, C}, or S = {C} yields Figure 8. In this figure, every path from E to D passes through {A, C}, so {A, C} is sufficient; however, the unblocked path E-A-B-D does *not* pass through C, so {C} is not sufficient. Applying M1 and M2 to Figure 5 with S = {C} yields Figure 9, in which the unblocked path E-A-B-D does not pass through C, so {C} is not sufficient. Applying M1 and M2 to Figure 5 with S = {} (the empty set) yields Figure 10, in which there is no unblocked path from E to D; thus, we need not adjust for anything given Figure 5.

When a graph contains many variables, it may become tedious to carry out M3. The back-door test may be simplified as follows. After we adjust for a set S, any unblocked backdoor path can only pass through variables that are ancestors of E, D, or a variable in S. Therefore, before applying the test, we may simplify the graph by dropping all variables outside of E, D, and S that are not ancestors of E or D or a variable in S.[23] This simplification may considerably reduce the number of backdoor paths from E to D. Applying this simplification to Figure 5 with S = {} leads us to drop C from the graph. Dropping C yields Figure 11, in which there is no back-door path from E to D. Thus, the empty set is sufficient to adjust for confounding in Figure 5, which is to say that there is no confounding in the figure. This is so, even though C would almost certainly be marginally associated with E and associated with D conditional on E, and so it would *appear* to be a confounder of the E-D effect if A and B were ignored.

Minimal Sufficiency

A set of variables may be sufficient for adjustment, but it may be unnecessary to adjust for all of the variables in the set. A set S of variables is *minimally sufficient* for adjustment if S is sufficient but no proper subset of S is sufficient. In Figure 1, both {A, C} and {B, C} are minimally sufficient sets, because some control is necessary and no single variable is sufficient for control. On the other hand, although {A, C} and {B, C} are both sufficient in Figure 5, neither is minimally sufficient, because no control is necessary (that is, the empty set is also sufficient). To find a minimally sufficient set, we may sequentially delete variables from a sufficient set until no more can be dropped without the new set failing the backdoor test.[24]

It is important to recognize that a set S may be sufficient for confounding adjustment, and yet adding variables to S may yield a set S* that is not sufficient. In other words, control of a set of variables may yield an unbiased measure of effect, and yet control of more variables may create bias.[6,11] Figure 5 is a simple example of this phenomenon, in which no control (S = {}) is

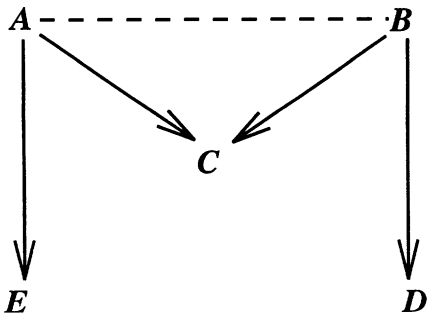

FIGURE 9.

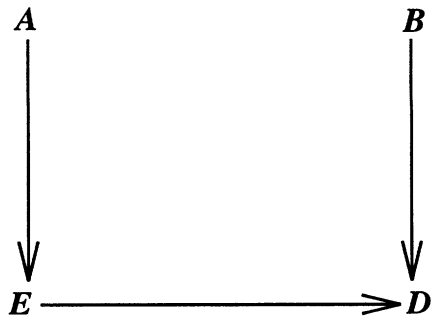

FIGURE 11.

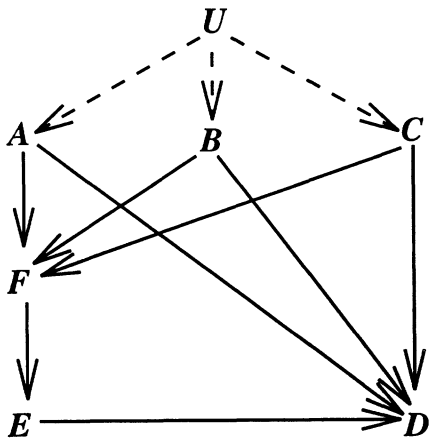

FIGURE 12.

sufficient, and yet control of C (S* = {C}) is not sufficient.

It is also important to recognize that there may be several different minimally sufficient sets, which may not even overlap with one another, and which may be quite disparate in size and in difficulty of measurement. Figure 12 provides an example in which all of the causes of D are associated with E only through a final common path that passes through F. Both {A, B, C} and {F} are minimally sufficient but have no variable in common.

Graphical Separation

The graphical criteria for sufficiency (criteria 1–3 above) involve a more general graphical concept that will prove useful in evaluating confounding criteria and variable subsets. We say a set of variables S *separates* two other sets R and T, or S *blocks* every path between R and T, if the following criteria are met:

S1. Every unblocked path from R to T is intercepted by a variable in S, and

S2. Every unblocked path from R to T generated by adjustment for the variables in S is intercepted by a variable in S.

(This concept is usually called "d-separation of R and T by S" in the graphical literature,[3,5,6] where d stands for "directional".) With this definition, we can say that S is sufficient for control of confounding under a given DAG if S contains no descendants of E or D, and S separates E from D in the graph obtained by deleting all arrows emanating from E. Thus, in Figure 8 (which is Figure 1 with the E-D arrow deleted), the set {A, C} separates the set {E} from the set {D}, and so does the set {B, C}, but the set {C} does not. In Figure 12, the set {F} separates {E} from {D} once the E-D arrow is deleted, and so does the set {A, B, C}.

The concept of separation is useful beyond the backdoor test, because it implies the statistical concept of stratum-specific independence: if S separates R and T, then every variable in R is unassociated with every variable in T within strata of S.[3,5,6,25] For example, in Figure 8, {A, C} separates {E} from {D}, and hence, under this graph, E and D are unassociated within A-C strata. Although the converse is not necessarily correct, the exceptions involve perfect cancellations of associations and so may be of little practical relevance in epidemiology.

Connection of Graphical and Statistical Criteria

Suppose that we have partitioned a sufficient subset of potential confounders in a problem into two subsets S and T, where no variable in S or T is affected by E or D. Although there is some variation in details, criteria based on statistical associations are often used to decide whether to treat S alone as sufficient for adjustment. Commonly, S is treated as sufficient if every potential confounder C in T satisfies at least one of the following criteria:

U1. C and E are unassociated (independent) within the strata defined by S; or

U2. C is unassociated with D within the strata defined by E and S.

For example, if S = {age, sex}, T = {birth year}, E = smoking, and D = myocardial infarction (MI), the criteria say that birth year need not be controlled once age and sex are controlled if either (1) smoking and birth year are unassociated within age-sex strata or (2) MI incidence and birth year are unassociated within smoking-age-sex strata.

Some authors use a less restrictive version of criterion U2, in which C is unassociated with D among the unexposed. Such usage is justifiable if the effect measures of interest refer or are standardized to the exposed population, as is often assumed.[10,11,26] Our version is needed, however, if one wishes C to be unnecessary regardless of which standard (reference) distribution is chosen.[12]

Consider the statistical criteria applied to Figure 1 with S = {C} and T = {A, B}. Apart from examples with perfect cancellation, the above criteria would detect the insufficiency of S. For example, within strata of C, E and A are associated because A affects E; and, within E-C strata, A is associated with D because A would be associated with B and B affects D.

Now consider Figure 5 with S = {} (the empty set) and T = {A, B, C}. Apart from examples with perfect cancellation, the above statistical criteria would fail to detect the sufficiency of S (that is, that no control is necessary), because C fails both criteria; E and C would be associated because both are affected by A; and C and D would be associated within strata of E because both are affected by B. Thus, the usual criteria for evaluating a set of confounders do not correspond perfectly with the graphical test; the criteria may not identify all of the sufficient sets and, in particular, may fail to identify minimally sufficient sets.

It is possible, however, to generalize the usual statistical criteria so that they identify all of the sufficient sets found by the backdoor test (see corollary 4.1 of Robins[9]). Suppose that S and T together are sufficient for adjustment. Then T will be unnecessary given S if T can be decomposed into two disjoint subsets T_1 and T_2 such that, within strata of S, both of the following criteria are met:

U1*. T_1 is unassociated with E within strata defined by S; *and*

U2*. T_2 is unassociated with D within strata defined by E, S, and T_1;

Note that variables in T_1 may be associated with variables in T_2; the criteria do require, however, that T_1 and T_2 have no variable in common and that all variables in T appear in either T_1 or T_2. To apply these criteria, we may begin by taking T_1 to be the largest subset of S that is independent of E and so satisfies U1*; we then check to see whether $T_2 = T - T_1$, the remainder of T after deleting T_1, satisfies U2*.

Whereas the usual approach requires *either* criterion U1 or U2 to hold for each variable in T to ignore T, we require *both* criteria U1* *and* U2* to hold. When considering just one variable beyond S, however, criteria U1 and U2 are special cases of criteria U1* and U2*. To see this fact, first note that the empty set {} is unassociated with everything (because it defines no strata), and hence it vacuously satisfies both U1* and U2*. Hence, if C satisfies criterion U1, T = {C} satisfies criteria U1* and U2* with T_1 = {C} and T_2 = {}; if C instead satisfies criterion U2, T = {C} satisfies criteria U1* and U2* with T_1 = {} and T_2 = {C}.

As an example, suppose S = {age, sex}, T = {birth year, height}, E = smoking, and D = MI. Then criteria U1* and U2* imply that neither birth year nor height need be controlled if any one of the following four conditions hold:

1. Within age-sex strata, smoking is unassociated with the compound variable birth year-height (T_1 = {birth year, height}, T_2 = {});
2. Within smoking-age-sex strata, the compound variable birth year-height is unassociated with MI (T_1 = {}, T_2 = {birth year, height});
3. Smoking and birth year are unassociated within age-sex strata, and height and MI are unassociated within smoking-age-sex-birth year strata (T_1 = {birth year}, T_2 = {height}); or
4. Smoking and height are unassociated within age-sex strata, and birth year and MI are unassociated within smoking-age-sex-height strata (T_1 = {height}, T_2 = {birth year}).

Each of these conditions is sufficient, even if birth year is associated with height.

Consider again Figure 5 with S = {} and T = {A, B, C}. Using T_1 = {B} and T_2 = {A, C}, we may show that T satisfies criteria U1* and U2* and that S (no adjustment) is sufficient. First, B and E are unassociated, so U1* is satisfied; second, within E-B strata, A-C is unassociated with D, so U2* is satisfied.

The preceding example illustrates a general theorem linking graphical and associational criteria. Suppose we have disjoint sets of variables S and T in a DAG that contain no descendant of E or D and together satisfy the backdoor test; then S alone satisfies the backdoor test only if T can be partitioned into disjoint subsets that satisfy criteria U1* and U2*.[9,27] Thus, graphical sufficiency implies satisfaction of our generalized statistical criteria. The advantage of the graphical approach is that it offers a straightforward visual means of checking criteria, at least in moderate-sized graphs, and it translates into an efficient algorithm for finding minimally sufficient subsets of control variables.[6,22] This algorithm does not depend on quantitative information and so can be applied in the design as well as the analysis stage of a study, as well as to situations in which some key potential confounders have not been measured. The graph also clearly displays the essential assumptions for the algorithm, such as the assumptions that S and T contain no variable affected by E or D.

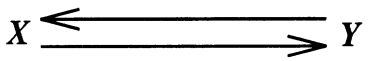

FIGURE 13.

It is possible for S and T to satisfy U1* and U2* even though S fails the backdoor test. In such a case S would still be sufficient for adjustment; thus, the backdoor test does not identify all sufficient subsets in all settings. Nonetheless, these cases involve perfect cancellations of associations and so may be of little practical relevance for epidemiology.

In a subsequent paper, we hope to discuss the relation of graphical criteria for nonconfounding to exchangeability and collapsibility criteria.[10–12,26] Briefly, if S and T satisfy U1* and U2*, then the different exposure groups will be exchangeable within strata of S, and both the risk difference and risk ratio (but not necessarily the odds ratio) will be collapsible over T.[9] Thus, if S passes the backdoor test there will be no confounding within strata of S, and, given stratification on S, T will contain no confounder according to the definitions in our previous writings.[11,12,26]

Discussion

A closed loop in a causal diagram represents reciprocal causation (feedback). Graphs with such loops are called *cyclic* or nonrecursive. We have limited our discussion to acyclic graphs, because cyclic graphs are interpretable as shorthand representations of acyclic graphs with multiple time-specific measurements of the variables. For example, the statement "X can cause Y and Y can cause X" could be represented in a cyclic graph as simple as Figure 13. Nonetheless, because causes must precede effects, the statement can only be meaningfully interpreted as saying that "the occurrence of X can cause a subsequent occurrence of Y, and vice versa." An acyclic representation of this statement requires time-specific versions of each variable, such as in Figure 14. Cyclic graphs can have a deceptively simple appearance relative to the complex time-dependent processes they represent. With proper translation into acyclic form, however, such graphs can be analyzed using the methods given here; such translation will also reveal exactly what time-series of measurements are needed for unconfounded effect estimation. For discussions of graphical methods for time-dependent variables and direct effects, see Robins[9] and Pearl and Robins.[27]

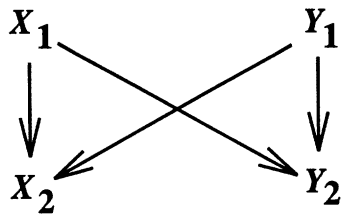

FIGURE 14.

Causal diagrams provide results equivalent to those obtainable using the more established counterfactual causal models of philosophy[28] and statistics[29]; see Robins[8,9] and Galles and Pearl[30] for descriptions of the connection. Although we have found counterfactual models useful in our previous work,[7,11] graphical models seem to have a broad intuitive appeal, and we are enthusiastic about their use in teaching principles for identification and control of confounding. Nonetheless, we must emphasize that no approach solves the central epistemologic problem of inferring causation from nonexperimental (observational) data. As realized by Hume centuries ago and reinforced by many authors since,[26,28,29] all causal inference is based on assumptions that cannot be derived from observations alone.

Even if we obtain randomized-trial data, we must assume that no bias occurred in allocation and compliance, or that any such bias can be handled by adjustment procedures; such assumptions are not always correct. In nonexperimental studies, our inferences are further limited by assumptions (often wishful) that we have adequately measured all of the important selection and confounding factors. Graphs can only help convey those assumptions and indicate what measurements are sufficient for adjustment, *given those assumptions*.

Because the graphical techniques used in this paper presume a qualitative understanding of the causal structure behind the data, they are less ambitious than those used in some of the graphical literature, which attempt to *infer* such structures from data.[5,31,32] The methods used for such inferences involve assumptions that may not be warranted in typical epidemiologic studies. Full descriptions and critiques of these methods are somewhat involved and appear elsewhere.[5,9,31–37] Because the methods are highly controversial, their use for drawing inferences (such as in the TETRAD software of Scheines *et al*[32]) should be cautioned by awareness of the controversy.

We have limited our presentation to graphical analyses of confounding. Of equal or greater importance to validity are problems of measurement error, which in most cases (and contrary to popular lore) cannot be validly handled by simple approaches, such as stratification on indicators of "information quality."[38] Graphs can, however, be used to convey and analyze assumptions about measurement processes. Important applications arise when a measurement can be affected by variables other than the one supposedly being measured. As a simple example, consider a case-control study of sleep position E and sudden infant death syndrome D. Suppose the measurement of E is parental response F to a question about sleep position; response bias would then correspond to the presence of an arrow from the study outcome D to the exposure measurement F, as in Figure 6. In a future article, we hope to describe the application of graphical models to validity questions that involve simultaneous consideration of different sources of bias.

In closing, we wish to emphasize that the methods we have discussed are purely qualitative and so do not address the quantitative problem of determining how much control is necessary to reduce bias to an acceptable level. Such determinations require much more information than demanded for purely graphical analysis, such as information about strength of associations among confounders and exposure, as well as strength of confounder effects on disease. This information is rarely known with any accuracy; as a consequence, estimates of residual bias are rarely if ever accurate. One way to address this problem is to conduct a *sensitivity analysis* of bias,[9,39–41] although such analyses may themselves depend on and hence be sensitive to various simplifying assumptions.[42] These issues exemplify the complexities one can expect to encounter in a quantitative analysis of bias.

Acknowledgments

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