Practice of Epidemiology

“Toward a Clearer Definition of Confounding” Revisited With Directed Acyclic Graphs

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In a 1993 paper (Am J Epidemiol. 1993;137(1):1–8), Weinberg considered whether a variable that is associated with the outcome and is affected by exposure but is not an intermediate variable between exposure and outcome should be considered a confounder in etiologic studies. As an example, she examined the common practice of adjusting for history of spontaneous abortion when estimating the effect of an exposure on the risk of spontaneous abortion. She showed algebraically that such an adjustment could substantially bias the results even though history of spontaneous abortion would meet some definitions of a confounder. Directed acyclic graphs (DAGs) were introduced into epidemiology several years later as a tool with which to identify confounders. The authors now revisit Weinberg’s paper using DAGs to represent scenarios that arise from her original assumptions. DAG theory is consistent with Weinberg’s finding that adjusting for history of spontaneous abortion introduces bias in her original scenario. In the authors’ examples, treating history of spontaneous abortion as a confounder introduces bias if it is a descendant of the exposure and is associated with the outcome conditional on exposure or is a child of a collider on a relevant undirected path. Thoughtful DAG analyses require clear research questions but are easily modified for examining different causal assumptions that may affect confounder assessment.

bias (epidemiology); causality; confounding factors (epidemiology); reproductive history

Abbreviation: DAG, directed acyclic graph.

In her 1993 paper, “Toward a Clearer Definition of Confounding,” Weinberg focused on clarifying the definition of a confounder in etiologic studies (1). Specifically, she noted a situation where a variable that did not confound the estimated effect would qualify as a confounder according to commonly applied criteria of the time: The variable was associated with exposure, was associated with the outcome among the unexposed, and was not an intermediate factor between the exposure and the outcome. As an illustrative example, she examined the common practice of adjusting for history of spontaneous abortion when estimating the causal effect of an exposure on the risk of spontaneous abortion. She showed, by example, that under simplified but biologically plausible assumptions, controlling for history of spontaneous abortion could substantially bias the estimated risk ratio.

Since the publication of Weinberg’s paper, the use of directed acyclic graphs (DAGs) to identify confounders has become increasingly common. Concurrently, it has become more widely recognized that a variable could appear to be a confounder by some conventional definitions but adjustment for that variable could induce bias (2–9). Numerous published texts provide introductions to DAGs (2–7, 10). In this paper, we assume a basic familiarity with DAGs while revisiting Weinberg’s original work, using DAGs to evaluate and expand upon her examples.

ORIGINAL ASSUMPTIONS

History of spontaneous abortion is predictive of pregnancy loss and is often adjusted for in studies of spontaneous abortion (11–13), presumably under the assumption that it serves as a proxy for unmeasured confounders rather than supposing that it causally affects the risk of subsequent spontaneous abortions. Weinberg described a hypothetical
study for estimating the effect of an exposure (E) (e.g., smoking) on the risk of spontaneous abortion in a current pregnancy (S_2) (1). The exposure was a risk factor for prior spontaneous abortion (S_1), but S_1 was not an intermediate variable between E and S_2. However, S_1 was associated with the outcome among the unexposed, a commonly applied criterion used to determine whether a variable is a confounder when the target population is the exposed group. Thus, S_1 has often been treated as a confounder.

For simplification, Weinberg limited the example to second pregnancies and assumed that a woman’s exposure status remained the same across pregnancies (1). Further, she assumed that E increased the risk of an occult abnormality (A) and that A also was the same across pregnancies. Finally, she assumed that the outcomes (S_1 and S_2) were independent, conditional on A, and that Pr[S_i|E, A] = Pr[S_i|A] for pregnancies i = 1, 2.

**THE ORIGINAL DAG**

We can use DAGs to represent possible underlying causal relations compatible with the statistical assumptions from Weinberg’s paper (1). In order to draw appropriate conclusions from a DAG, it is necessary to assume that the DAG represents the true causal relations and that it is not missing any variable that causes any pair of variables in the graph (5, 7). We consider several DAGs that represent variations in the scenario considered by Weinberg. Our interest is in determining whether different DAGs compatible with the scenario described by Weinberg lead us to the same conclusions she reached originally (1) and whether biologically plausible revisions would cause us to revise those conclusions.

The construction and interpretation of a DAG differs depending on the causal contrast of interest and the hypothesized causal relations. First, we will consider an exposure that occurs prior to both pregnancies (e.g., in utero exposure of the pregnant woman to smoking). Formally, let E represent a dichotomous exposure where 1 indicates exposure and 0 indicates no exposure, and let S_2 represent a dichotomous outcome where 1 indicates that the second pregnancy ended in a loss and 0 indicates that it ended in a birth. Assuming that the target population is the exposed group, let S_2=0 represent the outcome of the second pregnancy if all exposed women were exposed and S_2=1 represent the outcome of the second pregnancy if all exposed women had instead been unexposed. Then the causal risk ratio would be Pr[S_2=1]/Pr[S_2=0]. In the data, only Pr[S_2=1] would be observed (indicated Pr[S_2=1E=1]). Pr[S_2=0] would be estimated from the experience of the unexposed group, Pr[S_2=1E=0]. If the (observed) experience of the unexposed group differed from the (unobserved) experience the exposed group would have had if they had been unexposed, then the estimated effect parameter would be biased. Confounding could exist in the unadjusted estimate or could be introduced by inappropriate adjustment for covariates. In this article, we evaluate several DAGs to determine whether adjustment for S_1 introduces bias. Formally, we assess whether Pr[S_2=1]/Pr[S_2=0] = Pr[S_2=1E=1, S_1]/Pr[S_2=1E=0, S_1].

**ADDING MULTIPLE EXPOSURES**

The DAGs shown in Figure 1 indicate that E and A both occur prior to or during the first pregnancy but affect both pregnancies. For some exposures that do not change (e.g., in
uterine exposures of the study participant) this might be appropriate, but for an exposure such as participant smoking, which can change, it is important to specify the exact research question. Are we interested in the effect of smoking during the first pregnancy on the outcome of the second pregnancy, or are we interested in the effect of smoking during the second pregnancy on that pregnancy? If the exposure of interest were smoking during the second pregnancy, the DAG would have to be modified to reflect the fact that smoking during the second pregnancy cannot affect the first pregnancy.

The DAGs shown in Figure 2 represent the same exposure (such as participant smoking) at 2 points in time through 2 nodes: \(E_1\) and \(E_2\) (designating smoking during the first and second pregnancies, respectively). In these DAGs, the exposure during each pregnancy produces its own underlying abnormality (such as poor response of the endometrium to pregnancy hormones (1)), which affects only the contemporaneous pregnancy. The new causal risk ratio of interest is \(\text{Pr}[S_2^{2} = 1] / \text{Pr}[S_2^{2} = 0] = 1\).

Our revised DAGs require us to modify Weinberg’s assumptions slightly. The original simplifying assumption that \(S_1\) and \(S_2\) are independent conditional on \(A\) is no longer unambiguous, because the abnormality may occur at 2 different points in time. However, we can be consistent with the spirit of the assumption in our revised DAG if \(S_1\) and \(S_2\) are independent conditional on \(A_1\) and \(A_2\). This is the case in DAG 2A, where \(S_1\) and \(S_2\) are not associated through any open paths that do not involve \(A_1\) and \(A_2\) and where conditioning on either would block the otherwise open paths \(S_1 \rightarrow A_1 \leftarrow U_a \rightarrow A_2 \rightarrow S_2\) and \(S_1 \rightarrow A_1 \leftarrow E_1 \rightarrow E_2 \rightarrow A_2 \rightarrow S_2\). In addition, we now assume \(\text{Pr}[S_1|A_1, E_1] = \text{Pr}[S_1|A_1]\) as an extension of the corresponding original assumption (1). This is represented by the fact that all paths from \(E_1\) to \(S_1\) go through \(A_1\). Weinberg’s assumptions that exposure status and abnormality status are the same for both pregnancies (\(E_1 = E_2\) and \(A_1 = A_2\)) are not required to evaluate the revised DAGs and are neither indicated nor contradicted.

In DAG 2A, \(\text{Pr}[S_2 | E_1 = E_2 = \text{true}] = \text{true} / \text{false} = 0\) is an unconfounded estimate of \(\text{Pr}[S_2^{2} = 1] / \text{Pr}[S_2^{2} = 0] = 1\) because the only backdoor path from \(E_2\) to \(S_2\) (\(E_2 \leftarrow E_1 \rightarrow A_1 \leftarrow U_a \rightarrow A_2 \rightarrow S_2\)) is blocked by the collider \(A_1\). As before, \(S_1\) is neither a confounder nor a child of an intermediate. It meets some conventional criteria for confounding because it is a child of the collider \(A_1\). Adjusting for \(S_1\) will open a backdoor path and bias the effect estimate (i.e., \(\text{Pr}[S_2^{2} = 1] / \text{Pr}[S_2^{2} = 0] = 1 \neq \text{true} = 1\) \(\text{true} / \text{false} = 0, S_1\)). Thus, as Weinberg described in the original paper (1), adjusting for \(S_1\) is not appropriate. The bias introduced by conditioning on \(S_1\) could be removed by adjusting for \(E_1\) or \(U_a\), provided that DAG 2A is correct and complete. However, if the DAG were missing variables, such as a shared cause of \(S_1\) and \(S_2\) (DAG 2B), bias could be introduced by adjusting for \(S_1\) that would not be removed by adjusting for \(U_a\). In addition, adjusting for \(E_1\), a close correlate of the exposure, would affect statistical efficiency.

In DAG 2B, the assumption that \(S_1\) and \(S_2\) are independent conditional on \(A_1\) and \(A_2\) is relaxed by adding an unmeasured shared cause of the pregnancy outcomes (\(U_a\)). This creates 2 backdoor paths from \(E_2\) to \(S_2\) (\(E_2 \rightarrow E_1 \rightarrow A_1 \leftarrow U_a \rightarrow A_2 \rightarrow S_2\) and \(E_2 \rightarrow E_1 \rightarrow A_1 \leftarrow S_1 \leftarrow U_a \rightarrow A_2 \rightarrow S_2\)), but both paths are unconditionally blocked by colliders (\(A_1\) and \(S_1\), respectively). Thus, as before, the unadjusted estimate would be an unbiased estimate of the causal contrast, while adjusting for \(S_1\) would open backdoor paths between \(E_2\) and \(S_2\), which would therefore introduce bias.

DAG 3A (Figure 3) is the same as DAG 2A and DAG 3B is the same as DAG 2B, except that in Figure 3 the association between \(E_1\) and \(E_2\) is due to the shared cause \(U_e\) (e.g., societal factors that determine smoking behavior) instead of \(E_1\)’s directly causing \(E_2\) (i.e., we no longer consider smoking addictive). In both DAG 3A and DAG 3B, as before, the unadjusted estimate for the effect of \(E_2\) on \(S_2\) is unbiased. In DAG 3A, we need not condition on any covariate, because the only backdoor path between \(E_2\) and \(S_2\) (\(E_2 \leftarrow U_a \rightarrow E_1 \rightarrow A_1 \leftarrow U_a \rightarrow A_2 \rightarrow S_2\)) is blocked by the collider \(A_1\). Once again, \(S_1\) is the child of the collider \(A_1\), so adjusting for \(S_1\) would also open a backdoor path and introduce bias. In DAG 3B, it is inappropriate to adjust for \(S_1\) because it is a collider as well as a child of a collider. This is also true in DAG 3C, which combines DAGs 2B and 3B by allowing \(E_2\) both to be affected by \(E_1\) and to have a shared cause with \(E_1\).

DAG 3D is similar to DAG 3C, but now \(S_1\) is allowed to affect the exposure of interest (\(E_2\)). This could occur if a...
Figure 3. A) Directed acyclic graph (DAG) 3A, in which an unknown variable \((U_d)\) causes exposure during the first \((E_1)\) and second \((E_2)\) pregnancies. Each exposure causes the corresponding underlying abnormality \((A_1\) and \(A_2\)). In addition, an unknown variable \((U_d)\) causes both underlying abnormalities, and each underlying abnormality causes the corresponding outcome \((S_1\) and \(S_2\)). B) DAG 3B, in which a shared cause \((U_e)\) of \(S_1\) and \(S_2\) is added to DAG 3A. C) DAG 3C, which builds on DAG 3B by allowing \(E_1\) to affect \(E_2\) directly. D) DAG 3D, which builds on DAG 3C by allowing the first outcome \((S_1)\) to affect the second exposure \((E_2)\).

DAGs that further alter the original assumptions

Figure 4 presents DAGs that substantially modify Weinberg’s original assumptions (1) despite being similar to the preceding DAGs. DAG 4A is similar to DAG 2A, except that \(A_1\) causes \(A_2\). This modification means that \(A_1\) is no longer a collider, so there is an open backdoor path from \(E_2\) to \(S_2\) \((E_2 \leftarrow E_1 \rightarrow A_1 \rightarrow A_2 \rightarrow S_2\)\). An unbiased estimate for the effect of \(E_2\) on \(S_2\) would require adjustment for \(E_1\) or \(A_1\). The simplest way to understand this is to note that under this DAG, \(E_1\) is a confounder because it causes both the exposure of interest \((E_2)\) and the outcome \((S_2)\). Theoretically, if neither \(E_1\) nor \(A_1\) were measured, adjusting for \(S_1\) could serve as a proxy for \(A_1\). However, the backdoor path would still remain open to the degree that \(S_1\) was not perfectly correlated with \(A_1\) (7). For DAG 4A, the effect estimate adjusted for \(S_1\) might be less biased than the unadjusted estimate. This conclusion is incompatible with Weinberg’s original calculations, because we have modified her assumptions.

DAGs 4B and 4C are similar to previous DAGs, except that \(A_1\) is only directly affected by \(E_1\). Although these DAGs would initially appear compatible with Weinberg’s example (1), they violate the assumption that \(S_1\) and \(S_2\) are associated among the unexposed, because the only path between the two pregnancy outcomes goes through the exposure of interest. Consequently, \(S_1\) would not meet some conventional criteria for a confounder, nor would it be a confounder based on the DAG. If the DAG is correct, if all variables are measured perfectly, if the adjusted model is specified correctly, and if there is no effect-measure modification, adjusting for \(S_1\), although unnecessary, would not bias the effect estimate \((i.e., \text{Pr}[S_1|E_2=1]/\text{Pr}[S_1|E_2=0] = \text{Pr}[S_2=1|E_2=1]/\text{Pr}[S_2=1|E_2=0]=\text{Pr}[S_2|S_1=1|E_2=1]/\text{Pr}[S_2|S_1=1|E_2=0,S_1])\) because \(S_1\) is not a risk factor for the outcome. However, adjustment could affect the precision of the estimate (7, 14).

Other examples from the original paper

Weinberg considered other scenarios in which a variable could be mistaken for a confounder (1). She described a woman modified her behavior based on the outcome of her first pregnancy. For example, a smoker who had a spontaneous abortion during her first pregnancy might quit smoking prior to her second pregnancy. This would violate Weinberg’s original assumption that exposure was the same across pregnancies (1). In DAG 3D, there are unconditionally open backdoor paths through \(S_1\) \((e.g., E_2 \rightarrow S_1 \leftarrow U_e \rightarrow S_2\)\). Thus, this is the first example in which the unadjusted estimate is biased \((i.e., \text{Pr}[S_1|E_2=1]/\text{Pr}[S_1|E_2=0] \neq \text{Pr}[S_2=1|E_2=1]/\text{Pr}[S_2=1|E_2=0])\). If \(U_e\) and \(U_d\) were measured, the simplest way to block the backdoor paths would be to condition on them. If they were unmeasured, then conditioning on \(S_1\) would be necessary, but \(S_1\) is not a collider on other backdoor paths \((E_2 \leftarrow E_1 \rightarrow A_1 \rightarrow S_1 \leftarrow U_e \rightarrow S_2\)\) and \(E_2 \leftarrow U_e \rightarrow E_1 \rightarrow A_1 \rightarrow S_1 \leftarrow U_e \rightarrow S_2\)\). Therefore, additional adjustment \((e.g., \text{adjusting for} E_1)\) would be needed to block the paths opened by conditioning on \(S_1\).
general situation where $E$ caused 2 events that were independent given $E$, and the causal contrast of interest was $\Pr[S_2=1]/\Pr[S_2=0] = 1$. The simplest case can be seen in DAG 5A (Figure 5), where the unadjusted estimate of the effect of $E$ on $S_2$ is not confounded. Nevertheless, as Weinberg reported, no bias would be introduced by adjusting for $S_1$ because $S_1$ is not associated with the outcome conditional on $E$ (1, 14). However, in the more realistic scenario where there is a shared cause ($U_s$) of $S_1$ and $S_2$, adjustment for $S_1$ is no longer benign. DAG 5B is analogous to Figure 1c in the original paper (1). Here again there is no confounding, so $\Pr[S_2=1]/\Pr[S_2=0] = \Pr[S_2=1|E=1]/\Pr[S_2=1|E=0]$; but in this case, adjustment for $S_1$ induces bias by opening the path $E \rightarrow S_1 \leftarrow U_s \rightarrow S_2$. In DAG 5C, however, $S_1$ is no longer a collider because there is no association between $E$ and $S_1$, so adjustment for $S_1$ is unnecessary but would not introduce bias.

Weinberg also discussed cases where spontaneous abortion might serve as a proxy for an unmeasured confounder (Figure 6). In Figure 5, $U_s$ is not a confounder because it is not unconditionally associated with $E$, but in Figure 6, $U_{se}$ is a confounder on a backdoor path from $E$ to $S_2$. DAG 6A represents a scenario described by Weinberg (1) in which $E$ is unrelated to the risk of $S_2$ and the unadjusted estimate would be biased because of the open backdoor path $E \leftarrow U_{se} \rightarrow S_2$. Adjusting for $U_{se}$ would block the backdoor path. Although $S_1$ is not a confounder, it could be used as a proxy for $U_{se}$ if $U_{se}$ were unmeasured. However, there would be residual confounding to the degree that $U_{se}$ and $S_1$ were not perfectly correlated. In addition, stratifying on $S_1$ (as Weinberg demonstrated (1)) could result in greater bias in one stratum than in another (7), causing spurious effect-measure modification. DAG 6B is the same as DAG 6A, except that $E$ is allowed to have an effect on $S_2$. This change would not alter the above conclusions about using $S_1$ as a proxy for $U_{se}$.

DAG 6C resembles DAG 6B, except that now $E$ affects both $S_1$ and $S_2$. $U_{se}$ is still a confounder, but $S_1$ is now a collider, so its ability to serve as a proxy for $U_{se}$ is compromised. While adjusting for $S_1$ as a proxy for $U_{se}$ might be intended to close the backdoor path $E \rightarrow U_{se} \rightarrow S_2$, it would open the backdoor path $E \rightarrow S_1 \leftarrow U_{se} \rightarrow S_2$. Whether the effect estimate adjusted for $S_1$ would be more or less biased than the unadjusted estimate would depend on information not captured in the DAG, such as the strength of the effects represented by each arrow. Thus, for this example, some bias is unavoidable unless $U_{se}$ is measured.

**DISCUSSION**

We have used DAGs to revisit the examples Weinberg provided in her landmark 1993 paper, where a variable appeared to be a confounder using commonly applied criteria but adjustment for the variable actually introduced bias (1). Given her assumptions, our conclusions based on several possible DAGs matched those she derived with algebraic examples. To summarize the conclusions of the specific examples we explored, bias may be introduced when a descendant of the exposure is adjusted for if there is a path from that descendant to the outcome that does not involve the exposure (e.g., DAG 1A). Bias also may be introduced by adjusting for a variable that is a collider or a child of a collider on a noncausal path between the exposure and the outcome of interest (e.g., DAG 2A). Both of these situations often plausibly apply to history of spontaneous abortion. Thus, under several different causal structures, bias would be introduced by adjusting for this variable. Even when the true DAG is unknown, it is useful to draw and evaluate several different likely possibilities because, as is illustrated here, the conclusions may be the same under several different causal structures.

History of spontaneous abortion could serve as a proxy for an unmeasured confounder if it is not subject to the
conditions just described (e.g., DAG 6B). However, residual
bias would remain to the degree that reproductive history
was imperfectly associated with the true unmeasured con-
founder, and this residual bias might be worse in one
stratum than in another (7), causing apparent effect-
measure modification. Thus, use of reproductive history as
a proxy for an unmeasured confounder requires careful
consideration.

The DAGs considered here also highlight the importance
of defining the specific research question. In Figure 1, we
considered an exposure that occurred prior to the first preg-
nancy outcome, whereas in Figures 2 and 3, we considered
an exposure that occurred just prior to the current preg-
nancy outcome. The evaluation of a potential confounder
needs to be made in the context of the specific research
question and the associated DAG.

As DAG theory has percolated into epidemiology, there
has been increasing awareness of the inadequacy of con-
ventional criteria for appropriately identifying confounders,
especially in the case where collider stratification bias may
occur (3, 7, 9). DAGs help us build useful etiologic models
by providing a transparent way to represent the causal rela-
tions between variables. They have simple rules that allow
the identification of confounders, and they allow complexi-
ty that cannot be illustrated as concisely using algebraic
proofs. However, DAGs do not provide information on the
magnitude of the effects or the magnitude of the bias intro-
duced by improper exclusion of confounders or inappropri-
ate adjustment for nonconfounders. Quantitative analyses
complement DAGs because they can be used to explore the
magnitude of these biases under specific assumptions. Nev-

ertheless, in order for a DAG (or an algebraic example) to
be effective, the research question must be clearly defined.
Even then, both approaches require simplifying assump-
tions. Despite their limitations, together quantitative sensi-
tivity analyses and DAGs improve our ability to make
causal inferences from observational data.

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